Øystein Grimstad

Toll-like receptor-mediated inflammatory responses in keratinocytes

Thesis for the degree of Philosophiae Doctor

Trondheim, September 2012

Norwegian University of Science and Technology
Faculty of Medicine
Department of Cancer Research and Molecular Medicine

NTNU – Trondheim
Norwegian University of
Science and Technology

ST. OLAVS HOSPITAL
TRONDHEIM UNIVERSITY HOSPITAL

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Norwegian University of Science and Technology

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ISBN 978-82-471-3767-3 (printed ver.)
ISBN 978-82-471-3768-0 (electronic ver.)
ISSN 1503-8181

Doctoral theses at NTNU, 2012:232

Printed by NTNU-trykk

Toll-liknende reseptor-mediert inflammasjon i keratinocytter

Gjennom arbeidet i denne avhandlingen har vi ønsket å finne mer ut av hvordan hudcellen selv setter i gang reparasjonsmekanismer etter ytre påvirkning, gjennom aktivering av hudcellens eget medfødte immunforsvar. Vi har hatt fokus på Toll-liknende reseptorer (TLR), som er en særlig viktig del av dette immunforsvaret

Det medfødte immunforsvaret gjenkjenner molekyler som evolusjonsmessig har som fellesnevner at de er assosierte med fare for organismen. Både fremmede molekyler fra mikrober og egne molekyler som varsler om skade kan gjenkjennes av det medfødte immunforsvaret. Aktivering av det medfødte immunsystemet setter i gang betennelsesreaksjoner. For å iverksette en effektiv betennelsesreaksjon, skiller aktiverte hudceller ut signalmolekyler, kalt cytokiner, som aktiverer flere andre celletyper og dessuten er med på å regulere betennelsesprosessens videre forløp

Vi begynte arbeidet med å analysere cytokinprofiler i sårvæske fra akutte sår. I tillegg så vi på hvordan celler i et sårmiljø reagerte på stimulering med ulike TLR-ligander og betennelsesfremmende cytokiner som er tilstede ved akutt betennelse. Analysene involverte i tillegg til hudceller også endotelceller (blodkarceller), fibroblaster (bindevevsceller), monocytter og nøytrofile ganulocytter (hvite blodceller).
Et hovedfunn var at hudceller er særs følsomme for en syntetisk TLR3-ligand, polyI:C. Denne liganden er en analog av dobbeltrådet RNA, som man blant annet finner i enkelte virus. Stimulering med polyI:C utløste kraftige produksjon og frigjøring av de fleste av de 27 molekylære mediatorer vi undersøkte for. Øvrige sentrale TLR-ligander utløste liten eller ingen frigjøring av disse signalmolekylene fra hudceller.
Dette funnet la grunnlaget for de videre studiene vi har gjort i denne avhandlingen, hvor vi forsøkte å finne mer ut av hvorfor hudceller er så følsomme for polyI:C, og hvordan polyI:C-stimulering fører til frigjøring av signalmolekyler viktige for igangsetting av betennelsesreaksjon.

Vi gikk videre med å karakterisere hvordan polyI:C stimulering virker så å si utelukkende gjennom TLR3-reseptoren, til tross for at det finnes andre potensielle reseptorer og signaleringsmekanismer for denne liganden. Vi fant videre at TLR3-stimulering førte til en dose-respons- avhengig celledød og samtidig frigjøring av det sentrale cytokinet CXCL-8. Celledød kan skje på ulike måter, og vi har beskrevet morfologiske karakteristika som gjorde det vanskelig å klassifisere celledøden som apoptose eller nekrose. Vi spekulerte i muligheten for at denne celledøden kunne passe med en tredje kategori; pyroptose. Dette er en type programmert celledød som karakteriseres av caspase-1 aktivering, men ikke de apoptotiske caspasene -8, -9 og -3/7. Vi fant også at stimulering med polyI:C sammen med en annen nukleinsyre beskyttet mot både toksisitet og inflammatorisk

respons. Denne effekten kunne vi tilskrive utkonkurrering av reseptor-mediert opptak av polyI:C i cellen.

I det siste arbeidet rettet vi fokus på hvordan TLR3-responser er avhengige av caspase-4-aktivering. Caspase-4 er et protein som inngår i programmert celledød og i inflammasjon. Vi fant at TLR3-stimulering i hudceller førte til en kraftig aktivering av gener assosiert med betennelsesprosesser, herunder proformen av det viktige cytokinet interleukin-1β og bestanddeler i andre medfødte immunforsvarssystemer (NLRP3 og caspase-1). Ved å blokkere caspase-4, blokkerte vi både frigjøring av IL-1β og celledød. Caspase-1-hemming blokkerte også for IL-1β-frigjøring, men mindre effektivt enn caspase-4-hemming. Dette plasserer caspase-4 oppstrøms for caspase-1 i kaskaden for IL-1β-frigjøring. Videre fant vi at spesifikk hemming av caspase-4, men ikke caspase-1, beskyttet mot celledød. TLR3 stimulering førte også til en tidlig aktivering av både den inflammatoriske caspase-1 og de apoptotiske caspasene-8, -9 og -3/7. Denne typen celledød av keratinocytter involverer således mekanismer som man observerer både ved apoptose og pyroptose.

Ny og viktig viten om det medfødte immunforsvaret publiseres så å si daglig. I denne avhandlingen har vi demonstrert nye mekanismer for hvordan hudcellen igangsetter betennelsesreaksjoner gjennom TLR3-aktivering.

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Finansieringskilde: Samarbeidsorganet mellom Helse Midt-Norge RHF og NTNU, og Institutt for kreftforskning og molekylær medisin

Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden Ph.d. i molekylærmedisin.
Disputas finner sted i auditorium MTA, Medisinsk teknisk forskningssenter tirsdag 11.september 2012, kl 12.15

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Acknowledgements

The work presented in this thesis was carried out at the Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology in Trondheim (NTNU), Norway. The work has been funded by the Liaison Committee between the Central Norway Regional Health Authority and the NTNU, in addition to grants of my supervisor Terje Espevik.

Kristin Ryggen, head of the Department of Dermatology, St Olavs Hospital is the person to whom I owe the biggest dept of gratitude for entering this research project. As part of an ambitious strategy for strengthening academia at the department, Christian Grønhøj-Larsen was engaged as professor in dermatology at IKM. Furthermore, I was encouraged to start with research and all things were straightened for me to do so. Christian sent me straight to Tokyo, where I had an amazing year as a rookie researcher at the Department of Preventive Molecular Medicine, University of Tokyo under Professor Kouji Matsushima.

Back in Trondheim, I contacted Terje to check if I was welcome to continue research with him. For some reason, he was all positive! I guess Brita Pukstad, my highly esteemed co-worker and sister-in-arms, had blazed the trail for me. The first year or so, I worked with at the time medical student Øystein Sandanger, who was an impressive research capacity in both procedural work and intellectual work. It was a real downer when he left the lab. I trained Liv, Bjørg, Unni and Randi in different lab procedures. They displayed so much talent, that I have let them assist me from time to time ever since, even though I constantly have to tidy up after them in the lab…

Brita, Jørgen Stenvik and Liv Ryan have been my closest co-workers (and Terje, of course). Without Brita, I'm not sure I would have continued this PhD project. For a while, I felt deep loneliness pottering around my keratinocytes. But you reappearing turned my hermit project to teamwork, and this was a true inspirational boost. Fortunately, Jørgen, which by the way is omniscient, also became engaged in keratinocyte work. I have learnt a lot from him in the projects we've been working on together. Liv has been my closest co-worker in the lab over these years, playing a pivotal role in all publications. Her skills in the lab have saved many of my results. If I were to do another PhD-project, I would first attempt to clone Liv, as it would undoubtedly save time and efforts in total!

I would like to thank Terje for outstanding supervision throughout these years. With his positivity and enthusiasm, he has been a wizard and a fantastic support at times where I have lost faith in what I have been doing. I am deeply impressed by his extensive knowledge, interest and insight in biological systems, and I have benefited greatly from this. Far too often, I have truly been barking up the wrong tree, and Terje has showed me onto the right track again. I am also grateful for that he always been available for time and help with both minor problems and more devastating discoveries. In addition to barging in to your office far too often, I

know have ruined at least one Easter vacation and a couple of weeks of your summer holidays.

Thanks also to my other co-workers in the Toll-group, who have been helping me every time I've needed their practical and theoretical expertise: Harald for blotting and transfections, Marcus for help with flowcytometry, Nadra Jesmine (now Myeloma group, free transfer from Toll) for transfections, Nathalie for ELISAs and not to forget Eivind for good collaboration in the lab and interesting discussions in the office. Eivind has also let me use his illustrations as a basis for some of the figures in this thesis.

I have had a tremendous time with the lab due to the good workplace environment. In particular, I have had great fun at lunchtime with my best lunch companions Asbjørn, Gaute and Harald.

Finally; thanks to my wife Elin and my son Einar for support in all ways, especially through this year when so many important life events have taken place.

Tromsø, August 2012
Øystein Grimstad

Abbreviations

ADP	Adenosine diphosphate
AIM2	Absent in melanoma, gene #2
ALR	AIM2-like receptor
AMP	Antimicrobial peptides
APAF1	Apoptotic protease activating factor 1
ASC	Apoptosis-associated speck-like protein containing a CARD
ATP	Adenisne triphosphate
Bcl-2	B-cell lymphoma 2
BIR	Baculoviral inhibitory repeat
CARD	Caspase recruitment Domain
CD	Cluster of differentiation
CIITA	Class II, major histocompatibility complex, transactivator
CpG	Cytosine followed by Guanosine with phosphatediester backbone of DNA
CLR	C-type lectin receptor
CNS	Central nervous system
CTLD	C-type lectin domain
CXCL-8	CXC chemokine-8 (previously IL-8)
DAI	DNA dependent activator of IFN-regulatory factors
DAMP	Damage associated molecular pattern
DC	Dendritic cell
DC-SIGN	Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin
DHX9	Human DEAH (Asp-Glu-Ala-His) box polypeptide 9 (an RNA helicase)
DHX36	RNA helicase associated with AU-rich element
DISC	Death-inducing signalling complex
DNA	Deoxyribonucleic acid
dsRNA	Double-stranded RNA
EGF	Epidermal growth factor

ER	Endoplasmic reticulum
FGF	Fibroblast growth factor
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte-macrophage colony stimulating factor
hBD	Human β-defensin
hToll	Human Toll-homologue
HMGB1	High mobility group box 1
ICAM-1	Intercellular Adhesion Molecule 1
IFN	Interferon
IL	Interleukin
IL-1RA	Interleukin-1 receptor antagonist
iNOS	Inducible nitric oxide synthase
IP-10	Interferon-inducible protein 10
IRAK4	Interleukin-1 receptor-associated kinase 4
IFI16	Gamma-interferon-inducible protein 16
IRF	Interferon regulatory factor
LPS	Lipopolysaccaride
LRR	Leucine-rich repeat
LRRFIP1	Leucine-rich repeat-containing protein
LTA	Lipoteichoic acid
MAL	MyD88 adaptor like (also named TIRAP)
MAPK	Mitogen-activated protein kinases
MC	Mast cell
MCP-1	Monocyte chemotactic protein 1
MDA5	Melanoma differentiation-associated gene 5
MHC	Major histocompatibility complex
Mincle	Macrophage inducible C-type lectin
MIP-1β	Macrophage inflammatory protein-1β
MMP	Matrix metalloproteinase
mRNA	Messenger RNA
MyD88	Myeloid differentiation factor-88

NACHT	Abbreviation from combining NAIP, CIITA, HET-E, and TP1 domains
NAIP	Neuronal apoptosis inhibitory protein
NF-κB	Nuclear factor kappa-light chain enhancer of activated B-cells
NOD	Nucleotide binding oligomerization domain
NLR	NOD-like receptor
NLRC	NOD-like receptor with a caspase recruiting domain
NLRP3	NOD-like receptor family, pyrin domain containing 3
NLRX	NOD-like receptor family x
NK-cell	Natural killer-cell
ODN	Oligodeoxynucleotide
PAMP	Pathogen-associated molecular pattern
PDGF	Platelet-derived growth factor
PolyI:C	Polyinosinic acid:polycytidylic acid
PYD	Pyrin-containing domain
PYHIN	Pyrin and HIN200 domain-containing protein
PRR	Pathogen recognition receptor
RANTES	Regulated on activation normal T-cell expressed
RIG-I	Retinoic acid inducible gene-I
RLR	RIG-I-like receptor
RNA	Ribonucleic acid
ROS	Reactive oxygen species
Src	Sarcoma tyrosine kinase
STAND	Signal transduction ATPases with numerous domains
STING	Stimulator of IFN genes
Syk	Spleen tyrosine kinase
ssRNA	Single-stranded RNA
TBK1/IKKi	Tank binding kinase 1/I-kappa-B kinase inducible
TGF	Transforming growth factor
Th-cell	T-helper cell
TIR	Toll-/IL-1 receptor
TLR	Toll-like receptor

TNF	Tumor necrosis factor
TNFR	TNF receptor
TRAF	TNF receptor associated factor
TRAM	TRIF-related adapter molecule
TRIF	TIR-domain-containing adapter protein inducing IFNβ
TSLP	Thymic stromal lymphopoietin
UPR	Unfolded protein response
UV	Ultraviolet
VCAM-1	Vascular cell adhesion protein 1
VEGF	Vascular endothelial growth factor
VISA	Virus-induced signalling adaptor

List of papers

Paper I

Grimstad Ø, Sandanger Ø, Ryan L, Otterdal K, Damaas JK, Pukstad B, Espevik T.
Cellular sources and inducers of cytokines present in acute wound fluid.
Wound Repair Regen. 2011 May-Jun;19(3):337-47

Paper II

Grimstad Ø, Pukstad B, Stenvik J, Espevik T.
Oligodeoxynucleotides inhibit Toll-like receptor 3 mediated cytotoxicity and CXCL8 release in keratinocytes.
Exp Dermatol. 2012 Jan; 21(1):7-12.

