

en  [European Cytokine Network](#)[Current issue](#)[Past issues](#)[Auti](#)[✦ Subscribe](#)

Volume 13, issue 4, December 2002 | Proceedings

Meeting report of the “Club Cytokine” (French Society of Immunology) meeting, in Le Croisic, France



Full text

Mariette Lisbonne¹ and Hélène Plun-Favreau²

1-FRE 2444. Hôpital Necker, 161 rue de Sèvres, 75015 Paris, France

2-INSERM U564. CHU 4, rue Larrey, 49033 Angers Cedex 01, France

In May of this year, the annual cytokine meeting organized by the French Society of Immunology was held for the second time in Le Croisic on Brittany's coast. The Toll-like/interleukin (IL)-1 receptor family and cytokine/virus interactions were the major topics chosen for presentations in plenary sessions, while selected short communications and posters were open to other fields of investigation.

The opening session dealt with the Toll-like receptor (TLR) family. In his brilliant introductory lecture based on the genetic data presently available, Fernando Bazan (DNAX, Palo Alto, CA) compared the evolution of these molecules in different species. He emphasized their crucial role in dorso-ventral polarization and anti-fungal immunity of *Drosophila*, as well as its importance in mammalian host defense. TLRs are type 1 membrane proteins analogous to the *toll* gene initially described in *Drosophila*. Ten human and twelve murine TLRs have been cloned to date. They all share a leucine-rich motif (LRR) in their extracellular domain, a single transmembrane domain and an intracellular sequence responsible for signal transduction. Receptor binding activates the nuclear factor (NF)-kappaB pathway and results in the induction of a variety of effector genes. The structure of TLRs and adapter molecules like MyD88 is characterized by a TIR (Toll-like IL-1R) domain common to many species. It has been useful in establishing the phylogenic relationship between TLRs. F. Bazan emphasized the variety of ligands recognized by TLRs, in spite of their similar structure, a feature they share with major histocompatibility complex molecules. To illustrate this notion, he took the example of TLR-4, which is an endotoxin sensor. The activation of this receptor does not occur in response to LPS alone, but requires LPS-binding protein (LBP) and CD14. Other adapter molecules, such as the recently discovered MD-2 protein can also confer responsiveness to endotoxin upon binding. F. Bazan noted that direct recognition between TLRs and their endogenous ligand has not yet been demonstrated *in vivo* for mammals, even though the protein termed Nodd1 might be a homologue of the ligand of *Drosophila* Toll Spatzle (Spl). The TLR family is the prototypic example of how innate immunity can initiate acquired immune responses by communicating its biological evaluation of a foreign antigen.

Jean-Luc Imler (UPR CNRS 9022, Strasbourg) presented a very complete overview of the present understanding of Toll receptors in *Drosophila*. The 9 different Toll receptor subtypes induce an intracellular signaling pathway leading to phosphorylation of molecules homologous to the NF-kappaB system, like Dorsal, Dif, Relish, Cactus&ldots; The activation of this transduction

pathway results in increased transcription of antimicrobial peptides, like drosomycin and dipterecin, the expression of which is controlled through Toll and IMD (Immune Deficiency) activation, respectively. The defense against Gram-positive bacteria and natural fungal infections involves Toll signaling, whereas Gram-negative bacteria are eliminated through the IMD pathway. Based on recent advances in the comprehension of the immune response in *Drosophila*, JL Imler proposed a model to explain how the insect could sense infection. Loss-of-function mutations have established that Toll does not function as a pattern recognition receptor but has to be activated through a cleaved form of the cytokine Spaetzle (Spl) (1). Other mutations revealed that fungi activate a novel serine protease encoded by the *persephone* gene which cleaves Spl and thus activates the Toll pathway (2). Gram-positive bacteria activate the same pathway through a circulating peptidoglycan recognition protein, PGRP-SA, and Gram-negative bacteria use PGRP-LC, which acts upstream of the *imd* gene (3, 4). JL Imler concluded his presentation with a comparison between Toll receptors and TLRs, pointing out that *Drosophila* contains a family of PGRP which plays a critical role in the detection of infection.

