

MEETING GREMI 2008

TH17-DERIVED CYTOKINES : NEW KIDS ON THE BLOCK OF INFLAMMATION

December, 12th, 2008 ; Institut Pasteur, Paris, France

Session 1

IL-17 and Th17 in rheumatoid arthritis

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IL-17 was identified in 1995/96 as a T cell derived cytokine with effects on inflammation and neutrophil activation. Rheumatoid arthritis (RA) has emerged as the best studied situation to justify the selection of IL-17 as a therapeutic target. By interacting often through synergy with other proinflammatory cytokines, IL-17 was found to induce bone and cartilage destruction. In 2006, the precise cell source of IL-17 was identified in the mouse. These cells were named Th17 and a key role for these cells was demonstrated in various situations associated with inflammation. These new findings confirmed and extended the results previously obtained following the identification of IL-17 as a T cell derived cytokine. At the same time, additional information was obtained on the other members of the IL-17 family and on the structure of the IL-17 receptor complex. Such knowledge has further extended the choice of possible modalities to control IL-17 A and F by acting on IL-17RA and IL-17RC. More recently, the role of IL-17 was shown in the chronicity of RA through an effect on reduced apoptosis of synoviocytes. Taken together, these results support the targeting of IL-17 in chronic inflammation associated with matrix destruction.

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Th memory for interleukin-17 expression is stable in vivo

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Based on the memory for the re-expression of certain cytokine genes, functionally different subsets of Th cells have been defined. In Th type 1 (Th1) and Th2 memory lymphocytes, the genes for the cytokines interferon-gamma (IFN-gamma) and interleukin (IL)-4 are imprinted for expression by epigenetic modification of the cytokine genes and the stable expression of the transcription factors T-bet and GATA-3, respectively. In Th17 cells, expression of the transcription factors RORgamma and RORalpha has been shown to be critical for IL-17 expression. We have analyzed the stability and plasticity of IL-17 memory in Th17 cells and their relationship to Th1 and Th2 cells. To this end, we have developed a cytometric IL-17 secretion assay for the isolation of viable Th cells secreting IL-17. In Th17 cells generated in vitro according to state-of-the-art protocols in the presence of TGF-beta, IL-6, IL-23, anti-IL-4 and anti-IFN-gamma, IL-17 expression remains conditional on continued TGF-beta/IL-6 or IL-23 signalling and is blocked by IFN-gamma and IL-4 signalling. These in vitro generated Th17 cells are converted to IFN-gamma expressing Th1 or IL-4 expressing Th2 cells in response to IL-12 and IL-4, respectively. However, when generated in vivo and isolated directly ex vivo, Th17 cells maintain their IL-17 memory upon subsequent in vitro culture, even in the absence of IL-23. Their cytokine memory is not modulated by adverse signals, such as IL-12 or IL-4. Thus, Th17 cells generated in vivo are a stable, functionally imprinted and distinct lineage of Th cell differentiation.

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Mechanisms of IL-17 induced hyperalgesia

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Chronic inflammatory pain relief in rheumatoid arthritis (RA) is often an unmet need for patients and anti-cytokine therapies are being investigated for their analgesic properties. We have investigated whether IL-17 induces pain in a model of hyperalgesia and its relationship to a known inducer of hyperalgesia, TNF. Both TNF and IL-17 fail to induce hyperalgesia in p55 TNF receptor knockout mice, indicating that IL-17-induced acute hyperalgesia is dependant on TNF. This is to be further investigated using a model of arthritic chronic pain collagen-induced arthritis (CIA).

Methods: C57/BL6 or TNF receptor 1 knockout (p55^{-/-}) mice were given an intra-plantar injection of 20ng TNF, 20ng IL-17 or vehicle (PBS +1% mouse plasma) into the right hind paw. Changes in weight distribution were measured over a 24h period post injection using a Linton weight incapitance tester. To measure thermal hyperalgesia the Hargreaves plantar hot-plate test was used over a 24h period after injection. Neutrophil infiltration was measured by histology and MPO assay. Blockade of neutrophil migration was with pre-treatment with a selectin competitive inhibitor, fucoidin (20mg/kg).