Paper III

Grimstad Ø, Husebye H, Espevik T.
TLR3 mediates release of IL-1β and cell death in keratinocytes in a caspase-4 dependent manner.
Manuscript submitted

1 Introduction

1.1 The immune system

The human body is under constant challenge from various physical, chemical and microbial agents. A highly developed system of biological structures and processes composes the immune system that protects the human body from disease. The immune system must detect a wide variety of agents, and also distinguish them from the organism's own healthy tissue. Another important role of the immune system is to identify and eliminate cancer cells.

The human microbial defence system can be regarded as consisting of three levels: (i) anatomical and physiological barriers; (ii) innate immunity; and (iii) adaptive immunity (Figure 1). The immune system protects organisms from infection with layered defences of increasing specificity. The first line of resistance consists of physical barriers such as skin and mucous membranes that prevents pathogens from entering the organism. If a pathogen breaches these barriers, an immediate, but non-specific innate immune response will be triggered by cell associated or secreted pattern recognition receptors. Should pathogens evade or survive these primary innate responses, the more elaborate adaptive immune system will be alarmed by the innate response. The adaptive immune system adapts its response during an infection to improve its recognition of the pathogen. This improved response is then retained after the pathogen has been eliminated, and allows the adaptive immune system to mount faster and stronger attacks next time this pathogen is encountered.

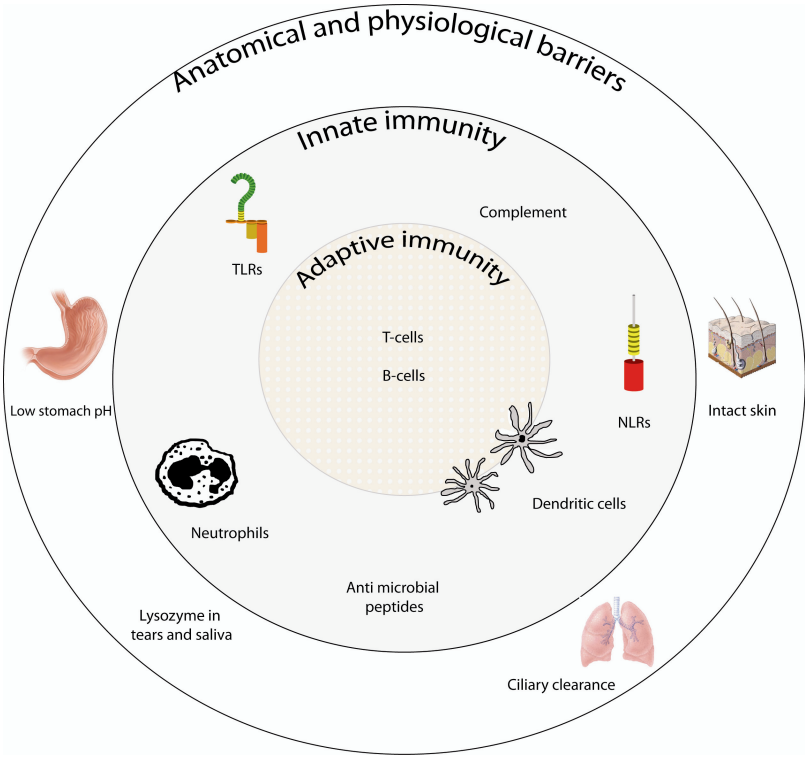

Figure 1. Three levels of human defence against infection.
The human microbial defence system can be viewed as consisting of three levels: (1) anatomical and physiological barriers; (2) innate immunity; and (3) adaptive immunity. Failure in any of these systems will greatly increase susceptibility to infection. NLRs, nucleotide oligomerisation domain (NOD)-like receptors; TLRs, toll-like receptors.

1.2 Pattern recognition receptors

Despite being referred to as non-specific, the innate immune system holds substantial specificity to conserved molecular patterns in various microorganisms, known as pathogen-associated molecular patterns (PAMPs). Receptors to these patterns are called pattern recognition receptors (PRRs) (1). Upon PAMP recognition, PRRs initiate series of signalling programs that execute the first line of host defensive responses necessary for killing infectious microbes. In addition,

PRR signalling simultaneously induces maturation of dendritic cells (DCs), which is responsible for alerting induction of the second line of host defence, so-called adaptive immunity (2). The PRRs are also activated by damaged endogenous components from damaged or dying cells, recognizing damage-associated molecular patterns (DAMPs). As the inflammatory response induced in response to DAMPs is similar to that observed during microbial infection, certain PRRs are also involved in the induction of sterile inflammation. DAMPs and PAMPs may occupy the same or neighbouring binding sites on TLRs. There is also evidence that DAMPs require different co-receptors and accessory molecules to PAMPs (3). It has been postulated that feedback between PAMPs and DAMPs via overlapping receptors may form an important connection between infection and inflammatory disease reactivation or intensification (4).

Intact microbial pathogens are usually composed of a number of PAMPs, which activate multiple PRRs. Moreover, different PRRs may recognize the same PAMP. At least five major classes of cell associated PRRs have been identified to date. They include transmembrane Toll-like receptors (TLRs), which are located at the extracellular surface or within endosomes. C-type lectin receptors are also membrane bound and characterized by the presence of a carbohydrate-binding domain. Of the cytoplasmic PRRs, there are three families: Nod-like-receptors (NLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), and DNA-sensors (5). In addition, numerous secreted PRRs exist; hereunder complement factors, ficolins, pentraxins and C-reactive protein. Activation of these PRRs can trigger the complement cascade, leading to opsonisation and phagocytosis. The secreted PRRs will not be discussed further in this thesis.

1.2.1 Toll-like receptors

Toll-like receptors (TLRs) were the first PRRs to be identified, and are also the most studied sub-group of PRRs. They receive their name from their similarity to the protein coded by the Toll gene identified in Drosophila in 1985 by Christiane

Nüsslein-Volhard. The gene in question, when mutated, makes the Drosophila flies look unusual, or “weird”. The researchers were so surprised that they spontaneously shouted out in German "Das ist ja toll!" which translates as "That's great!" (6). Subsequently, the same receptor was described as important in resistance to fungal infections in Drosophila (7). The first reported human Toll-like receptor was described by Nomura and colleagues in 1994 (8). A human homologue (hToll) was suggested to be involved in activation of NF-κB and induction of proinflammatory cytokines (7), later to be recognized as a receptor critical for cellular activation induced by the gram-negative cell wall component lipopolysaccharide (LPS) (9).

The TLRs are the best characterized and recognize a wide range of PAMPs (10-12). TLRs are transmembrane proteins and comprise an ectodomain, which contains leucine-rich repeats that mediate the recognition of ligands, a transmembrane region, and cytosolic Toll-IL-1 receptor (TIR) domains that activate downstream signalling pathways. They are expressed either on the cell surface or associated with intracellular vesicles. To date, thirteen mammalian TLRs have been identified; in human ten functional TLRs are found. Each TLR detects distinct PAMPs derived from viruses, bacteria, mycobacteria, fungi, and parasites. These include lipoproteins (recognized by TLR1, TLR2, and TLR6), double-stranded (ds) RNA (TLR3), lipopolysaccharide (LPS) (TLR4), flagellin (TLR5), single-stranded (ss) RNA (TLR7 and TLR8), and DNA (TLR9) (2). The ligand for TLR10 is not known, but is believed to cooperate with TLR2 in the sensing of microbes and fungi through a different signalling function from TLR2 subfamily members (13).

TLR1, TLR2, TLR4, TLR5, and TLR6 are localized on the cell surface and largely recognize microbial membrane components. TLR3, TLR7, TLR8, and TLR9 are expressed within intracellular vesicles such as the endoplasmic reticulum, endosomes, lysosomes, and endolysosomes (14). The proper cellular localization of TLRs is thought to be important for ligand accessibility, the maintenance of tolerance to self molecules such as nucleic acids and downstream signal

transduction (15). For instance, TLR3 and TLR7 localise in the same intracellular compartments often found adjacent to phagosomes containing apoptotic bodies, suggesting that TLR3 and 7 can be triggered by nucleic acids from apoptotic cells (16).

Upon recognition, either as homodimers or heterodimers, with their respective ligands, TLRs recruit a specific set of adaptor molecules that harbours TIR domains, such as MyD88 and TRIF, and initiate downstream signalling events that lead to the secretion of inflammatory cytokines, type I IFN, chemokines, and antimicrobial peptides (15, 17). These responses cause recruitment of neutrophils, activation of macrophages, and induction of IFN-stimulated genes, resulting in direct killing of the infected pathogens. Moreover, activation of TLR signalling leads to maturation of DCs, contributing to the induction of adaptive immunity.

Individual TLRs selectively recruit distinct adaptor molecules, providing specific immunological responses tailored to the infecting microbes (11). TLR3 and TLR4 generate both type I interferon and inflammatory cytokine responses, while cell surface TLR1-TLR2, TLR2-TLR6 and TLR5 induce mainly inflammatory cytokines. These differences are explained by the signalling through different signalling pathways of the TIR domain–containing adaptor molecules, including MyD88, MAL (TIRAP), TRIF and TRAM.

TLR signalling pathways can be largely classified as either MyD88-dependent pathways, which drive the induction of inflammatory cytokines, or TRIF-dependent pathways, which are responsible for the induction of type I interferon as well as inflammatory cytokines (11, 17). The MyD88-dependent pathway is universally used by all TLRs except TLR3. Through this, transcription factor NF-κB and mitogen-activated protein kinases (MAPKs) induce inflammatory cytokines. In contrast, TRIF is used by TLR3 and TLR4 and induces alternative pathways that lead to activation of the transcription factors IRF3 and NF-κB and the consequent induction of type I interferon and inflammatory cytokines. TLR7 and TLR9 recruit MyD88 along with IRAK4 and TRAF6, which activate IRF5 and

NF-κB for inflammatory cytokine induction and IRF7 for type I interferon induction. TRAM and MAL function as sorting adaptors that recruit TRIF to TLR4 and MyD88 to TLR2 and TLR4, respectively (2, 18).

An overview of TLR-signalling is given in figure 2.

