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French society of immunology, cytokines

Full text

In early June this year, the traditional meeting on Cytokines organised by the French Society of Immunology (namely M. Dy, A. Vasquez, H. Gascan, Y. Jacques) did not take place in Paris as usual, but close to the sea side in a very charming town on the Brittany coast, Le Croisic. Several sessions were organised to give an update on cytokines, their receptors and their signalling pathways, in various contexts such as immunology, haematology, apoptosis and cellular differentiation. Beside plenary sessions, selected posters were presented as short communications.

The opening session focused on the IL-12 cytokine family. G. Trinchieri (Schering-Plough, Dardilly, France) gave an overview of the biological effects of IL-12. This cytokine is a heterodimeric, proinflammatory cytokine consisting of a light chain, defined as p35, disulfide-linked to a heavier chain, p40. The p35 subunit is similar to other alpha-helix hematopoeitin cytokines, whereas the p40 subunit is similar to the extracellular portion of a hematopoeitin receptor, and is most closely related to the IL-6 or CNTF alpha receptor. IL-12 is inducible by the activation of toll-like receptors 2, 4 and 9 and other receptors such as CD44, RANKL, CD40 ligands. G. Trinchieri emphasized the immunoregulatory function of IL-12 and the ability of this cytokine to promote the secretion of IL-2 and IFN-gamma, and to inhibit the production of IL-4, IL-5, IL-6 and IL-10. The highlight of this presentation was the control of IL-12 secretion. It has been reported that the p35 alpha-chain is the limiting factor in the control of IL-12 heterodimer production. New results concerning the post-translational control of p35 by glycosylation were presented. Deglycosylation experiments using neuraminidase and Endo-F to examine intracellular *versus* extracellular IL-12 heterodimer revealed that the p35 chain was modified with sialic acid adducts to N-linked oligosasccharides before secretion. Inhibition of N-glycosylation by tunicamycin altered the formation and the secretion of the heterodimer p70. There was no association of the alpha and beta chain in the absence of glycosylation of p35, however secretion of p40 was not altered. This modification of p35 during maturation affected the cleavage of leader peptide. There are two cleavage events of p35, one independent of glycosylation and one where glycosylation is absolutly necessary [1]. Lastly, data about inactivation of p35/p40 and beta1/beta2 receptor chains were presented. These experiments showed a major deficit in mice deficient for p40 or beta1, but no defects were observed in the case of inactivation of p35 or beta2.

O. Devergne (INSERM U. 131, Paris, France) presented an overview on EBI3 protein (Epstein-Barr virus-induced gene 3). EBI3 is a soluble hematopoietin component related to the p40 subunit of IL-12. This protein shares 30% homology with CNTFR and p40. EBI3 is localized in the endoplasmic reticulum in association with the molecular chaperone calnexin. In cells transfected with an expression vector coding for EBI3 and p35, EBI3 co-immunoprecipitates with the p35 subunit of IL-12. This association is not covalent. *In vivo*, EBI3 extract from the trophoblast component of a human full-term normal placenta, co-immunoprecipitates with p35, indicating that EBI3 forms a heterodimer with p35. The biological effects of this heterodimer, and in particular the antagonist effect

on IL-12, was suggested but no data were presented to support this idea [2, 3]. Finally, O. Devergne presented new data on the localisation of EBI3. It is expressed in placenta cells, trophoblast and some populations of the extra-villous trophoblast. During pregnancy, a soluble form of EBI3 is detected in serum, but is not associated with any known function. At the end of her talk, some questions about the inactivation of EBI3 and its potential effects on pregnancy were raised, but this work is in progress.