The third speaker, Nathalie Thieblemont (UMR CNRS 8603, Paris), focused her talk on lipopolysaccharides (LPS) and TLR-4. LPS, present in the outer membrane of Gram-negative bacteria, must first interact with a complex of proteins to become effective as an inducer of cellular activation. First, LPS-binding protein (LBP) catalyses its transfer to membrane-bound or soluble CD14, a lipid binding protein that facilitates the interactions between LPS and cell components but does not allow signal transduction. Another adapter protein, MD-2, is retained on the cell surface through interaction with TLR-4, which represents the signaling subunit of the complex involved in the recognition of LPS. In the first part of her talk, N. Thieblemont stressed the fact that depending on its molecular structure LPS can interact with TLR-2 or TLR-4 and behave like an agonist or an antagonist. Other molecules, such as heat shock protein (Hsp) and mycobacterial phosphatidyl-inositol mannosides (PIMs) are also susceptible to activate the TLR-4 pathway. Furthermore, some extracts containing lipoteichoic acids (LTA) depend on TLR-2 for their activity whereas others inhibit TLR-4 signaling. N. Thieblemont underlined the fact that there are still many open questions concerning the complex interactions of endotoxin and protein complexes allowing the induction of defense mechanisms. In the second part of her communication she presented results concerning TLR-4 and NKT cells. She showed that migration of NKT cells into lesions is induced not only by

PIMs of *Mycobacterium tuberculosis* (5) but also by a variety of glycolipids from pathogens, such as LPS or LTA. TLR-4 is effectively expressed by NKT cells and required for their recruitment to inflammatory sites, as demonstrated by its inhibition in the presence of a TLR-4 antagonist. These results were confirmed in TLR-4 deficient mice, since NKT cells were not recruited to the site of inflammation in this strain.

The last speaker, Paulo Vieira (URA CNRS 1961, Paris) discussed the expression and activation of Toll-like receptors, specifically TLR-7. The latter is displayed on different spleen cell subsets, namely IgM-positive B cells and plasmacytoid dendritic cells (PDC), but not on T cells, monocytes and NK cells. TLR-7 expression increases during B cell differentiation and both PDC and B cells express high levels of TLR-7 and TLR-9, which respond directly to synthetic oligodeoxynucleotides containing a CpG motif (CpG ODN). In CpG ODN-stimulated PDC and B cells, TLR-9 expression decreased rapidly, as opposed to TLR-7 that was upregulated in PDC and decreased in B cells (6). P. Vieira concluded his presentation by providing us with some data on the recently developed TLR-7^{-/-} mice. This deficiency does apparently not impair the differentiation process or modify the number of both B cells and PDC. P. Vieira is presently screening TLR-7⁺ cells for potential ligands, since the identity of the naturally occurring partner of this receptor remains elusive.

Short oral presentations closed this session on the TL/IL-1 receptor family. The talk of B. Abel *et al.* concerned the requirement of TLR-4 in the control of chronic *Mycobacterium tuberculosis* infection in mice. The data presented by S.C. Gangloff *et al.*, demonstrated the influence of LPS and lipid A structure on the activation of murine macrophages *via* CD14 and TLR-4-dependent or -independent pathways. A paper by E. Schneider *et al.*, showed that pro-Th1 cytokines promote Fas-dependent apoptosis of immature peripheral basophils. I. Dorval *et al.*, presented a study on LIF-R that is expressed in a short dysfunctional form by germinal cells engaged in meiosis. The next talk by D. Derouet *et al.*, dealt with the secretion of the composite cytokines CLC/CLF and CLC/solCNTFR. These data established that the secretion of these cytokines is regulated by an N-glycosylation of CLC. In the last presentation, Y. Wittrand *et al.*, reported on the function of osteoprotegerin in the regulation of the expression of the protease responsible for osteoclast resorption.

The second session of this meeting focused on current events about cytokines.

F. Dautry (UPR CNRS 1983, Villejuif, France) started this session with an overview on expression regulation mechanisms by double strand (ds) RNAs and their utilisation in functional genomic, applicable to cytokines study. After an introduction about the physiological role of these dsRNAs and their development as a new technology, F. Dautry focused our attention on their potential utilisation for mammalian cell culture study. One reef of this technology is that dsRNAs induce a strong interferon type response in these cells, limiting their application to embryonic stem cells, less inductive in interferon. Until now, nevertheless, numerous genes have been inactivated in mammalian cells, allowing a saving of time in functional genomic study, even if this inhibition is never complete. However, it is still difficult today to use this technology, especially because of the difficulty for dsRNAs to penetrate in cells and because of the delicate choice of the expression vector.