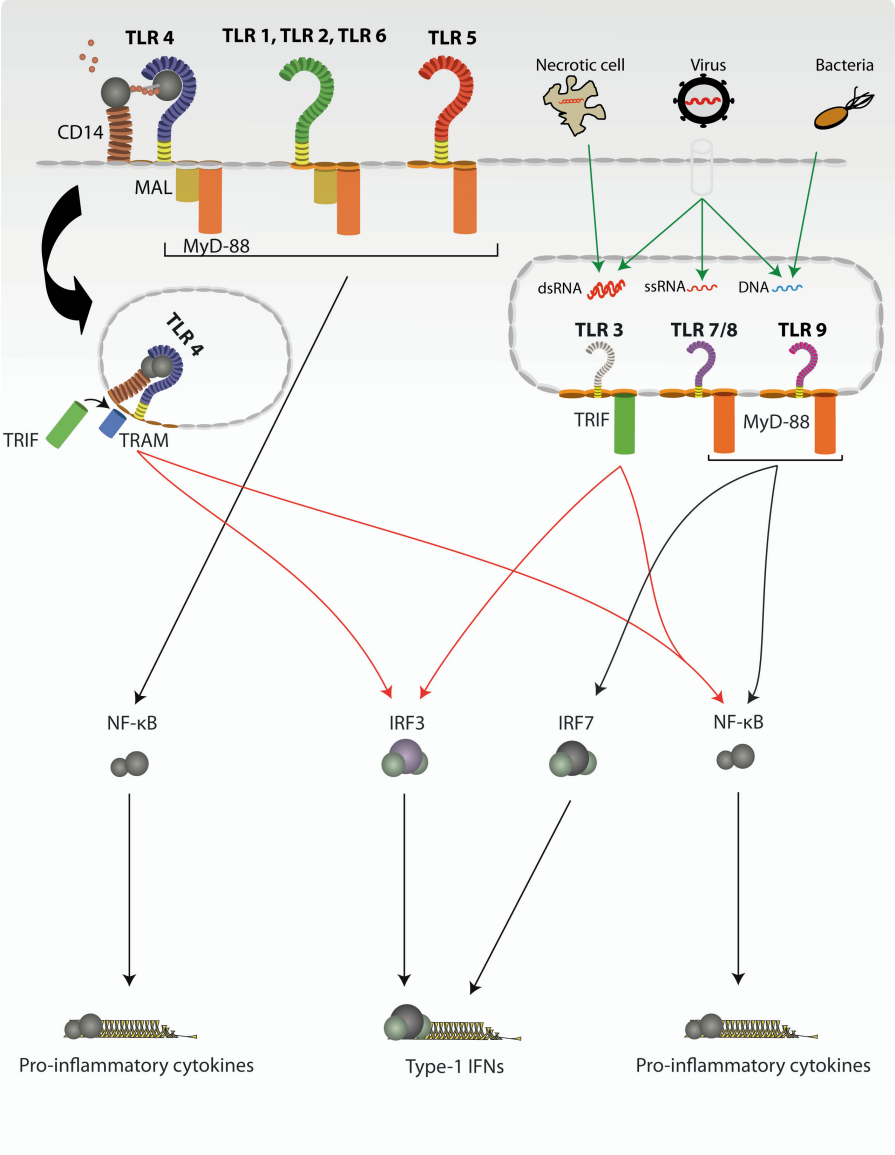

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Figure 2. Toll-like-receptor signalling.
Toll-like receptor signalling pathways result in activation of transcription of pro-inflammatory cytokines. TLRs signal through two different pathways: the MyD88-dependent pathway and the MyD88-independent/TRIF-dependent pathway. TLR1, 2, 5, 6, 7, 8 and 9 signal through the MyD88-dependent pathway (→). TLR3 signals through the TRIF-dependent pathway (→). TLR4 is special as it signals through both pathways. Activation of NFκB leads to transcription of pro-inflammatory cytokines and chemokines, while activation of IRF3 and IRF7 induce transcription of type-I interferons. This schematic overview shows simplified sequential activation of proteins.

1.2.2 C-type lectins

The CLRs encompass a diverse family of proteins unified by the possession of at least one C-type lectin domain (CTLD), a structurally conserved motif that recognises an array of both endogenous and exogenous ligands. Similar to other PRRs, such as the Toll-like receptors (TLRs), CLRs are involved in host defence against pathogenic infection. In contrast to TLRs, which recognize various PAMPs such as lipopolysaccharides, proteoglycans and nucleic acids, CLRs mostly recognise carbohydrates on pathogens (19). Fungal cell walls contain multiple types of carbohydrates, such as mannans, β-glucans and chitin. Therefore, CLRs play a central role in the recognition and shaping of immune responses to fungal pathogens. The collaboration of TLRs and CLRs together tailors the host immune responses in fungal infections (19). CLRs are commonly expressed on myeloid cells of the immune system, but are also expressed on mucosal epithelial cells where the host is in contact with the microbial flora and potential pathogens, e.g. the gut and respiratory tract. Some CLRs directly activate intracellular signalling cascades via intrinsic signalling motifs, such as Syk/CARD-pathways, while others make use of adaptor molecules to initiate signal transduction (20). CLR signalling cascades can act to promote, modulate or repress cytokine production in host cells, helping to determine the host immune response and outcome of infection (21). Examples of central CLRs are Dectin-1, Dectin-2, DC-SIGN, Mincle (macrophage inducible C-type lectin) and the mannose receptor. In addition, the collectins

comprise a group of soluble CLRs, all of which have been implicated in inducing or modulating cytokines in response to fungi.

1.2.3 NOD-like receptors and inflammasomes

NOD-like receptors (NLRs) is short for Nucleotide Oligomerization Domain receptors.
This is a large family of PRRs that respond to various stimuli, including PAMPs, non-PAMP particles and cellular stresses (22, 23). Divergence in the mechanism of NLRs is also reflected by functions beyond pathogen recognition, as NLRs are involved in many different cellular processes (24). NLRs are found to play roles in signal transduction, cell death, development and reproduction, autophagy, autoimmune and inflammatory diseases (24). Still, the functions and signalling pathways of a large subset of NLRs remains obscure (25).

NLRs belong to the signal transduction ATPases with numerous domains (STAND) subclade of the AAA-ATPase superfamily. They are characterized by a centrally located nucleotide-binding domain, a variable number of highly polymorphic C-terminal leucine-rich repeats (LRRs), and diverse N-termini (Figure 3). STAND proteins are molecular switches regulated via nucleotide binding. The ADP-bound form represents the resting "off" state. Upon recognition of endogenous or exogenous ligands, a conformational change allows ADP to be exchanged for ATP. This initiates either activation of NF-κB or MAP kinases to induce the production of inflammatory cytokines, or activate a multiprotein-complex; the inflammasome (26). Inflammasomes can be reckoned as a subgroup of NLRs, although a member in the HIN200 family (AIM2) is also an inflammasome. Most of the inflammasomes contain a PYD-domain, in contrast to the NODs that contain a CARD-domain. The exception is NLRP1 that possesses both PYD- and CARD domains. The inflammasome initiates the proteolytic cleavage of various caspases resulting in the maturation and production of

inflammatory cytokines, such as IL-1β and IL-18, in addition to initiation of pyroptosis in macrophages (27).

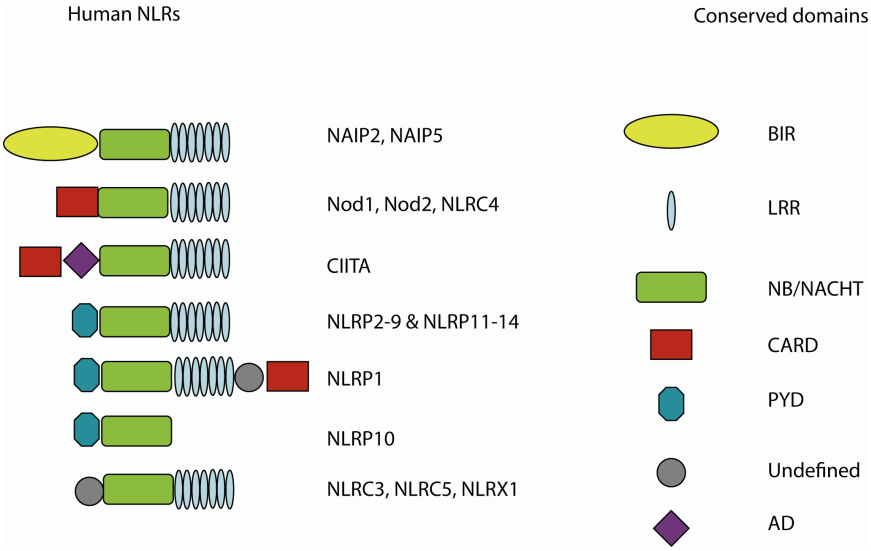

Fig 3. Structure of different Nod-like receptors.
The conserved domains of NLR proteins are represented. N-terminal baculoviral inhibitory repeat (BIR) domain, caspase recruitment domain (CARD), pyrin domain (PYD), activation domain (AD), and undefined domains are specific to animals.

The term inflammasome was also chosen to highlight structural and functional similarities with APAF1, a component in another well-known caspase-activating complex, the apoptosome, a molecular platform that triggers apoptosis.
Inflammasomes are assembled after sensing a structurally diverse repertoire of PAMPs and DAMPs. The range of activation signals sensed by each protein is distinct, but may include overlapping signals (28).
NLRP3, the best characterized inflammasome, is activated by a large variety of signals with strikingly structural diversity, including PAMPs, DAMPs and bacterial toxins (29-32), whereas the AIM2 (not belonging to NLRs, see DNA-sensors below) and NLRC4 inflammasomes are activated only by specific PAMPs, double-stranded DNA (dsDNA) and specific bacterial proteins, respectively (33, 34).
Several models have been proposed to explain how these signals are sensed. Mounting evidence now indicates a primordial role of the mitochondria in NLR

activation (35, 36). Two recent studies suggest that the NLRP3 inflammasome ultimately senses mitochondrial dysfunction and initiates inflammatory responses following specific forms of cellular stress through sensing of reactive oxygen species (ROS) (35, 37). It remains unclear what the ligand for NLRP3 is, but one possibility is this ligand is released from the ROS-generating damaged mitochondria. Still, there are also other theories on direct and indirect recognition of activation signals of the inflammasome (28). Figur 4 illustrates the current view on NLRP3 inflammasome activation (38).

Inflammasome activity needs to be tightly regulated by the host to avoid the excess production of cytokines or overt cell death. Regulation occurs at transcriptional and post-transcriptional levels. the expression of inflammasome sensors, in particular NLRP3, is relatively low in many cell types and requires a priming signal to be induced (39), alternative splicing of inflammasome components (40), subcellular location and trafficking of inflammasome components (41), and downregulation either through secreted factors or cell–cell interactions leading to transcriptional and post-transcriptional downregulation of inflammasome activity (42, 43).