The third speaker, R. Kastelein (DNAX, Palo Alto, USA) started his talk with the presentation of a new cytokine, IL-50 or human thymic stromal lymphopoietin (hTSLP). This new cytokine acts *via* the IL-7 receptor alpha chain and an orphan receptor, hRdelta2. This orphan receptor is related to the gamma2 chain and murine TSLP receptor. The activation of this complex, IL-7Ralpha and hTSLPR, by IL-50 leads to phosphorylation of STAT3 and STAT5. IL-50 or human TSLP acts on myeloid and dendritic cells. It induces the release of T cell-attracting chemokines (TARC) by monocytes and $CD11c^+$ dendritic cells. hTSLP enhances the maturation of $CD11c^+$ dendritic cells (induction of the co-stimulatory molecules CD40 and CD80) and displays enhanced capacity to elicit proliferation of naive T cells [4]. In the second part, he presented the new cytokine IL-23. It is composed of a novel subunit, p19 and the p40 subunit of IL-12 and shows biological activities similar to IL-12 but is also distinct from IL-12. IL-23 is secreted by activated dendritic cells and bound to the beta1 chain of the IL-12 receptor but fails to engage the IL-12 Rbeta2. After binding to the beta1 chain and the novel receptor subunit, IL-23 induces the phosphorylation of STAT4. The biological activities of this new heterodimeric cytokine are restricted to T cells. IL-23 induces Th1 differentiation of T cell $CD4^+$ from cord blood and induces a strong proliferation of mouse and human T memory cell. This last activity is unique, as IL-12 has no effect on this cell type. Like IL-12, IL-23 induces the secretion of IFN-gamma by T cell [5]. Transgenic mice overexpressing IL-23 die rapidly, with a chronic inflammation. Short oral presentations closed this session on the IL-12 cytokine family. The work of Leite-de-Moraes *et al.*, described the ability of IL-12 to induce *in vivo* the production of INF-gamma and TNF-alpha in NK T cells. Data presented by L. Derré *et al.,* demonstrated that IL-12 induces the receptor CD94/NKG2A on a T cell clone $CD8^+$. A short presentation focused on CLC (cardiotrophin-like cytokine), the new member of IL-6 cytokine family. H. Plun-Favreau *et al.*, demonstrated that co-expression of CLC and soluble CNTF receptor in mammalian cells generated a secreted composite cytokine, which displayed activities on cells expressing LIF receptor and gp130. The last short

presentation by J. Bitard *et al.*, focused on the binding site of LIF on the LIF receptor. The data presented showed that LIF bound to the Ig domain of the LIF receptor.

The second session of this meeting focused on two cytokine families, the IL-10 and the IL-2/IL-15 family. J.C. Renauld (Ludwig Institute for Cancer Research, Brussel, Belgium) started this session by presenting a new cytokine related to IL-10, called IL-TIF or IL-22. Isolation of this new molecule was performed by a cDNA substraction after stimulation of mouse T cells by IL-9. The cDNA regulated by IL-9 encoded a gene of 180 amino acids and revealed 22% identity with IL-10. This novel cytokine was designated IL-TIF for IL-10-related T cell-derived inducible factor or IL-22 and is mainly expressed in the thymus and brain. *In vivo*, transgenic mice for IL-9 did not modify the expression of IL-22. The biological activities of IL-22 are mediated by a heterodimeric receptor. This receptor is composed of the beta chain of the IL-10 receptor and CRF2-9. CRF2-9 was originally described as an orphan receptor called ZCYTOR11. The activation of this receptor leads to phosphorylation of Jak1, Tyk2 and STAT 1,3. Other signalling pathways are recruited by this receptor, as MAP kinase, p90 RSK and p38. IL-22 acts on mesengial, melanoma, intestine, lung, HUVEC, and hepathoma cells but does not activate monocyte cells. *In vivo*, IL-22 up-regulates acute phase reactant production by liver cells, indicating that this cytokine has a potential role in the inflammatory process [6]. The end of this talk focused on cloning of a new receptor, CRF2-10. This soluble receptor shares 33% amino acid identity with the extracellular domain of the IL-22 receptor. In fact, this new soluble receptor is able to bind to IL-22 and inhibits the activity of this cytokine. The IL-22 binding protein, IL-22BP, is expressed in various tissues with maximal expression in breast cells [7]. Concerning interleukin-15 and its receptors, S. Bulfone-Pons (University of Lübeck, Germany) presented new data concerning IL-15 and its role in the immune system. Beside the known role of this cytokine in Th1 development, she described the implication of IL-15 in Th2 response by using a murine model of allergic sensitisation to ovalbumin (OVA). Intraperitoneal injection of IL-15 enhances production of IgE in response to OVA injections and induces IL-4 and IL-5 production whereas injection of a soluble alpha chain of the IL-15 receptor, acting as an IL-15 antagonist, suppresses the production of IgE and prevents the OVA-induced allergic pulmonary inflammation. These data highlighted a new role of IL-15 in enhancing a Th2 response. New results concerning the role of the different chains of the IL-15 receptor were presented. IL-15 receptor is made up of three chains alpha