S. Dupuis (INSERM U550, Paris, France) emphasised the implication of the transcription factor STAT1 in antimycobacterial and antiviral immunity. Effectively, a Mendelian susceptibility to mycobacterial infections exists. Following infection, mycobacteria are phagocytated by macrophages which subsequently secrete interleukin-12 (IL-12). This cytokine acts on NK T cells which in turn secrete interferon γ (IFN γ). Finally, IFN γ acts on macrophages to eliminate mycobacteria through the STAT1 signalling pathway. Several mutations have been observed in patients affected by mycobacterial infections, particularly on IL-12, IL-12Rb1, IFN γ R1, IFN γ R2 and STAT1. IFN γ homodimeres binding on IFN γ R1 lead to the homodimerization and the recruitment of IFN γ R2. Subsequently, JAK kinases are activated and phosphorylate STAT1 transcription factors. Then, phosphorylated STAT1 proteins can homodimerize and translocate to the nucleus to activate the transcription of specific genes. An attenuated nuclear translocation of STAT1 homodimeres has been observed in response to IFN γ in a female patient. This phenotype was similar to that observed in patients displaying a mutation on gIFNR1 gene. Following IFN α binding on its receptor, STAT1 is also recruited. After phosphorylation, STAT1 can be homodimerised but equally heterotrimerised to form STAT1/STAT3/p48 trimeres. In this patient, an attenuated nuclear translocation of STAT1 homodimeres was also observed in response to aIFN, with no abnormalities in heterotrimeres translocation. Sequence genome analysis of the patient indicated the existence of a heterozygote mutation in STAT1 gene in position 706. Effectively, several patients were carrying a similar mutation in the cohort. Then, transfection experiments have been performed using the mutated allele.

In response to IFN γ or IFN α , no nuclear translocation of STAT1 homodimers was observed. This led to the conclusion that the observed phenotype to IFN γ (antibacterial immunity) is dominant, whereas the phenotype observed to an IFN α (antiviral immunity) response is recessive.

The third speaker, Eric Lelièvre (INSERM U564, Angers, France) presented the characterization of a new cytokine receptor related to gp130 and called GPL (for "gp130 like receptor"). Gp130 is the shared receptor chain of the IL-6 cytokine family of receptors. GPL cDNA has been cloned based on its homologies with gp130 genomic sequence. mRNAs are expressed in glioblastoma and melanoma cell lines. It can also be detected in freshly isolated monocytes and dendritic cells. Like all members of type I receptors family, GPL contains conserved motives in its sequence, like the WSXWS box in its extracellular domain. Different isoforms have been identified, a long one and a short one, with an almost completely truncated intracellular domain. A phylogenetic tree and a protein modelling study confirmed the homology level between the GPL and gp130. Western blotting experiments allowed the detection of a 98 kDa receptor. Finally, real time quantitative PCR experiments have been performed and showed that this new receptor expression was strongly upregulated by IFN γ in freshly isolated dendritic cells. Identification of its cognate ligand is under investigation.

The last plenary session focused on cytokines and viruses. Nanou Pham (Hôpital Beaujon, Clichy, France) emphasised the role of cytokines in response to hepatitis B virus (HBV). In patients affected by acute B hepatitis, CD8 T cells play a major role in HBV infected hepatocytes lysis, through Fas/FasL pathway. Furthermore, some cytokines, particularly IFN γ , TNF α and IFN α/β play a crucial role in virus elimination through posttranscriptional mechanisms, inhibiting gene expression and HBV replication. Moreover, inflammatory response, implicating IFN γ but equally CXC chemokines IP-10 and MIG, induces serious hepatic lesions observed in patients affected by acute or chronic hepatitis.

The second speaker, Augustin Valenzuela (Institut Pasteur, Paris, France) presented an overview on chemokines and anti-viral response, with the example of human immunodeficiency virus (HIV). Chemokines play different biological roles *in vivo*, particularly in the development of embryonic and immune system. These proteins equally orchestrate immunologic and inflammatory responses. Chemokine receptors are equally numerous and can be shared by different

chemokines, explaining partly redundancy and pleiotropy of these proteins. Chemokines and their receptors are implicated in a number of diseases and particularly viral infections. Some viruses use the chemokine system as a toolbox for facilitating different steps in infection and pathogenesis. Viruses have thoroughly corrupted the chemokine system through molecular mimicry of proteins implicated in chemokine system. To date, more than 30 distinct virally encoded chemokines and chemokine receptor mimics have been identified, and the HIV is one of them.