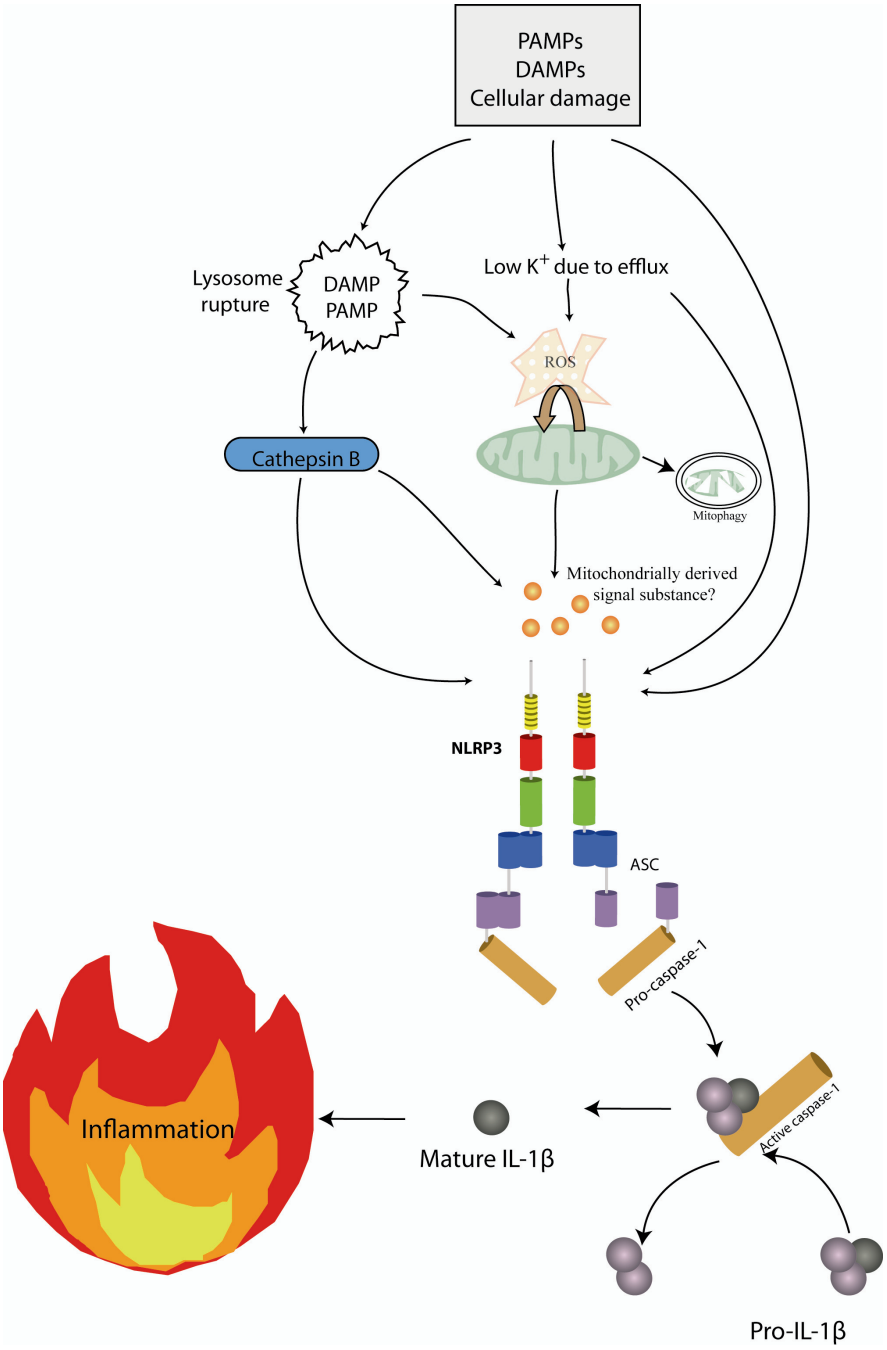

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Figure 4. Supposed mechanisms for NLRP3 activation.
Three different models for activation of the NLRP3 inflammasome are prevailing (38):
The channel model - Cellular stress or damage induced by DAMPs and PAMPs results in potassium efflux through pore formation. This potassium disturbance may activate the NLRP3 inflammasome directly or through allowing cytoplasmic entry of extracellular factors that are direct NLRP3 ligands.
The lysosome rupture model - Lysosomal rupture due to organelle damage leads to cytoplasmic release of cathepsin B, which either directly or through cleaving an unidentified substrate induces activation of NLRP3.
The ROS model - Both lysosomal damage and potassium efflux leads to mitochondrial dysfunction and the generation of ROS. The NLRP3 inflammasome is then triggered by one or several unknown intermediates, possibly originating from the mitochondrium. Mitophagy prevents further NLRP3 inflammasome activation by clearance of ROS-producing mitochondria.

1.2.4 RIG-I-like receptors

The RIG-I-like receptors (RLRs) family has three known members: retinoic acid-inducible gene (RIG-I), melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology-2 (LGP2) (44). The RLRs recognize viral RNAs in the cytoplasm. RNA virus infection leads to the generation of dsRNA and RNAs with 5'-triphosphate ends in infected cells. Long dsRNA is not normally present in cells, and the 5'- ends of host RNAs are typically capped and sensed by RIG-I and MDA5. The role of LGP2 is still unclear, but it is suggested to play a regulatory role in RIG-I/MDA5 signalling (45, 46). In response to detection of viral RNAs, RIG-I and MDA5 associate with an adapter protein designated virus-induced signalling adapter (VISA) (47, 48). RLRs induce inflammatory cytokines and type I interferons, through NF-κB- and IRF3/7-pathways, respectively (49, 50). The inflammatory cytokines initiate and co-ordinate various innate immune responses through recruitment of professional immune cells (51, 52). The production of type I interferons induces an antiviral state by altering various cellular processes. This inhibits viral replication, induces apoptosis in infected cells, increases the lytic capacity of natural killer cells, up-regulates the expression of MHC class I molecules and activates various components of the adaptive immune response.

1.2.5 DNA-sensors

Just over the last few years, this class of PRRs has gained a growing number of members. Like the cytosolic RNA recognition pathways, cytosolic DNA recognition also leads ultimately to production of type I IFNs. What is clear is the essential role of the recently new player in the pathways, stimulator of IFN genes (STING) in cytosolic DNA sensing pathways. STING is detected in the endoplasmic reticulum (ER) and upon activation complexes with signalling components including TBK1, leading to phosphorylation of IRF-3 (53, 54) Much less clear is the mechanisms or receptors which act upstream of STING. However, the signalling pathways downstream of DNA sensors are poorly characterized (55). Apart from the transcription factors nuclear factor (NF)-κB and IFN regulatory factor 3 (IRF3), strong evidence exists for a central role for TANK-binding kinase-1 (TBK1) in addition to STING (56).

The sensors display some selectivity in regards of cell type, the pathogens sensed, and the exact nature of the DNA ligand tested. However, current evidence renders it unlikely that these diverse sensors display differential selectivity for different types of DNA. Rather they may all simply sense cytosolic dsDNA in different cell types (56). Among the characterized DNA-sensors, we find DNA-dependent activator of IFN-regulatory factors (DAI), RNA polymerase III, leucine-rich repeat (LRR)-containing protein (LRRFIP1), DHX9 and DHX36 (55, 57).

Another cytosolic DNA receptor, AIM2, forms an inflammasome with ASC to trigger caspase-1 activation (33, 58). Very recently, IFI16 has also been proposed to mediate inflammasome activation, in response to Kaposi's sarcoma-associated virus infection of endothelial cells (59). Interestingly, IFI16 is proposed to sense viral DNA in the nucleus, indicating that IFI16 may have alternative DNA sensing functions in the nucleus and the cytosol. Both AIM2 and IFI16 belong to a protein family termed the pyrin and HIN domain (PYHIN) family, of which there are four known human members. It is recently suggested the existence of a brand new

family of PRRs termed Aim2-like Receptors (ALRs), consisting of AIM2 and IFI16, and possibly other members of the PYHIN-family (60).

A complete overview of PRR-signalling is shown in Figure 5.

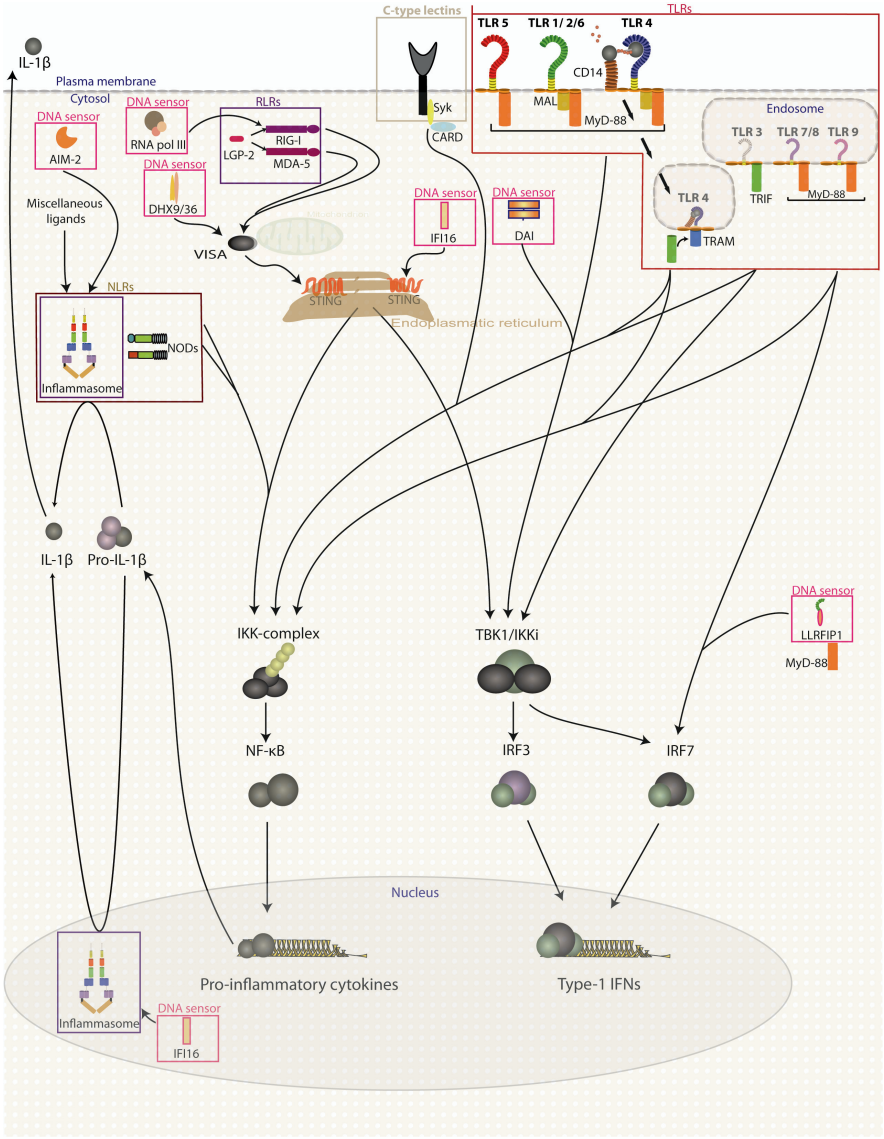

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Fig 5 Overview of PRR mediated signalling.
Toll-like receptor (TLR) signalling. Plasma membrane-localized TLRs, such as TLR4, TLR5, TLR11, and TLR2 (TLR2 forms a heterodimer with TLR1 or TLR6 to form a functional receptor complex) and endosomal-localized TLRs, such as TLR3, TLR7, and TLR9, activate TLR signalling pathways. All TLRs, except TLR3, recruit MyD88 and activate MyD88- dependent signalling. TLR1, 2, 4, and 6 all recruit the additional adaptor molecule MAL for activation of MyD88. TLR3 recruits TRIF and activates TRIF-dependent signalling. TLR4 relocates to endosomes after ligand binding, where it also activates TRIF-dependent signalling through an additional adaptor molecule, TRAM. MyD88-dependent signalling is initiated through the recruitment and activation of various signalling molecules, which in turn activate the IKK complex. The active IKK complex activates NF-κB subunits to initiate the transcription of inflammatory cytokine genes. TLR7 and TLR9 ligands induces MyD88-dependent type I interferon production through a direct interaction between MyD88 and IRF7 via IRAK family proteins and phosphorylated IRF7. Phosphorylated IRF7 translocates to the nucleus and initiates the transcription of type I interferons. In addition the TLR7 and TLR9-mediated signalling pathways activate NF-κB via an MyD88-dependent signalling pathway. TLR3 activate the TRIF-dependent signalling pathway through recruitment of TRIF to induce transcription of inflammatory cytokines and type I interferons through the IKK- complex and TBK1/IKKi, respectively, via the activation of NF-κB and IRF3/IRF7.
C-type lectins signalling. Recognition of carbohydrate ligands by C-type lectins activate intracellular signalling cascades such as Syk or Src-kinases, which in turn activates CARD-complexes, eventually leading to activation of NF-κB and subsequent secretion of proinflammatory cytokines.
RIG-I-like receptor (RLR) signalling. Recognition of ligands by cytosolic sensors, such as RIG-I and MDA5, activates signalling through the mitochondria-localized adaptor protein VISA leading to the activation of NF-κB and IRF3/IRF7 through the IKK complex and TBK1/IKKi, respectively, which results in the production of inflammatory cytokines and type I interferons. LGP2, another member of the RLR family, regulates the RIG-I- and MDA5-mediated signalling pathways.
*Nod-like receptor (NLR) signalling***.** Recognition of ligands by NOD1 and NOD2 initiates activation of NF-κB via the IKK complex. Another member of the NLR family constitutes the multi-protein complex termed the inflammasome. This is required for the maturation or activation of pro-IL-1 family cytokines to its bioactive IL-1 family cytokines. Activation of the inflammasome requires two steps: 1- NF-κB-dependent up-regulation of the pro-forms of the cytokine. 2- Conversion of the inactive form of the cytokine to a bioactive form by the inflammasome.
*Cytosolic DNA sensor-dependent signalling***.** DNA in the cytoplasm of cells are sensed by various cytosolic DNA sensors which activate NF-κB and IRF3/IRF7 via the IKK complex and TBK1/IKKi. Upon activation, the ER-localized protein STING complexes with TBK1 and IKK-complex. Recognition of DNA by AIM2 and IFI16 also induces the maturation of proIL-1β to IL-1β through an inflammasome complex consisting of ASC and caspase-1.

1.3 The skin as an immune organ

The skin is more than an immunologically inert anatomical barrier to the hostile exterior. An expedient architectural structure and cellular composition the skin provides protection from injury and infection.