Results: Both IL-17 and TNF induce inflammatory pain in a murine model of acute hyperalgesia with TNF inducing pain earlier than IL-17 in the model of thermal hyperalgesia. IL-17 induced pain and TNF induced pain are prevented in TNF receptor 1 (p55^{-/-}) knockout mice but not in p75^{-/-} mice. IL-17 and TNF induced migration of neutrophils into the plantar tissue and blockade of neutrophils prevented hyperalgesia.

Conclusions: IL-17 induced hyperalgesia is dependant on TNF. However, there is some evidence that during chronic inflammatory pain, IL-17 is acting independently of TNF. The importance of cellular infiltration in hyperalgesia was also highlighted with the prevention of neutrophil migration abolishing hyperalgesia. Further studies are ongoing to characterise IL-17 and TNF expression during chronic inflammatory pain using the murine arthritis model CIA.

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Session 2

In vivo equilibrium of pro-inflammatory and regulatory ROR γ t+ T cells

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The nuclear hormone receptor ROR γ t is required for the generation of Th17 cells expressing the pro-inflammatory cytokine interleukin (IL)-17. In vivo however, less than half of ROR γ t+ T cells express IL-17. We show that ROR γ t+ T cells include Foxp3+ cells that coexist with IL-17-producing ROR γ t+ T cells in all tissues examined. The Foxp3+ ROR γ t+ T cells express IL-10 and CCL20, and function as regulatory T cells. Furthermore, the ratio of Foxp3+ to IL-17-producing ROR γ t+ T cells remains remarkably constant in mice enduring infection and inflammation. This equilibrium is tuned in favor of IL-10 production by Foxp3 and CCL20, and in favor of IL-17 production by IL-6 and IL-23. In lung and skin, the largest population of ROR γ t+ T cells express the gd TCR, and produce the highest levels of IL-17 independently of IL-6. Thus, potentially antagonistic pro-inflammatory IL-17-producing and regulatory Foxp3+ ROR γ t+ T cells coexist and are tightly controlled, suggesting that a perturbed equilibrium in ROR γ t+ T cells might lead to decreased immunoreactivity or, in contrast, to pathologic inflammation.

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Inhibition of Th2 skewed response in neonates promotes the development of Th17 type effector T cells

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A skewing towards a Th2-type response qualifies today the immunological status of the neonates. This may account for their sensitivity to infectious agents and their propensity to develop allergic pathologies as well as transplantation tolerance. We evaluated here the effects of the neutralization of IL-4, a key cytokine involved in the development of a Th2-type immune response and in the regulation of IL-17 dependent response, in glance with the possible appearance of a Th17 cell-mediated inflammatory immune response. We showed that hyper IgE response, lymphoid organ hyperplasia and transplantation tolerance are abrogated in BALB/c mice immunized at birth with (A/J x BALB/c)F1 spleen cells if they are submitted to anti-IL4 neutralizing mAb treatment. mRNA levels of IL-4, IL-5 and IL-13 were inhibited in the spleen of F1 spleen cells and anti-IL-4 mAb injected mice whereas mRNA levels of IL-17A, IL-17F and IL-22 were enhanced. This was confirmed by the fact that intracellular IL-17A protein was detected in a higher percentage of CD4⁺ T lymphocytes in animals immunized at birth with alloantigens and inhibited for the Th2 pathway with a similar percentage of IFN-gamma producing CD4⁺ T cells compared with mice immunized with F1 spleen cells and isotype control mAb. (A/J x BALB/c)F1 skin allografts were acutely rejected in mice immunized at birth with semi-allogeneic spleen cells plus anti-IL-4 neutralizing mAb with a massive neutrophils infiltrate and a significant increased of IL-17A mRNA into the graft. Our findings suggest that full acquisition of function by effector Th17 cells may be reinforced when Th2 pathway is prevented early in life. This may have an impact in terms of choice of vaccine adjuvants and development of autoimmune diseases.