(specific for IL-15), beta and gamma (shared by IL-2). On memory CD8 T cells, IL-15-induced proliferation requires the beta and gamma chain, whereas its anti-apoptotic effect can be mediated by the alpha chain, in the absence of beta and gamma chain (M. Berard *et al.*). This latter observation was also confirmed in a model of ceramide-induced apoptosis in a human B cell line, where there is no implication of the beta chain (S. Bulfone-Paus). The role of IL-15 in T cells has also been described in an IL-15 overexpressing transgenic model (S. Dubois *et al.*), emphasing the role of IL-15 in blocking IL-2-induced activation induced cell death (AICD). IL-15 seems to set activate T cells in a quiescent state similar to anergy, blocking AICD. These results clearly demonstrate that IL-15 and IL-2 act differentially and favour opposing actions, which tend to emphasise two competing major goals of the immune response: maintenance of the peripheral self-tolerance for IL-2 and maintenance and survival of CD4 and CD8 T cells for IL-15. In the context of hematopoeisis, B. Azzarone *et al.* showed new data identifying a hybrid receptor GM-CSFRbeta/IL-15Rgamma involved in the GM-CSF dependant activation of Stat5.

The last plenary session focused on cytokine implication in apoptosis and cell differentiation. Apoptosis plays a central role in development and homeostasis of metazoans. In the immune system, apoptosis is essential as it leads to destruction of infected, autoreactive or cancer cells, and to deletion of activated T lymphocytes at the end of the immune response. The signalling pathways of apoptosis can be divided into two components, involving either the mitochondria or death receptors (Fas, TNF-R, DR3, 4 et 5). Activation of one of those pathways ultimately results in activation of caspases, proteases leading to morphological characteristics of apoptotic cells. In plenary sessions, an update and new data on apoptosis in the immune and hematopoietic system were presented, including several short communications, mainly on apoptotic pathways in immune pathologies. O. Hermine (URA CNRS 1461, Paris, France) emphasised the role of caspases in the erythroid maturation, demonstrating that these proteins, transiently activated *via* the mitochondrial pathway during erythroblast differentiation, activate proteins involved in DNA and nucleus condensation. Activity of caspases may then account for the nuclear structural changes associated with the maturation of erythroblasts [8]. Such activation of caspases has been demonstrated in other enucleation systems (keratinocytes, crystalline lens cells). P. Auberger (INSERM U. 526, Nice, France) presented new data on the role of Src kinases in apoptosis in T cells. He identified the protein Fyn as a substrate of caspases in death receptor-mediated apoptosis in the

Jurkat cell line. Cleavage of this protein increases its kinase activity and its translocation from the plasma membrane to the cytoplasm [9]. His data also support a role for Fyn in TCR-induced activation of the caspases in a murine T cell model. Another set of data presented by J. Bertoglio (INSERM U. 461, Chatenay-Malabry, France) illustrated the implication of small GTPases Rho in apoptosis. One of the Rho effectors, the serine/threonine kinase ROCK possesses a DETD motif, a motif recognised for cleavage by caspases. Like PAK, a Rac effector, ROCK is also cleavable by these proteases, and this cleavage induces its activation [10]. One may then postulate that caspases reorganise cell structures indirectly by activating proteins involved in actin cytoskeleton regulation. A. Atfi (INSERM U. 482, Paris, France) presented new data on TGF-beta signalling pathway and highlighted the role of the Jun kinase cascade both in apoptosis induced by the protein Smad7 and in the suppression of the Smad2 transcriptional activity [11, 12]. Several short oral communications focused on apoptosis in pathologies, as dysregulation of apoptotic pathways is often associated with defects in maintaining homeostasis in the immune and hematopoetic compartments. The work of E. Schneider *et al.* demonstrated that the Fas/Fas-L pathway can confer an immune privilege to thyrocytes in the context of experimental autoimmune thyroiditis (EAT) and that this Fas-dependent protection required IL-10. In another immune pathology, the autoimmune lymphoproliferative syndrome type II, C. Vonarbourg *et al.* suggested that the functional defect in apoptosis associated with this disease could be due to a defect in the Fas signalling pathway and illustrated a Fas-induced cell death dependent of FADD but independent of caspases. Data on signalling pathways involved in TGF-beta-induced apoptosis were presented by M.F. Bourgeade. She described the MAPK/p38 kinase pathway as necessary in TGF-beta-induced activation of caspases in a model of Burkitt's lymphoma, highlighting differences in caspases activation induced by TGF-beta or by death receptors, which require adaptor proteins like FADD, TRADD. E. Schneider *et al.*, assessed the implication of Fas/Fas-L in murine hematopoiesis. She presented data supporting the implication of a subset of NK cells in Fas-mediated apoptosis of hematopoietic progenitors, not directly but *via* TGF-beta secretion.

In conclusion, characterisation of new cytokines and dissection of signalling pathways have been the main focus of this meeting. Data presented were of a high quality and a number have been published in international journals since this meeting. The common interests of the participants lead to exciting and

enriching debates and everybody agreed to meet again next year at the same place to share new results.

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