The skin consists of two layers, the epidermis and dermis. The epidermis is the surface layer, consisting of a keratinized, stratified and squamous epithelium that is under constant exposure to the outside. The epidermis consists mainly of keratinocytes in various stages of differentiation, in addition to a few skin antigen-presenting cells, dendritic epidermal T-cells and pigment-producing melanocytes. Under the epidermis, the dermis is a connective tissue composed of structural collagen and elastic fibres, in addition to a mixture of other extracellular matrix protein. In contrast to the epidermis, the dermis consists of a large variety of cell types, including fibroblasts, macrophages, mast cells, T cells, and dendritic cells (DCs). The fibroblast is the main stromal cell in the dermis. Fibroblasts have highly specialized roles in conditioning the cellular and cytokine environment in areas of inflammation by virtue of the complex array of factors they express (61). If the epidermal barrier is disrupted, pathogens as well as allergens make contact with resident innate immune cells in the skin. DCs are professional antigen-presenting cells, which are ideally located to detect any skin invading pathogen and allergen. DCs are a heterogeneous population of immune cells, which are thought to exert different functions depending on their origin, their state of activation and their location. In the skin, DC subsets are classified as Langerhans cells (epidermal DCs), resident dermal myeloid DCs, plasmacytoid DCs, and myeloid dermal inflammatory DCs (62). A major function of DCs is the initiation of adaptive immune responses, but the skin DCs are also involved in innate immune responses. Of particular interest is how TLR activation can instruct adaptive immune responses by inducing a Th-1 type immune response. Activation of TLRs on DCs can promote upregulation of co-stimulatory molecules that help promote interaction and stimulation of antigen specific T cells of the adaptive immune

response and induction of T helper 1 (Th-1) cell-mediated immune responses (63). Langerhans cells participate in mediating TLR responses, and seem particularly responsive to TLR2 and TLR 7/8 ligands. DCs contribute to host defence against bacterial infection via IL-1R/MyD88 signalling in resident skin by neutrophil recruitment to localized Staphylococcus aureus infection in the skin. Also autocrine or paracrine activation of DCs or Langerhans cells by IL-1β is one of the suggested mechanisms leading to the control of bacterial skin infection (64). DC-derived IL-1 and IL-23 are also involved in the promotion of IL-17 production in memory T-cells, which can contribute to the protection against certain bacteria (65). Mast cells (MC) are for many regarded as the "allergy cell". Still, a crucial role of MCs in innate host defence is today well established (66). For instance, activation of skin MCs is crucial for the induction of protective innate immune responses to skin infection with Pseudomonas aeruginosa (67). MCs also protects against infection with invasive group A Streptococcus, where skin MC-derived production of the anti-microbial peptide (AMP) cathelicidin is an essential mediator leading to bacterial killing and possibly also to enhanced recruitment of neutrophils to the site of infection (68). MCs are also capable of modulating long term inflammatory skin reactions to environmental danger signals such as UV-irradiation (69, 70). The epidermal melanocyte protects human skin against carcinogenic UV irradiation by providing melanin. Melanocytes also exhibit a variety of functions. For example, human melanocytes have the capacity to express HLA-DR, CD40 and adhesion molecules, such as ICAM-1 and VCAM-1(71) and various soluble mediators of inflammation such as IL-1β, IL-6 and CXCL-8 (72).

1.4 Keratinocytes as immune cells

Immunologists in general have tended to focus on leukocytes as the central cell of the immune response, but in skin the keratinocyte is an essential and underappreciated part of immunological function (73).

The epidermis is in constant contact with multiple microbes (1 million/cm^2). Therefore, an important and difficult task is to ensure reliable immunosurveillance and efficient defence against pathogens, and also avoid excessive immune responses, which might result in auto-immunity and chronic inflammation (74). At this interface between self and non-self, microorganisms compete for the colonization of the surface. Keratinocytes are specialized in many ways to exert their crucial role as outpost of the innate defence system. Only the innermost, basal layer of epidermal cells has the capacity for DNA synthesis and mitosis. Triggered by still an unidentified signal, the process of terminal differentiation is initiated. After approximately six weeks, the now dead, flat, enucleated and keratin-filled corneocytes in the stratum corneum is shed from the surface of the epidermis. The entire epidermis and in particular the top layer of dead cells plays a role as the first barrier against the environment. In the upper layer of the epidermis the cells build a physical barrier, the stratum corneum, against penetration of microbes and allergens. The nucleated epidermis is tightly locked together by desmosomes and is embedded in a hydrophobic intercellular matrix (62). Damage signals mediated through PRRs activate keratinocytes to enhance the production of constitutively expressed AMPs and can additionally induce the production and secretion of other mediators. This enables optimal innate immune responses either directly or through interaction with other cells.

Keratinocytes have been shown to express TLRs 1, 2, 3, 5, 6 and 9 (75-78), whereas there is more controversy about expression of TLR4 in cultured primary keratinocytes (77, 79). There is no constitutive expression of TLR7 or TLR8 in keratinocytes (75, 79). TLR2 activation (in concert with TLR1 or TLR6) in keratinocytes results in activation of NF-κB and subsequent production of chemokines, iNOS and matrix metalloproteinase-9 (76). Mimicking viral infection, activation of TLR3 by its ligand, dsRNA (poly I:C), on human keratinocytes induces production of CXCL-8, TNF, IL-18, and type I interferon, and the chemokines -9 and IP-10 (75, 79, 80). TLR5 activation in human keratinocytes by its ligand flagellin, results in production of TNF, CXCL-8, and the antimicrobial peptides human β-defensins 2 and 3 (hBD2 and hBD3) (75, 79, 81). TLR9

activation with oligodeoxynucleotides also induces several chemokines, promoting memory T-cell responses and production of type I interferon (79). AMPs are vital elements in skin defence, as they possess a broad spectrum of antimicrobial activity as evidenced by their ability to exhibit multifunctional roles in defending against pathogenic insult (73). They do not only directly interact with pathogens but also modulate host immune responses. Keratinocytes are the most important producers of AMPs in the skin, the synthesis mainly taking place in the stratum granulosum, packaged into lamellar bodies, and then transported to the stratum corneum (82). There are described more than ten different classes of AMPs originating from keratinocytes, among them different subsets of the two most important families defensins and cathelicidins (73).

The physical barrier in the skin is mainly comprised by the stratum corneum and consists of protein-enriched cells and lipid-enriched intercellular domains. The nucleated epidermis also contributes to the barrier through tight, gap and adherens junctions, as well as through desmosomes and cytoskeletal elements.
The chemical barrier exists through the presence of highly organized lipids, acids, hydrolytic enzymes in particular in the upper layers of the epidermis. Also, on the surface, the dry skin surface with low pH (around 5.0) is hostile to many microorganisms. In addition, the presence of non-pathogenic microorganisms on the epidermis surface also defends against pathogens by limiting nutritional availability and through chemical secretions (83).

1.5 Programmed cell death in relation to inflammatory processes

Timely cell death is essential in normal growth and development, but also important in host defence. Through activation of different PRRs, cell death can arise from within the cell itself, or from a variety of extracellular sources (84). When these receptors are triggered, cells can die in an immunogenic or non-

physiological way and rapidly initiate host defence responses. Different types of programmed cell death can therefore lead to the extracellular release of molecules and structures that can potently induce the innate immune system (85).

In a review from 1994, Emmanuel Farber concluded in a review paper "that there is no field of basic cell biology and cell pathology that is more confusing and more unintelligible than the area of apoptosis versus necrosis" (86), and this opinion still holds considerable support 18 years later (87). From previously being viewed as either apoptosis or necrosis, several other forms of programmed cell death are now described. Pyroptosis (88) and autophagic cell death (89) are considered to be the two other major forms of programmed cell death. In addition, NETosis (90), necroptosis (91), mitotic catastrophe (92), and lysosomal membrane permeabilization (93) are described as other forms of cell death. These latter forms of cell death will not be discussed here.
Morphologically, apoptosis is associated with cell shrinkage, membrane blebbing, and chromatin condensation. It is a cell-intrinsic programmed suicide mechanism that results in the controlled breakdown of the cell into apoptotic bodies(89).
Two main evolutionarily conserved protein families are involved in apoptosis, namely the Bcl-2 family of proteins, which control mitochondrial integrity (94) and the cysteinyl aspartate-specific proteases or caspases, which mediate the execution phase of apoptosis (95).

Necrotic cell death is characterized by DNA and nuclear fragmentation, loss of cell volume, formation of cytoplasmic and membrane blebs, packaging of cellular contents and phosphatidylserine externalization. Apoptotic cells are rapidly removed by neighbouring phagocytes without causing inflammatory response (96). Necrosis has been considered an accidental and uncontrolled form of cell death lacking underlying signalling events, but it has become evident that in certain conditions, necrosis is the result of a strictly regulated interplay of signalling events, which are initiated by a diverse range of stimuli, including PRRs (97). Necrotic cells increase their volume and permeability, maintain the uncondensed DNA content, and lose their cellular contents including uric acid, adenine

triphosphate, purine metabolites, high-mobility group box 1 protein (HMGB-1), heat shock proteins among others, which activate immune cells (96).

Autophagy is another programmed process that might culminate in cell death. It is considered a protective process induced under stress conditions by which cells engulf large portions of their own cytoplasm or damaged organelles. This pathway is essential for maintaining cell viability under starvation and stress conditions, through nutrient recycling and toxic metabolite degradation. However, too excessive autophagy culminates in a silent cell death (98).

Pyroptosis is a programmed cell death that uniquely depends on the inflammatory caspase-1 activity. As a member of the inflammatory caspases, it is not involved in apoptotic cell death (88), and the apoptotic caspases usually do not contribute to pyroptosis (99). Active caspase-1 is believed to be a central executor of pyroptotic cell death and acts mainly by inducing the formation of discretely sized ion-permeable pores in the plasma membrane (100). The resulting osmotic pressure leads to water influx, cell swelling and ultimately cell lysis. The inflammatory response following cleavage of the proinflammatory cytokines pro-IL-1β and pro-IL-18 into their active forms is not required for the execution of cell death (101). Although caspase-1 activation is associated with an inflammatory response, it is still unclear whether it is directly linked to pyroptotic cell death (89). Cells dying by pyroptosis have biochemical and morphological features of both apoptotic and necrotic cells (88), with loss of mitochondrial membrane potential and plasma membrane integrity, release of cytoplasmic contents into the extracellular milieu as observed in necrosis. On the other hand, pyroptotic cells undergo DNA fragmentation and nuclear condensation, however without the oligonucleosomal fragmentation pattern characteristic of apoptosis (102).

1.6 Caspases in inflammation and cell death

Caspases are proteases produced in cells as catalytically inactive zymogens and usually undergo proteolytic processing during activation (103). In addition to their central role in programmed cell death, caspases are involved in many other vital process, including differentiation, enucleation, pruning of axons and dendrites, sperm differentiation, immunity, compensatory proliferation, and even learning and memory (104).
Caspases play central roles in initiating apoptosis and pyroptosis but are not involved in other programmed cell death pathways (87).

Caspases are traditionally classified as “apoptotic” and “pro-inflammatory” (Figure 6).
The subsets of caspases that cleave substrates during apoptosis are known as effector caspases (caspase-3, -6, and -7). These are activated by the initiator caspases such as caspase-2, -8, -9 and -10 Initiators are further divided into caspases participating in the extrinsic (caspase-8 and -10) or intrinsic (caspase-9) apoptotic pathway (105).

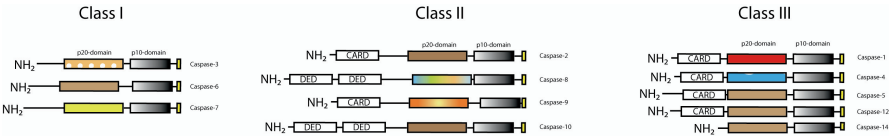

Figure 6. Caspase structure.
Three major classes of caspases are presented. Class I: apoptosis effector caspases, class II: apoptosis initiator caspases, class III: inflammatory caspases: The CARD, the DED, and the large (p20) and small (p10) catalytic subunits are indicated. The p20 subunits of the caspases discussed in this thesis are coloured

.

Activation of the different initiator caspases depends on the engagement and activation of platforms that integrate cellular signals, recruit initiator caspases via their death-fold domain, and promote dimerization of the caspases. These events

together lead to the formation of an active enzyme proficient enough to initiate specific signalling cascades (105). Examples of these platforms are death-inducing signalling complex (DISC) for caspase-8 and -10, the PIDDosome for caspase-2, and the apoptosome for caspase-9 (95).