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Blockade of TNF in collagen-induced arthritis reveals a novel immunoregulatory pathway for Th1 and Th17 cells

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IL-17 is implicated in the pathogenesis of rheumatoid arthritis and has previously been shown to be induced by TNF in vitro. The aim of this study was to assess the impact of TNF inhibition on IL-17 production in collagen-induced arthritis, a model of rheumatoid arthritis.

TNF blockade using TNFR-Fc fusion protein or anti-TNF mAb reduced arthritis severity but, unexpectedly, expanded populations of Th1 and Th17 cells, which were shown by adoptive transfer to be pathogenic. Th1 and Th17 cell populations were also expanded in collagen immunized TNFR p55^{-/-}, but not p75^{-/-}, mice. The expression of IL-12/IL-23 p40 was upregulated in lymph nodes from p55^{-/-} mice, and the expansion of Th1/Th17 cells was abrogated by blockade of p40. Treatment of macrophages with rTNF also inhibited p40 production in vitro. These findings indicate that at least one of the ways in which TNF regulates Th1/Th17 responses in arthritis is by downregulating the expression of p40.

Finally, although TNF blockade increased numbers of Th1 and Th17 cells in lymph nodes, it inhibited their accumulation in the joint, thereby providing an explanation for the paradox that anti-TNF therapy ameliorates arthritis despite increasing numbers of pathogenic T cells.

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Modulation of Th17 differentiation and function by environmental toxins

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Th17 cells are a novel CD4 T cell subset important for the defense against fungal infections and certain extracellular bacteria. Excessive Th17 responses are also responsible for a number of autoimmune diseases, such as rheumatoid arthritis, myocarditis or multiple sclerosis. Th17 differentiate in response to IL-6 and TGF β , further supported by IL-1 β and IL-21 and express the lineage defining transcription factors ROR γ t and ROR α . Furthermore, the transcription factor aryl hydrocarbon receptor (AhR) is selectively expressed in Th17 cells and its activation is important for optimal development of this T cell subset. In addition aryl hydrocarbon receptor ligation promotes the expression of IL-22, another Th17 cytokine. Endogenous ligands of AhR such as tryptophan metabolites constitute important modulators of the Th17 program in vivo and in vitro and high affinity agonists of AhR may contribute to excessive Th17 expansion resulting in exacerbation of autoimmune conditions. Thus, AhR activation in response to endogenous and exogenous ligands may constitute environmental stimuli that interact with genetic predisposition to certain autoimmune conditions.

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Session 3

Do neutrophils and Th17 cells cross-talk ?

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T helper 17 cells (Th17) are a subset of CD4⁺ T cells that play an active role in inflammation and autoimmune diseases. These cells produce two members of the interleukin-17 (IL-17) family, IL-17A and IL-17F, which trigger events that ultimately lead to the recruitment and activation of neutrophils and monocytes. Oddly, very little is known on the direct effects of these cytokines on neutrophils. It has been recently reported, for instance, that IL-17A attenuates the anti-apoptotic effects of GM-CSF on neutrophils and induces the secretion of IL-6, CXCL8/IL-8 and TNF α by monocytes. More recently, human Th17 cells have been characterized and were shown to display the chemokine receptors CCR2, CCR4, CCR6 and CXCR3. In this regard, we, and others, have uncovered that neutrophils, when appropriately activated, express CCL20/MIP-3 α , CCL22/MDC, CCL2/MCP-1 and CXCL9/10/11, the specific ligands of CCR6, CCR4, CCR2 and CXCR3, respectively. Based on these premises, the aim of this study was: i) to evaluate the potential biological effects of IL-17A and IL-17F on neutrophils; ii) to define whether neutrophils are able to recruit Th17 cells. Preliminary experiments did not reproduce the published findings on the effects of IL-17 on GM-CSF-dependent neutrophil survival and we are currently clarifying the reasons behind these contradictory findings. We are also evaluating whether IL-17A and/or IL-17F modify the pattern of cytokine/chemokine production or other functional responses of human neutrophils. We are currently performing chemotaxis experiments, testing the ability of supernatants harvested from neutrophils to induce the recruitment of Th17 cells from purified CD4⁺ T cells. Our experiments will uncover the reciprocal interactions of phagocytes and Th17 cells through the potential recruitment of Th17 cells on one hand and the modulation of phagocyte functions by IL-17 members on the other hand.