The third speaker, Karl-Joseph Kallen (Christian Albrecht Universität, Kiel, Germany) presented a viral cytokine, the viral interleukin-6 (vIL-6). This cytokine is produced by cells infected by HHV-8 virus and is encoded by the virus genome. Like IL-6, vIL-6 acts through the transducing subunit gp130. vIL-6 is active on CD34 cells and induces STAT3 phosphorylation on HepG2 cell lines. Furthermore, vIL-6 is active on endothelial cells and can induce Kaposi sarcoma cell lines proliferation

The last speaker, Daniel Olive (INSERM U119, Marseille) focused his talk on viruses and TNF family, especially a newly identified TNF family member, LIGHT. LIGHT is a costimulatory molecule for T cells and binds to LT β R and herpes virus entry mediator (HEVM) *in vitro*. LIGHT expression on T cells is regulated at transcriptional and posttranscriptional levels. Furthermore, LIGHT is able to down-modulate its own receptor expression. HEVM-LIGHT interaction also induces the dendritic cells maturation. LIGHT can equally synergize with CD40L to increase cytokine secretion, CTL priming or IFN- γ production.

Short oral presentations on cytokines and viruses closed this session. The work of Yamina Benasser and Elmostafa Bahraoui described the ability of HIV-1 Tat protein to induce IL-10 production by human monocytes. Data presented by C. Rogez demonstrated that IFN- τ plays an anti-HIV activity mediated through IL-6. A short presentation by J. Estaquier focused on the process CD4 T cell death induced by HIV. S. Gagnard demonstrated that filamentous bacteriophage induces rapid maturation of dendritic cells. M. Lisbonne demonstrated that ligand-activated NK T lymphocytes promptly produce IL-3 and GM-CSF *in vivo*. The last short presentation by E. Rippert focused on the role of protein G signalling pathways in functional differentiation by T lymphocytes.

References

1. Levashina EA, Langley E, Green C, Gubb D, Ashburner M, Hoffmann JA, Reichhart JM. 1999. Constitutive activation of toll-mediated antifungal defense in serpin- deficient *Drosophila*. *Science* 285 : 1917.
2. Ligoxygakis P, Pelte N, Hoffmann JA, Reichhart JM. 2002. Activation of *Drosophila* Toll during fungal infection by a blood serine protease. *Science* 297 : 114.
3. Michel T, Reichhart JM, Hoffmann JA, Royet J. 2001. *Drosophila* Toll is activated by Gram-positive bacteria through a circulating peptidoglycan recognition protein. *Nature* 414 : 756.
4. Gottar M, Gobert V, Michel T, Belvin M, Duyk G, Hoffmann JA, Ferrandon D, Royet J. 2002. The *Drosophila* immune response against Gram-negative bacteria is mediated by a peptidoglycan recognition protein. *Nature* 416 : 640.
5. Apostolou I, Takahama Y, Belmant C, Kawano T, Huerre M, Marchal G, Cui J, Taniguchi M, Nakauchi H, Fournie JJ, Kourilsky P, Gachelin G. 1999. Murine natural killer T (NKT) cells [correction of natural killer cells] contribute to the granulomatous reaction caused by mycobacterial cell walls. *Proc Natl Acad Sci USA* 96 : 5141.
6. Kadowaki, N., Ho, S., Antonenko, S., Malefyt, R. W., Kastelein, R. A., Bazan, F., Liu, Y. J. (2001). Subsets of human dendritic cell precursors express different toll-like receptors and respond to different microbial antigens. *J Exp Med* 194 : 863.

Authors

Mariette Lisbonne, H  l  ne Plun-Favreau

FRE 2444. H  pital Necker, 161 rue de S  vres, 75015 Paris, France

In this issue

○ European Cytokine Society president's address

Josef van Damme

○ Losing balance : cytokine signaling and cell death in the context of hepatocyte injury and hepatic failure

Tom Luedde, Christian Liedtke, Michael P Manns, Christian Trautwein
liver failure, apoptosis, tumor necrosis factor, NF-KB, interleukin-6, Fas

○ Presented at the 4th symposium on Cytokines and apoptosis in the cardiovascular system, Halle, Germany, June 6-7, 2002

○ Activated STAT-1 pathway in the myocardium as a novel therapeutic target in ischaemia/reperfusion injury

Anastasis Stephanou
STAT, heart, ischaemia/reperfusion, apoptosis

○ A subset of caspase substrates functions as the Jekyll and Hyde of apoptosis

Jian-Yan Yang, Christian Widmann
RasGAP, MEKK1, caspase substrates, apoptosis, survival

○ Compromised IFN-gamma production in the elderly leads to both acute and latent viral antigen stimulation: contribution to the immune risk phenotype?

Qin Ouyang, Wolfgang M Wagner, Anders Wikby, Ed Remarque, Graham Pawelec
Aging, T-cell, IFN-g, CMV, EBV, immune risk phenotype, longitudinal study

○ Cytokines in chronic heart failure: possible involvement in the neurohormonal and the cytokine systems at the cAMP level?