Executioner caspases are activated by cleavage of the catalytic domain. In contrast to the apoptotic caspases, initiator and effector functions have not been defined for the inflammatory caspases. This understanding is now challenged by new discoveries in keratinocytes (106). In addition to the already mentioned caspase-1, caspase-4 and caspase-5 are also reckoned as inflammatory caspases, though their functions are less well defined (87). Studies on the mouse caspase-11, the orthologue to human caspase-4 suggests that caspase-11 rather than caspase-1 may be the critical effector of deleterious inflammatory responses (107). In a recent publication on keratinocytes, it is shown that caspase-4 is required for activation of inflammasomes, and that the active site of caspase-4 is required for activation of caspase-1, the latter most likely represents a substrate of caspase-4 (106).

A large number of proteins have been reported to be in vivo caspase substrates (108, 109), and the list of annotated caspase substrates continues to increase. Still, most candidates lack functional evidence linking cleavage to a role in apoptosis. Only by removing irrelevant “bystander” substrates from the list of caspase substrates, it will be possible to gain a more realistic understanding of how caspases drive apoptotic cell death.

Another factor is that caspase substrate specificity overlaps. Commonly used caspase substrates and inhibitors lack the specificity required to monitor individual caspase activity (110). For instance, fluoromethylketone inhibitors exhibit no specificity towards different caspases even at low concentrations (111). In contrast, aldehyde inhibitor caspases shows a considerably higher specificity (110).

2. Aim of the study

Innate immunity in keratinocytes is not only involved in the direct fight against pathogens but turns out to be crucial for many inflammatory processes centrally involved in dermatological diseases. We wanted to achieve a better understanding of how the keratinocyte functions as an important initiator of skin inflammation as a non-professional cell.

Specifically, we sought to:

- Determine the repertoire and sensitivity to Toll-like receptors in keratinocytes
- Investigate how Toll-like receptor signalling in keratinocytes contributes to inflammation through characterization of inflammatory responses
- Investigate toxic and inflammatory responses of Toll-like receptor ligands on keratinocytes, and to see if these responses can be limited by intervention
- Describe new mechanisms of TLR mediated inflammation and cell death in keratinocytes

3. Summary of papers

Paper I

"Cellular sources and inducers of cytokines present in acute wound fluid"

In this paper we quantified the levels of cytokines and growth factors in acute wound fluid, using a BioPlex cytokine 27-plex panel for: TNF-α, IFN-γ, IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p70, IL-13, IL-15, IL-17, MCP-1, IP-10, RANTES, MIP-1α, MIP-1β, G-CSF, GM-CSF, Eotaxin, FGF, VEGF and PDGF.

To obtain an overview of the initial inflammatory response in the acute wound healing process, we collected wound fluid from surgical drains the first postoperative day after reduction mammoplasty. As little is published about the cellular sources of different cytokines and growth factors in acute wounds and the stimuli inducing them, we stimulated different cell types present in the acute wound bed to gather more information about this. The cell types we stimulated were keratinocytes, monocytes, fibroblasts, endothelial cells, granulocytes and monocytes. We stimulated the cells with the pro-inflammatory cytokines TNF, IL-1β and IL-6 in addition to the anti-inflammatory IL-10. Also, we wanted to characterize the responses induced by the TLR-ligands pam3Cys (TLR2/TLR1), polyI:C (TLR3) and LPS (TLR4). Supernatants from the stimulated cells were also subjected to 27-plex BioPlex analyses.

In wound fluid, we found highest levels of IL-6 and CXCL-8. The levels of the potent pro-inflammatory cytokine IL-1β were surprisingly low in wound fluid, while its negative regulator IL-1RA was present at much higher levels. IL-1β was the most potent inducer of signal molecule production in the cell types we stimulated. We therefore underscore the importance of strong regulation of IL-1β-signalling in our discussion.

Furthermore, we found that all cytokines detected in wound fluid could also be determined in supernatant from at least one of the cell types we stimulated.

Each cell type showed characteristic patterns for sensitivity of ligands and production of signal molecules after stimulation. Keratinocytes in particular showed surprising sensitivity to the TLR3 ligand polyI:C, eliciting production of almost all cytokines we examined for.

Paper II

"Oligodeoxynucleotides inhibit TLR3 mediated cytotoxicity and CXCL8 release in keratinocytes"

After the discovery of polyI:C as a strong inducer of cytokine production in Paper I, we wanted to investigate more closely the effects of polyI:C in keratinocytes. PolyI:C induced a TLR3-dependent release of the chemokine CXCL-8 that was preceded by secretion of cellular break-down products associated with cell necrosis. Morphological studies on the polyI:C mediated cytotoxicity showed mixed features of apoptosis and necrosis, making it difficult to classify what kind cell death polyI:C actually induces in keratinocytes. However, we speculate if IL-1β dependent pyroptosis can be the right answer. This is a matter we follow in Paper III.
Also, we show competitive uptake between oligodeoxynucleotides and polyI:C. Co-stimulation with these two nucleic acid structures inhibit both TLR3 dependent polyI:C induced cytokine production and cytotoxicity.

Paper III

"Toll-like receptor-3 stimulation induces caspase-4 dependent inflammatory cell death in keratinocytes"

The intriguing findings in Paper II of polyI:C induced inflammation and cell death, which we proposed to be a pyroptosis, called for further investigations. We addressed the involvement of inflammatory caspases in inflammation and cell death, through induction and processing of pro-IL-1β and activation of apoptotic caspases, respectively. Stimulation with the ligand polyI:C induced a TLR3 dependent transcription and of pro-IL-1β, but also a dose-dependent cytotoxicity. Further processing of IL-1β into its cleaved bioactive form dependent on NLRP3 or ASC was found to be minimal. IL-1β release could be inhibited using caspase-1- or caspase-4- inhibitors, the latter being a more potent inhibitor. Inhibiting caspase-4 also abolished polyI:C induced cell toxicity, whereas caspase-1 did not. We suggest that caspase-4 acts upstream of caspase-1 and the inflammasome for processing of IL-1β, but independently of caspase-1 in cell death induction. We also showed that polyI:C stimulation induced a TLR3 dependent activation of caspases-8, -9 and -3. All together, we demonstrated in this paper that TLR3 stimulation of keratinocytes induced an inflammatory cell death that also involves activation of both inflammatory and apoptotic caspases. This type of cell death is difficult to classify as pyroptotic, as that mode of programmed cell death is not supposed to involve apoptotic caspases.

4. Discussion

4.1 Inflammation in the skin

Inflammatory skin diseases cause considerable morbidity in patients, such as in the chronic and relapsing inflammatory skin disorders like psoriasis and atopic dermatitis. Inflammation is a protective means by the organism to restore a homeostatic state after disturbance by a harmful or unwanted stimulus. The term inflammation is consequently used for a broad range of conditions depending on the eliciting stimuli. Infections activate the innate immune system rapidly and induce an inflammatory response, initiating a defence against the invading pathogen. Tissue damage from laceration, contusion or sunburn also results in local and acute inflammation, thereby allowing an efficient tissue repair response. But as exemplified by the chronic, relapsing skin disorders, inflammation can also be undesirable. Such is the case when the immune system reacts to self, or when the inflammation enters chronic and destructive states. During the last decade, the innate immune system has been shown to play a central role in several inflammatory skin diseases and healing processes.

4.2 Keratinocytes as innate immune cells in skin inflammatory disease

Immunologists have tended to focus on leukocytes as the central cell of the immune response, but in skin the keratinocyte is an essential and underappreciated part of the immunological function (73). An important and difficult task for the epidermal cells is to ensure proper immunosurveillance and efficient defence against pathogens, and also avoid excessive immune responses, which might result in auto-immunity and chronic inflammation (74).

Keratinocytes are central skin sentinels that recognize foreign and dangerous agents, i.e. (PAMPs) of microbial origin and damage-associated molecular patterns (DAMPs), such as irritants and toxins, through Toll-like receptors (TLRs) and the inflammasome machinery. In **Paper I and Paper II** we demonstrate a particular sensitivity of keratinocytes to the viral dsRNA-mimic, polyI:C. TLR3, RIG-I, MDA5, and possibly IFN-inducible double-stranded RNA-activated protein kinase, can recognize dsRNA (112). TLR3 is located in endosomes and, in some types of cells, also on the cell surface, whereas the other three dsRNA sensors, RIG-I, MDA5 and protein kinase, are located in the cytosol (113). In **Paper II and Paper III,** we found that polyI:C induced inflammation and toxicity were TLR3-dependent, indicating that the cytosolic sensing in keratinocytes does not play a vital role when stimulating with extracellular dsRNA.

Keratinocytes produce an innate immune response to TLR-stimulation. In addition to induction of anti microbial peptide-production, keratinocytes secrete numerous cytokines, including IL-1, IL-6, IL-10, IL-18 and TNF (114). In **Paper I**, we showed that the cytokines IL-2, IL-9, IL-13 are also components in the armamentarium of the keratinocyte after TLR-stimulation. Of particular interest with regard to the skin in health and disease is the production of IL-1β by keratinocytes, as we focused on in **Paper I and III**, and this matter will be dealt with later.

Keratinocytes are also important sources of chemokines and express chemokine receptors, and can modulate an immune response by attracting different cell types into the skin. By expressing CC-chemokine ligand 20 (CCL20), CXC-chemokine ligand 9 (CXCL9), CXCL10 and CXCL11 activated keratinocytes selectively attract effector T cells to the skin during diseases that are characterized by T cell infiltration, such as psoriasis (114). In **Paper I**, we also demonstrated that TLR3 stimulation induces the CC-chemokine MIP-1β (also known as CCL4), a chemokine that in a recent paper appear to be pivotal for the skin recruitment of proinflammatory cells and clinical severity in psoriasis (115).

4.3 Receptor-mediated uptake of polyI:C and induction of TLR3-dependent responses in keratinocytes

In **Paper II**, we showed that uptake of polyI:C was inhibited by concomitant addition of oligodeoxynucleotides (ODNs) to the medium. A number of studies agree that oligonucleotides enter cells by receptor-mediated endocytosis because: uptake of oligonucleotides is a saturable process (116, 117), and oligonucleotides have been found in intracellular vesicles (117). PolyI:C has in one paper been demonstrated to enter the cell through a clathrin dependent endocytic pathway (118), whereas others suggest a noncaveolar/ clathrin-independent pathways for cellular uptake of oligonucleotides (119). However, the receptors that are responsible for cellular entry of oligonucleotides have not been identified, but many candidates exist.

In an attempt to find specific receptors responsible for uptake of polyI:C or ODNs, we interfered with several receptors through either inhibition with different scavenger receptor antibodies (blocking antibodies for Scavenger receptor class A) or silencing using small interfering RNA siRNA for different scavenger receptor sequences (Macrophage scavenger receptor 1, Scavenger receptor class A member 3, Scavenger receptor class B member 1 and 2, and Receptor for Advanced Glycation Endproducts). Unfortunately, we did not succeed in inhibiting polyI:C or ODNs in any of our experiments (data not shown). Our result thus support the current view that uptake of free nucleic acids occurs through different mechanisms. After endocytic entry, polyI:C will encounter TLR3, which is normally located in acidic endosomes. The luminal ectodomain encounters dsRNA and promote the formation of a dimer of the two lateral surfaces of the receptor. Then, the two C-termini are brought in close proximity for signal transduction. This again promotes recruitment of the adapter molecule TRIF to the cytoplasmic domain of TLR3, initiating signalling pathways that activate downstream transcription factors (120).

The length of dsRNA fragments needed to induce a TLR3 mediated immune response is debated, though. There seems to be considerable variation among different cell types, but the dsRNA length required for signal transduction is in general suggested to be at least 40 to 50 base pairs (121). However, others have shown that the dsRNA length threshold varies considerably among cell types, and that synthetic small interfering dsRNA duplexes as short as 23 base pairs can induce a potent IFN response through TLR3 (122). Off-target effects in siRNA experiments may therefore be a problem in one cell type and not in another (122).

An interesting question is why keratinocytes are so sensitive to TLR3-ligands. Infection in the skin with any of the eight members of dsRNA familiy viruses (123) is a rather infrequent problem. Other sources of viral dsRNA can be derived from the replication of other RNA and DNA viruses which produce dsRNA as a by-product of replication (124). TLR3 is mostly thought of as an intracellular receptor, resident on the membranes of endosomal vesicles. However, weak cell surface TLR3- expression has been demonstrated in keratinocytes (125). Viral infection of epithelial cells appears to induce localisation of TLR3 to the cell surface where it serves to sensitize or "prime" the cells to better recognise and respond to subsequent viral challenge (126).
However, multiple evidences indicate that the receptor must serve other purposes than merely recognizing limited types of viruses.