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Th17 cells are the dominant T cell subtype primed by *Shigella flexneri* mediating protective immunity upon re-infection

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Shigella, a gram-negative bacterium capable of invading colonic epithelial cells, causes bacillary dysentery characterized by severe bloody diarrhea which results from acute inflammation and subsequent tissue destruction. Although it is known that protective serotype-specific antibodies are induced upon natural infection, the nature of the elicited T cell response and its protective efficacy remain poorly understood. By examining the T cell response using a murine model of infection, we observe that *Shigella flexneri* primes antigen-specific CD4+, but not CD8+, T cell immunity. Furthermore, we demonstrate the induction of a strong predominance of interleukin-17 producing CD4+ (Th17) cells over interferon- γ producing Th1 cells. Importantly, the elicited Th17 pool gives rise to an enhanced recall response up to 12 months after priming, suggesting the presence of a long-term memory state. Although clearance of primary infection is only slightly reduced in the absence of T cells and independent of IL-17, we demonstrate that T cell-derived IL-17 is essential for protective immunity upon re-infection. These findings reveal a unique function of antigen-specific Th17 immunity upon infection with *S. flexneri*, highlighting the importance of this immune effector arm for secondary immune responses.

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Biology and functions of IL-17-producing invariant NKT (iNKT17) cells

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Invariant Natural Killer T (iNKT) cells are an important source of both T helper type 1 (Th1) and Th2 cytokines, through which they can exert beneficial as well as deleterious effects in a variety of inflammatory diseases. This functional heterogeneity raises the question in how far phenotypically distinct subpopulations are responsible for such contrasting activities. We have recently identify a particular set of iNKT cells that lack the NK1.1 marker (NK1.1^{neg}) and secrete high amounts of IL-17 and low levels of IFN- γ and IL-4. NK1.1^{neg}iNKT cells produce IL-17 upon synthetic (α -galactosylceramide (α -GalCer) or PBS-57) but also natural (lipopolysaccharides or glycolipids derived from *Sphingomonas sp* and *Borrelia burgdorferi*) ligands stimulation. NK1.1^{neg}iNKT cells are more frequent in the lung, consistent with a role in the natural immunity to inhaled antigens. Indeed, airway neutrophilia induced by α -GalCer or lipopolysaccharides instillation was significantly reduced in iNKT-cell deficient $J\alpha 18^{-/-}$ mice, which produced significantly less IL-17 in their bronchoalveolar lavage fluid than wild-type controls. Our findings revealed that NK1.1^{neg}iNKT lymphocytes represent a new population of IL-17-producing cells that can contribute to neutrophil recruitment through preferential IL-17 secretion. We proposed to name them iNKT17 cells.

The mechanisms leading to the acquisition of this new iNKT17 cell activity are unknown, but we recently evinced their presence in the thymus, predominantly among a subset regarded so far as an immature stage of thymic iNKT cell development. Actually, our results demonstrate a new alternative thymic pathway leading to the development of iNKT17 cells. Based on these findings we propose that the capacity of iNKT cells to produce IL-17 is acquired in the thymus to give rise to a more specific iNKT cell subset implicated in inflammatory responses.