Claudia Werner, Harald Loppnow, Mathias Rauchhaus, Armin Wessel, Karl Werdan, Reiner Buchhorn
Adult, b-blocker, children, chronic heart failure, cyclic AMP, cytokine, infant, interleukin, soluble TNF receptor, tumor necrosis factor

○ Effects of tumor necrosis factor-alpha and interleukin-6 in elderly populations

Helle Bruunsgaard

TNF- α , IL-6, aging, mortality, inflammation

○ Energetic depression caused by mitochondrial dysfunction

Frank Norbert Gellerich, Sonata Trumbeckaite, Ying Chen, Marcus Deschauer, Tobias Müller, Stephan Zierz

Mitochondria, outer membrane, inner membrane, mitochondrial disease, sepsis, phosphorylation potential

○ Senescence: the cost of being young and healthy?

Graham Pawelec

○ The regulation of death-associated protein (DAP) kinase in apoptosis

Galit Shohat, Taly Spivak-Kroizman, Miriam Eisenstein, Adi Kimchi

apoptosis, DAPk, autophosphorylation, negative regulation

○ Neisseria meningitidis can induce pro-inflammatory cytokine production via pathways independent from CD14 and toll-like receptor 4

Tom Sprong, Peter van der Ley, Liana Steeghs, Will J Taw, Trees JW Verver-Janssen, Mihai G Netea, Jos WM van der Meer, Marcel van Deuren

Neisseria meningitidis, lipopolysaccharide, endotoxin, cytokines, CD14, TLR4

○ Evaluation of tumor necrosis factor alpha production in ex vivo short term culture whole blood from women with polycystic ovary syndrome

A Veronica Araya, Adam Aguirre, Carmen Romero, Cristian Miranda, Maria Carmen Molina, Arturo Ferreira

LPS, polycystic ovary syndrome, TNF- α , whole blood cell culture

○ Plasma levels of IL-12, IL-18 and TGF-beta in Plasmodium falciparum malaria

Lucia Malaguarnera, Salvatore Pignatelli, Jacques Simporè, Mariano Malaguarnera and Salvatore Musumeco

IL-12, IL-18, TGF- β , Plasmodium falciparum

○ In vitro analysis of IGn-gamma and IL-12 production and their effects in ileal Crohn's disease

Stefaan Colpaert, Kathleen Vastraelen, Zhanju Liu, Philippe Maerten, Chong Shen, Freddy Penninckx, Karel Geboes, Paul Rutgeerts, Jan L Ceuppens
IL-12, IFN-g, anti-IL-12/ anti-IFN-g, in vitro, Crohn's disease

○ Differential modulation of IL-2- and IL-4-mediated early activation of normal human B lymphocytes by the caspase inhibitor zVAD-fmk

Shahul Mouhamad, Damien Arnoult, Marie-Thérèse Auffredou, Jérôme Estaquier, Aimé Vazquez
IL-2, IL-4, B lymphocyte, caspase, proliferation, cell cycle entry

○ Prolactin-cytokine network in the defence against *Acanthamoeba castellanii* in murine microglia

Nunzia Benedetto, Claude Auriault
Prolactin, cytokine, *A. castellanii*, MGC.

○ CINC-1 mediates the sympathetic component of inflammatory mechanical hypersensitivity in rats

Berenice B Lorenzetti, Fabiane H Veiga, Claudio A Canetti, Stephen Poole, Fernando Q Cunha, Sergio H Ferreira
Inflammatory hyperalgesia, CINC-1, tumour necrosis factor alpha, interleukin-1b, interleukin-8, sympathetic mediators, prostaglandin E2

○ A CXC chemokine sequence isolated from the rainbow trout *Oncorhynchus mykiss* resembles the closely related interferon-gamma-inducible chemokines CXCL9, CXCL10 and CXCL11

Kerry J Laing, Niels Bols, Christopher J Secombes
Chemokine, rainbow trout, IP10, I-TAC, Mig

○ Meeting report of the “Club Cytokine” (French Society of Immunology) meeting, in Le Croisic, France

Mariette Lisbonne, Hélène Plun-Favreau

Les éditions JLE

30 rue Berthollet, Bât. A,
94110 Arcueil, France

+ 33 (0)1 46 73 06 60

contact@jle.com

Publishing Policy

Books and e-books

Want to publish ?

 Become a partner



John Libbey Eurotext Arnette doin Pradel

Lavoisier hermes TEC & DOC Médecine
SCIENCES