Proofs of TLR3 as an endogenous sensor of cell damage appeared with the discovery of RNA sensing from necrotic cells and tissue, whereas RNA from apoptotic cells did not mediate TLR3 signalling (127, 128). Lai et al found that RNA from necrotic cells triggers TLR3 in undamaged cells, leading to a local release of proinflammatory cytokines (129). Cell necrosis is a common feature at the wound edge. In wild type mice, the mRNA level and protein expression of TLR3 is significantly upregulated in wounded skin (130). TLR3-deficient mice produce significantly less IL-6 and TNF at wound edges compared to wild-type controls, concluding that TLR3 activation is required for normal inflammation after injury (129).

TLR3 can be activated though the presence of secondary structures, such as hairpins, which have dsRNA regions in endogenous host single-stranded mRNA (127). Nucleoside modifications, such as methylation, can further regulate the immunogenicity of the RNA. There is reduced signalling of common mammalian modifications of RNA through TLR3 compared to minimally modified viral nucleic acids (131). It is also interesting how a well-orchestrated degradation of cellular RNA occurs in apoptotic cells, but not in necrotic cells (131). This suggests that sudden damage to self during necrosis can lead to release of RNA with limited modification. This may induce a TLR3 response, whereas an apoptotic cell death elicits little inflammation through TLR3 due to a more planned RNA degradation.

4.4 Skin diseases with suggested TLR3 involvement

Atopic dermatitis is the most common chronic inflammatory skin disease of early childhood. It is characterized by dry skin, a cutaneous barrier defect, enhanced allergen priming, susceptibility to cutaneous bacterial colonization and infection (especially Staphylococcus aureus infection), and cutaneous inflammation driven by type 2 helper T (Th2) cells (132).

TLR3 mediated signalling has been suggested to play a role in maintaining an inflammatory environment in the skin through driving the thymic stromal lymphopoietin (TSLP) production in keratinocytes. TSLP is highly expressed by keratinocytes in the lesions of atopic dermatitis patients and in allergic diseases also involving the skin (133). The barrier defect in atopic dermatitis may lead to subsequent tissue damage with release of endogenous RNA as initiator of TLR3 sensing (113). The TLR3–NF-κB axis triggers production of TSLP (134), which can actively drive a Th2 cytokine response, potentially through effects on DCs, granulocytes, natural killer cells and CD4+ T cells, inhibiting the Th1 responses that normally are induced by TLR-stimulation (135). Deficiency or aberrant expression of the filaggrin protein, essential for the regulation of epidermal

homeostasis is strongly associated with atopic dermatitis (136). In an *in vitro* model, TLSP release is highly increased in filaggrin knockdown after TLR3 stimulation. This suggests that reduced filaggrin levels may influence innate immune responses via TLR stimuli and may contribute to the pathogenesis of inflammatory skin disease via TSLP expression (137)

Injury to the skin such as surgery, cuts, abrasions, and burns have been documented as initiation sites for progressive depigmentation. Intercellular cell adhesion molecules (ICAM-1) are involved in cell–cell interactions of leukocytes and target cells, and thus play an important part in the initiation of immunologic and inflammatory reactions (138). As ICAM-1 expression has been observed in melanocytes around active vitiligo patches, it has been hypothesized that the excessive expression of ICAM-1 in melanocytes makes these cells a target for infiltrating T lymphocytes (139, 140). A novel publication points at RNA released from necrotic keratinocytes as an endogenous TLR3 ligand for the stimulation of ICAM-1 and other proinflammatory gene expression in human melanocytes (141). TLR3 might thus be involved in the pathogenesis of local depigmentation following skin physical trauma.

In patients with systemic sclerosis, or scleroderma, resident and infiltrating cells in the dermis secrete soluble mediators, such as TGF-β, that activate fibroblasts. Production of large amounts inflammatory cytokines and chemokines initiate skin fibrosis and chronic inflammation. Patients with scleroderma have identified dysregulation of type I interferon (IFN) pathways. Type I IFN has no apparent role in regulating TGF-β activity in the skin, but has been shown to increase TLR3 expression on human dermal fibroblasts, resulting in enhanced TLR3-induced IL-6- and TGF-β production (142, 143). Induction of TLR3 expression and signalling may thus increase the inflammatory potential of dermal fibroblasts.

Altogether, TLR3 activation is probably a mechanism of detecting injury and maintaining homeostasis.

4.5 Interleukin-1 and inflammasomes in keratinocytes and skin associated diseases

We have had a focus on interleukin (IL)-1 in **paper I** and **III**. As a highly active and pleiotropic pro-inflammatory cytokine, IL-1 plays an important role in an efficient tissue repair response against trauma or infection (144, 145). Biological responses of IL-1 are mediated by the IL-1 receptor type I (IL-1RI), which is ubiquitously expressed. The prominent role of IL-1 signalling for inflammation is demonstrated through IL-1RI and TLRs sharing the same cytoplasmic signalling domain, the Toll/interleukin-1 receptor (TIR) domain (144). Agonists of IL-1RI are IL-1α and -β, which are both initially expressed with an amino-terminal propeptide. Pro-IL-1β does not bind or activate IL-1RI, whereas pro-IL-1α has the same biological activity as mature IL-1α (144).

Expression of IL-1 is regulated at the transcriptional level by nuclear factor κB (NF-κB). Pro-IL-1α and -β lack a signal peptide for protein secretion and thus leave the cell through one or several poorly understood mechanisms, called unconventional protein secretion (146). This protein secretion is independent of the classical endoplasmic reticulum (ER)/Golgi pathway. Caspase-1 activity is required for the activation of pro IL-1β in cytosol, but also for the unconventional secretion of pro IL-1α and of many other proteins involved in inflammation, repair and cytoprotection (147). Activity of IL-1 is also regulated by the secreted IL-1 receptor antagonist (IL-1Ra), which prevents binding of IL-1α and - β to IL-1RI through blockade of the receptor.
Keratinocytes are known as major producers of IL-1α, and mechanisms of induction as well as biologic effects of IL-1α are well described (144, 148-150). Activation and secretion of IL-1β is more complex, but keratinocytes express all inflammasome proteins in vitro and most likely also in vivo (148, 151). Recent papers have demonstrated involvement of inflammasome activation in keratinocytes upon UVB-irradiation (106, 148, 152). The question whether keratinocytes are able to activate caspase-1 was previously a matter of controversy

(153), but in line with previous findings we establish keratinocytes as major producers of IL-1β in the skin (148). However, we conclude in **Paper III** that TLR3-stimulation does not induce a powerful activation of the NLRP3-inflammasome, as very little of the induced pro-IL-1β is processed to cleaved IL-1β. This suggests that TLR3 induced cell death with subsequent release of pro-IL-1β plays a role in local inflammation through other mechanisms.

As shown in **Paper I**, TLR3-stimulation induces release of numerous cytokines, with the primary task of recruiting leukocytes. Epidermal injury, independent of infiltrating inflammatory cells, generates prominent chemotactic activity toward neutrophils in injured skin because of CXCL-8 production (154). Neutrophils are short-lived cells, dying within hours after emigration, and release of unprocessed IL-1β from intracellular stores is expected. As a consequence, extracellularly processing of IL-1β is reported for a variety of proteases of leucocyte origin. Proteinase-3 from neutrophils provides an alternative mechanism for the cleavage and release of IL-1β (155). Other proteases, such as elastase, matrix metalloproteinase 9, chymases and granzyme A released by neutrophils and mast cells in an acute wound bed process IL-1β extracellularly (144, 156, 157).

IL-1β activity is important in inflammatory and allergic skin diseases such as psoriasis or contact dermatitis, demonstrating the importance of IL-1β in the skin (158, 159). As non-professional immune cells, keratinocytes orchestrate infiltrating T cells in inflammatory skin conditions through IL-1β production (148, 160). In **Paper I,** we emphasize the role of IL-1β as a powerful inducer of many cytokines and growth factors in acute wound healing. Levels of IL-1β have been shown to correlate with the important chemokine CXCL-8 (145), a chemokine we focused on in **Paper II**. We also support the view of keratinocytes as potentially important producers of IL-1β, as we have found considerable release of the cytokine after polyI:C stimulation in both **Paper I and III**.

IL-1β-mediated diseases are often called “auto-inflammatory” and the dominant finding is the release of the active form of IL-1β driven by endogenous molecules (161). Aberrant activity of the IL-1β and the inflammasomes is involved in the pathogenesis of many diseases, including skin diseases (144). Inhibition of the activity of IL-1β through IL-1Ra (anakinra), soluble receptors for IL-1 (rilonacept) and human mAbs to IL-1β (canakinumab and Xoma 052) have been used as successful treatment to neutralize IL-1β specifically in many auto-inflammatory conditions, including the ones discussed below (161).

Cryopyrin-associated periodic syndrome is associated with mutations in the NLRP3 gene. These mutations result in constitutive activation of the NLRP3 inflammasome and, therefore, in uncontrolled activity of IL-1β. This demonstrates the importance of NLRP3 and of IL-1β in humans. The clinical findings are recurrent urticaria-like rashes, typical periodic fever episodes, bone/joint manifestations, and CNS involvement (162).

Deficiency in IL-1Ra due to homozygous mutations in this gene causes life-threatening auto-inflammation, affecting mainly the skin (severe pustulosis and ichthyosiform lesions) and the bones, similar to symptoms of patients suffering from cryopyrin-associated periodic syndrome (74).

The triad of sterile pyogenic arthritis, pyoderma gangrenosum and acne is known by the acronym of PAPA syndrome. It is a rare autosomal dominant disease of early onset, caused by mutations in the proline serine threonine phosphatase-interacting protein 1 (163). The molecular mechanism behind PAPA syndrome is still unknown, but the mutant protein is suspected to inhibit the anti-inflammatory activity of pyrin, leading to elevated IL-1β levels (164, 165).

Cytophagic histiocytic panniculitis is characterized by daily high spiking fevers and severe panniculitis. Patients may have a rapidly fatal disease course, a longer disease course with intermittent remissions and exacerbations for many years prior to death, or a nonfatal acute or intermittent course responsive to treatment. A

number of genetic mutations central to cytotoxic T cell and NK cell function can lead to this syndrome characterized by massive secretion of cytokines, including IL-1β, produced by activated macrophages (166).

IL-1β plays a role in the carciogenesis, tumour angiogenesis, development and invasiveness in experimental tumour models (167-170). Melanoma cells produce numerous cytokines associated with invasiveness and aggressiveness (171). These include IL-6, CXCL1–3, CXCL-8, CCL5 (RANTES) and monocyte chemotactic protein-1 (MCP-1, also known as CCL2). All of these cytokines can be regulated by the active (secreted) form of IL-1β (172), suggesting that IL-1β plays a critical role in melanoma pathogenesis (173). Therefore, as preclinical evidence provides ample support for reducing IL-1 activity in treating human metastatic disease, treatment with agents blocking the IL-1β effects may have a place in treating metastatic malignant melanoma.

4.6 TLR3-mediated cell death and caspase activation in keratinocytes

The traditional dichotomous classification of caspases as “apoptotic” and “pro-inflammatory” is still prevailing. Nevertheless, most apoptotic candidates (caspase-2, -3, -6, -7, -8, -9, and -10) have at least one non-apoptotic role attributed to them (174). Similarly, typical “non-apoptotic” members such as caspase-1, -4, and -5 have been proposed to induce pyroptosis (175, 176). The only truly remaining non-apoptotic human candidate may therefore be caspase-14, a mediator in keratinocyte differentiation (177).

In **Paper III** we demonstrate that polyI:C induces both pro-caspase-1 and pro-IL-1β mRNA. Caspase-1 is required for the activation of pro-IL-1β. The requirement of caspase-4 in inflammation has until recently been poorly characterized (23, 178). Our findings are in line with a parallel finding, showing that caspase-4 is required for activation of caspase-1, the latter most likely representing a substrate

of caspase-4 (106). We further demonstrated that polyI:C activated caspase-4, and that this induced both the extrinsic and intrinsic apoptotic pathways through caspase-8 and caspase-9 activation, respectively. In caspase-inhibitor experiments, we observed that polyI:C induced cytotoxicity was abolished when caspase-4 was inhibited. We therefore conclude that caspase-4 plays an important role in both inflammation and cell death in keratinocytes.

Human caspase-4 and -5 are poorly characterized (178, 179). Both caspases have been suggested as functional orthologues of the murine caspase-11 (26, 180, 181), but caspase-4 has also been suggested as the murine caspase-12 homolog (182, 183). Recently, caspase-11 has been shown to trigger caspase-1-independent macrophage death and caspase-1-dependent IL-1β production in response to a subset of inflammasome activators in mice (107). This suggests that caspase-11 rather than caspase-1 may be the critical effector of deleterious inflammatory responses in mice (107).