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Session 4

Injury induced lung inflammation and the role of TH17 cells

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The molecular mechanisms of acute lung injury resulting in inflammation and fibrosis are not well established. Injury by several agents such as bleomycin, silica, MSU or alum leads to the pulmonary expression of IL-1 β triggering chemokine release with the recruitment of neutrophils and lymphocytes. The inflammatory response is abrogated in IL-1R1-deficient mice. Pulmonary IL-1 β production and inflammation required activation of the NALP3 inflammasome, which is composed of ASC and caspase-1, as genetic deletion of each component reduces the response. Further, p19/IL-23 and IL-17 are expressed in the injured lung and the inflammatory response is reduced in IL-17R deficient mice. Therefore the data suggest that injury induced inflammasome activation with IL-1 β production leads to p19-IL-17 expression, which participates in the effector phase of lung Inflammatory response.

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Autoreactive T Helper 17 lymphocytes are expanded in multiple sclerosis and inhibited by type I IFN

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Murine Th17 cells are responsible for EAE, the model of multiple sclerosis (MS). IFNbeta is used in the therapy of MS but the mechanism of its action have not been clarified yet. The kinetics of IFNs receptors during the differentiation of IL-23-driven differentiation of Th17 from healthy PBMC was evaluated. On developing Th17 lymphocytes a correlation exists between the early up-regulation of IFNGR2 surface expression and the transient ability of IFNbeta to activate STAT1 and suppress Th17 differentiation. Later on, developing Th17 cells display an increased IFNalpha receptor (IFNAR1) surface expression compared to developing Th1 cells, and a strong ability of type I IFNs to induced-STAT1 activation and apoptosis in differentiated Th17. Analysis of PBMC from never-treated patients with relapsing-remitting (RR)-MS showed that Th17 cells are expanded during the active phases of MS, and decreased during stability, while Th1 cells are slightly expanded in both active and stable patients compared to healthy donors. IFN-GR1 is more expressed on Th17 than on Th1 cells from MS patients, and IFNbeta treatment strongly reduces the number of Th17 cells but not that of Th1 cells. As Th17 in the peripheral blood of AMS were found to be MBP-specific, these data indicate that Th17 cells play a role in the pathogenesis of MS. The enhanced IFNAR1 expression and type I IFN responsiveness on Th17 cells may explain the mechanism of the effectiveness of its administration in MS patients.

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Modulation of Th17 Function for the Treatment of Autoimmune Diseases

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Interleukin-17A (IL-17) is a member of the IL-17 family of cytokines (IL-17A-F) and together with IL-17F is predominantly secreted from activated T-helper (Th) 17 lymphocytes. IL-17 induces the production of proinflammatory cytokines such as IL-6, G-CSF, GM-CSF, IL-1 β , TGF- β , TNF- α), chemokines (IL-8, GRO- α , MCP-1) and prostaglandins (e.g. PGE₂) from many different cell types including fibroblasts, endothelial cells, epithelial cells, keratinocytes and macrophages. Neutralization of IL-17 has been demonstrated to ameliorate disease severity in animal models of Rheumatoid Arthritis (RA) and Multiple Sclerosis (MS) and elevated levels of IL-17 have been reported in the synovial fluid of patients with RA, suggesting a role in disease pathogenesis. We have used phage display technology to select and optimize a IL-17 specific neutralizing monoclonal antibody (mAb), MEDI-571, suitable for preclinical safety studies in non-human primates and clinical development in subjects with RA. MEDI-571 neutralizes IL-17 biological activity with high potency (IC₅₀=0.2nM) and also binds to and neutralizes IL17A/F heterodimers *in vitro*. MEDI-571 inhibits cynomolgus monkey IL-17 with a 6-fold lower potency compared with human IL-17, but does not cross-react with murine IL-17. Co-crystallization of MEDI-517 Fab with IL-17 identified crucial amino acid residues that were optimized during affinity maturation and are either involved in IL-17 binding or the stabilization of the MEDI-571/IL-17 complex. Neutralization of IL-17 in autoimmune diseases such as RA and MS will provide further evidence for the role of IL-17 in disease pathogenesis and hopefully provide novel ways of treatment for patients suffering from these debilitating inflammatory disorders in the near future.