Through which TLR3-dependent mechanisms polyI:C induces caspase-4 activation remains to be unravelled. There is staggering evidence to suggest that caspase-4 mediated cell death is connected with death ER-stress. First, caspase-4 is localized to the ER (182). Second, caspase-4 closely associates with several essential proteins in ER stress-induced cell death pathways, such as glucose-regulated protein 78 and inositol-requiring enzyme 1 (184), APAF1, a protein involved in death protease mediated cell death (185), TRAF6, a member of the TNF receptor-associated factor (186) and CARD-only protein, a regulator of procaspase-1 (187). Third, different strategies for knocking down caspase-4 expression in with siRNA, introduction of caspase-4 antisense nucleotides, expression of inactive caspase-4 and micro-injections of caspase-4 antibodies have all abolished ER stress-induced cell death in different cell types (188-192). Fourth, caspase-4-inhibitors have effectively blocked ER-induced cell death melanoma cells (193), lung and esophageal cells (194), retinal pigment epithelial cells (195) and neuroblastoma cells (196). Fifth, overexpression of caspase-4 in COS-7 cells induces activation of caspase-3 and -9 (197).

Factors that perturb ER function and contribute to the development of ER stress include increases in protein synthesis or protein misfolding rates that exceed the capacity of protein chaperones, alterations in calcium stores in the ER lumen, oxidative stress and disturbances to the redox balance in the ER lumen (198). In **Paper I**, we observed that polyI:C was a powerful inductor of almost all chemokines, cytokines and growth factors we measured for in a high throughput protein based luminex assay. Also in **Paper III**, we observed in precipitate from supernatant and in lysate for Western blotting that polyI:C stimulated cells released considerably higher amounts of protein than un-stimulated cells. Therefore, we suggest that TLR3-mediated increase in protein synthesis is a candidate mechanism for induction of ER stress.

Secreted and membrane proteins fold and mature in the lumen of the ER before they are delivered to other compartments in the endomembrane system, displayed on the cell surface, or released extracellularly. A collection of signalling pathways are collectively termed the unfolded protein response (UPR). This mechanism monitors conditions in the ER through sensing an insufficiency in the ER's protein-folding capacity. If the status of the ER lumen is hampered, this is communicated back to gene expression programs in the nucleus. This transcriptional control is accompanied by mechanisms that transiently decrease the flux of proteins entering the ER (147, 199). In conditions of prolonged stress, the goal of the UPR changes from being one that promotes cellular survival to one that commits the cell to a pathway of apoptosis. Juxtaposition of ER and mitochondria promotes inter-organelle crosstalk and mediates cell death. The apoptotic crosstalk between the two organelles is tightly controlled by the anti-apoptotic mitochondrial Bcl-2 protein family. Initiation of signalling pathways converge on Bcl-2, favouring a pro-apoptotic drive at the mitochondria by proteins that cause mitochondrial damage, cytochrome c release and eventual caspase 3 activation (200). Interestingly, both caspase 8-mediated extrinsic pathway and caspase 9/mitochondria-mediated intrinsic pathway has being demonstrated in TLR3 mediated cell death (201, 202).

Human caspase-4 activation has recently been shown to be the initiating event in the caspase-dependent apoptotic pathway (203, 204). Overexpression of caspase-4 induces cleavage of caspase-9 and caspase-3 without releasing cytochrome-c from the mitochondria (197, 204). Cleavage of caspase-4 is not affected by the overexpression of Bcl-2, which prevents signal transduction on the mitochondria. In addition, the overexpression of caspase-4 does not induce efflux of cytochrome-c from mitochondria to cytosol (197). Caspase-4 can thus activate downstream caspases independently of mitochondrial apoptotic signalling, but downstream events from caspase-4 are not fully understood. Based on what we know about caspase-4 dependent cell death, we propose a model for how this may come about in Figure 6.

We therefore suggest that the traditional classification of caspases probably needs revisal based on our and others recent discoveries regarding functions of particularly caspase-4 (107, 195, 203, 204).

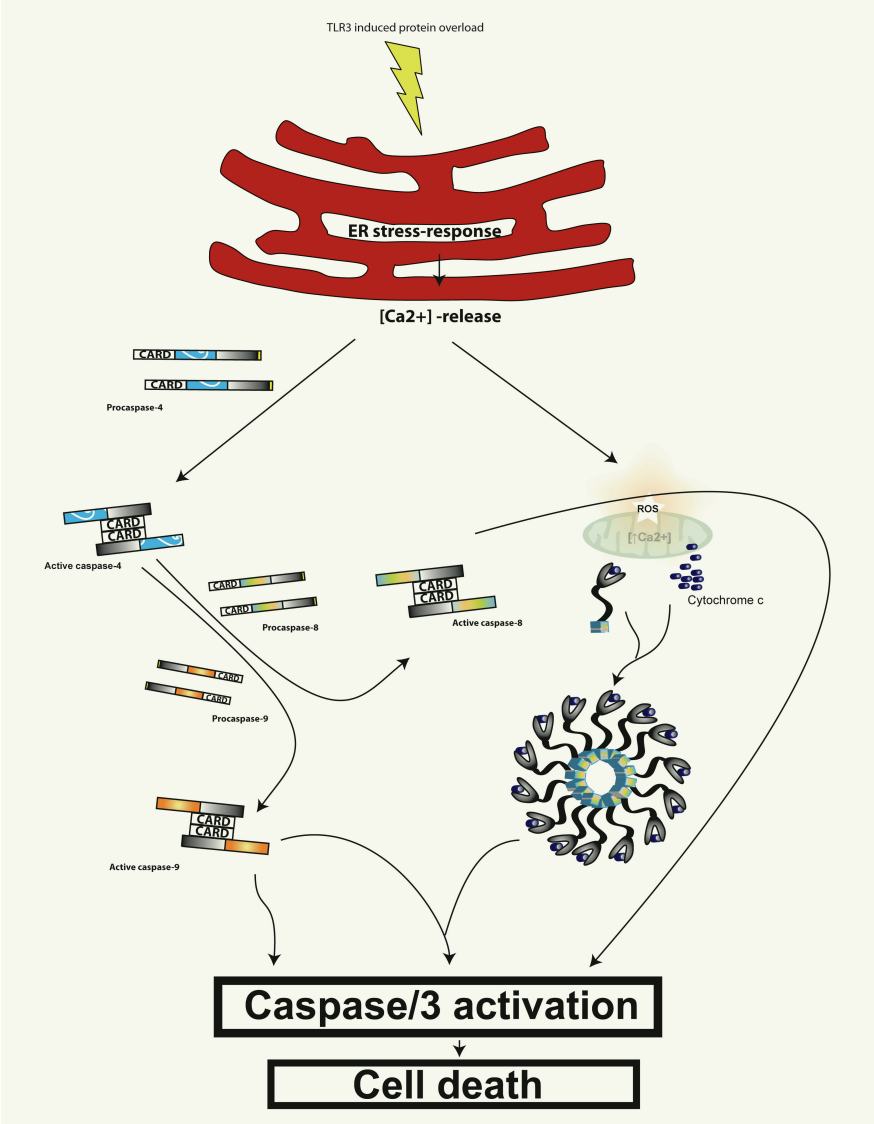

Figure 6. Possible mechanism for TLR3 induced caspase-4 dependent cell death.

TLR3 stimulation leads to transcription of several proinflammatory genes. Proteins are translocated into the ER lumen in an unfolded state and require protein chaperones and catalysts of protein folding to attain their final appropriate conformation. Processes that prevent accumulation of unfolded proteins in the ER lumen are triggered, as the capacity of the ER as a regulator for protein folding and

secretion is exceeded. Unable to adapt sufficiently to alterations in client protein-folding load in the ER lumen, changes in intralumenal calcium are induced. Mitochondrial- dependent and independent pathways are engaged. Caspase- 4 is an ER-associated proximal effector in the caspase activation cascade that activates procaspase-9 to cleave procaspase-3, the primary executioner of cell death. Caspase-4 also activates procaspase-8, which also in turn activates caspase-3. Mitochondrial ROS can be generated as a result of ER stress-induced Ca^{+2} release and depolarization of the inner mitochondrial membrane. Thus, oxidative stress in association of unresolved ER stress also contributes to pathways of cell death.

5. Concluding remarks

The keratinocyte has an active role in local immune responses in the skin. Providing the first-line innate responses, keratinocytes contribute to the adaptive immune responses that can be associated with clinical disease. Keratinocytes can also enhance and shape subsequent inflammation in response to stimuli and promote specific types of immune bias.

In the present study, we have revealed new aspects of how inflammation is regulated by innate immune receptors. In particular TLR3 expressed by keratinocytes is a potent mediator of inflammation through release of conventionally secreted cytokines and chemokines. In addition, coincidental TLR3 mediated cell death in keratinocytes contributes to considerable release of the pro-form of the highly proinflammatory cytokine interleukin-1β. This can contribute to further local inflammation through extracellular processing of inflammatory cells attracted to a site of injury. TLR3-dependent toxicity and proinflammatory responses were inhibited by concomitant stimulation with oligodeoxynucleotides. In cases of unwanted inflammation, such as in UV-induced damage, treatment with oligodeoxynucleotides is a possible therapeutic agent.

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11. Tor-Erik Widerøe: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.
12. Anton Hole: ALTERATIONS OF MONOCYTE AND LYMPHOCYTE FUNCTIONS IN REALTION TO SURGERY UNDER EPIDURAL OR GENERAL ANAESTHESIA.
13. Terje Terjesen: FRACTURE HEALING AND STRESS-PROTECTION AFTER METAL PLATE FIXATION AND EXTERNAL FIXATION.
14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
15. Inggard Lereim: TRAFFIC ACCIDENTS AND THEIR CONSEQUENCES.
16. Bjørn Magne Eggen: STUDIES IN CYTOTOXICITY IN HUMAN ADHERENT MONONUCLEAR BLOOD CELLS.
17. Trond Haug: FACTORS REGULATING BEHAVIORAL EFFECTS OG DRUGS.

1985

18. Sven Erik Gisvold: RESUSCITATION AFTER COMPLETE GLOBAL BRAIN ISCHEMIA.
19. Terje Espevik: THE CYTOSKELETON OF HUMAN MONOCYTES.
20. Lars Bevanger: STUDIES OF THE Ibc (c) PROTEIN ANTIGENS OF GROUP B STREPTOCOCCI.
21. Ole-Jan Iversen: RETROVIRUS-LIKE PARTICLES IN THE PATHOGENESIS OF PSORIASIS.
22. Lasse Eriksen: EVALUATION AND TREATMENT OF ALCOHOL DEPENDENT BEHAVIOUR.
23. Per I. Lundmo: ANDROGEN METABOLISM IN THE PROSTATE.

1986

24. Dagfinn Berntzen: ANALYSIS AND MANAGEMENT OF EXPERIMENTAL AND CLINICAL PAIN.
25. Odd Arnold Kildahl-Andersen: PRODUCTION AND CHARACTERIZATION OF MONOCYTE-DERIVED CYTOTOXIN AND ITS ROLE IN MONOCYTE-MEDIATED CYTOTOXICITY.
26. Ola Dale: VOLATILE ANAESTHETICS.

1987

27. Per Martin Kleveland: STUDIES ON GASTRIN.
28. Audun N. Øksendal: THE CALCIUM PARADOX AND THE HEART.
29. Vilhjalmur R. Finsen: HIP FRACTURES

1988

30. Rigmor Austgulen: TUMOR NECROSIS FACTOR: A MONOCYTE-DERIVED REGULATOR OF CELLULAR GROWTH.
31. Tom-Harald Edna: HEAD INJURIES ADMITTED TO HOSPITAL.
32. Joseph D. Borsi: NEW ASPECTS OF THE CLINICAL PHARMACOKINETICS OF METHOTREXATE.
33. Olav F. M. Sellevold: GLUCOCORTICOIDS IN MYOCARDIAL PROTECTION.
34. Terje Skjærpe: NONINVASIVE QUANTITATION OF GLOBAL PARAMETERS ON LEFT VENTRICULAR FUNCTION: THE SYSTOLIC PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT.
35. Eyvind Rødahl: STUDIES OF IMMUNE COMPLEXES AND RETROVIRUS-LIKE ANTIGENS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.
36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

1989

43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

1990

52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

1991

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

1993

82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

1994

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.

133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

1999

141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.

162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT

192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

2003

216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.

217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
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