NEW ASPECTS IN THE IMMUNO-PATHOGENESIS OF AUTOIMMUNITY

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Over the last few decades we are observing a dramatic change in prevalences and incidences of the pattern of major diseases, particularly in Westernized and industrialized countries around the world. On the one hand side, many (acute) infectious diseases are markedly decreasing, including bacterial, viral and fungal infections. On the other side, almost all chronic inflammatory diseases are sharply increasing at the same time. This includes allergies and asthma as well as autoimmune diseases, regardless whether they are belonging to the group of systemic autoimmune disorders or organ-specific diseases. The question arises, whether this is just a coincidence or if this is the result of a cause-effect relationship.

The clinical manifestation and development of the phenotype of autoimmune diseases is strongly dependent on a marked dysregulation on the level of innate and adaptive immune responses. More recent data also indicate that the peripheral nervous system seems to be also involved in triggering the initiation and effector phase of chronic inflammatory conditions. These imbalances in both, the immune and nervous system, are the result of a complex interplay between a genetic disposition and environmental factors. Particularly regarding the development of the immuno-pathogenesis of autoimmune diseases, major advances have been made over the last two decades (Figure 1)

Figure 1. Development of autoimmunity depends on gen-environment interactions

A major breakthrough in the understanding of the importance of adaptive immunity in this context was the development of the so termed "TH-1/TH-2 Concept" which had been developed about two decades ago. The development of such distinct T-cell subsets has been originally described in the mouse and could be later also extrapolated and proven in the human immune system.

The phenotype of these T-cell subpopulations is defined by the cytokine pattern secreted by such T-cells. A leader-cytokine of TH-1 T-cells is interferon γ (IFN-γ), whereas TH-2 cells are defined by the secretion of IL-4, IL-5, IL-9 and IL-13. These T-cells play an important role in the regulation of normal immune functions (Figure 2).

- Normal Functions -

TH-1	TH-2	TH-3
• many bacterial, viral, fungal and protozoic infections	• helminthic infections	• (oral)tolerance
• anti-tumor immunity	• successful pregnancy	• successful pregnancy
• IgM, IgG	• IgA, IgE	• IgA

Figure 2. Normal functions of T-cell effector subsets

TH-1 T-cell responses are needed to defend many infections, including bacterial, viral, fungal and protozoic infections. These cells also have anti-tumor activities, and regulate the production of IgG and IgM isotypes. In contrast, TH-2 cells are needed to defend helminthic infections, they play an important role in maintenance of successful pregnancy, and they induce isotype-switching towards IgE and IgA (Figure 2).

The next important advancement in this field was the discovery that such T-cell responses are out of balance in many chronic inflammatory diseases. An enhanced or augmented TH-1 response profile was identified in many organ-specific autoimmune diseases, but also in other clinical conditions (Figure 3)

- role in disease -

TH-1	TH-2	TH-3
• organ-specific autoimmunity	• atopic disease	?
• contact dermatitis (typ IV allergy)	• systemic sclerosis	
• psoriasis	• progression to AIDS	
• M. Crohn	• chronic CvHD	
• allotransplantat rejection	• Omenn's syndrome	
• Helicobacter pylori		
• artherosclerosis		

Figure 3. The role of TH-1 and TH-2 T-cells in human disease

Originally the concept has been put forward that the dysregulation on the level of TH-1 and TH-2 immunity is just a matter of balance between these two distinct subpopulations. However, it now becomes clear that this is not the case under all circumstances. In contrast, the presences of TH-1 or TH-2 T-cell effector responses in diseases are regarded as an imbalanced inflammatory response. This leads to the

question: What are the control mechanisms to prevent or inhibit an existing TH-1/TH-2 dysbalance? In previous years it was difficult or even impossible to identify "immuno-suppressive" T-cell responses. This has led to a great conflict among leading immunologist whether such immuno-supressors are existing at all and how they could work possibly. More recently now, due to new technologies and major advancements in the field of T-cell effector responses, this concept of anti-inflammatory T-cell activities are being observed in a new light. The hallmark in this context was the identification of a new T-cell subset producing two important anti-inflammatory cytokines, namely IL-10 and TGF-β. This T-cell subset is now being termed as "regulatory T-cells" (Figure 4). Further advancement in this field indicates that there are several distinct subgroups of regulatory T-cells. Regulatory T-cells have been identified within the CD4, but also the CD8 compartment, and even more recently a subset of NK-T-cells has been shown to possess also regulatory T-cell activities. In general, there are two major sources of regulatory T-cells. One group originates in the thymus. On the other hand, under certain conditions, regular T-cells can also develop in the periphery.
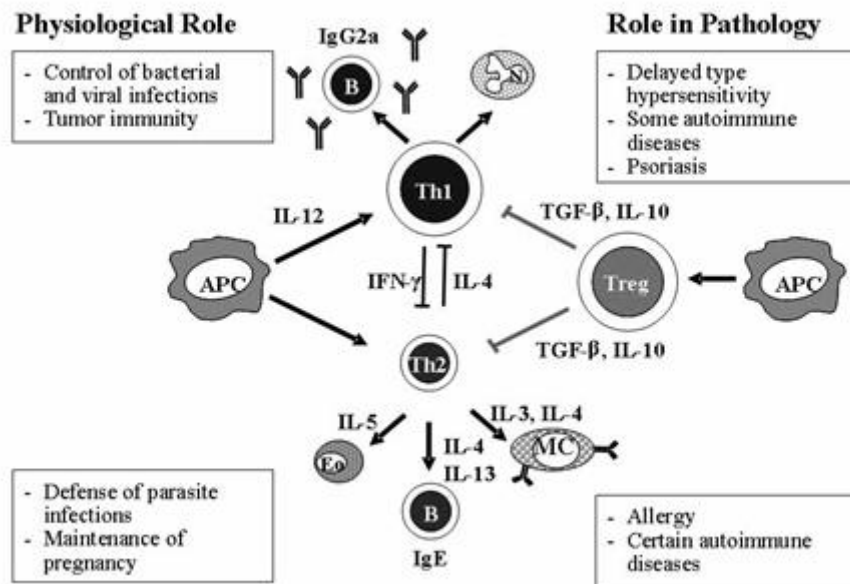

Figure 4. Control mechanism of the TH-1/TH-2 effector response

The development of pro- as well as anti-inflammatory T-cell subsets is strongly dependent on the instruction by the innate immune system. In this regard, dendritic cells (DCs) play a decisive role. Whereas immature DCs are excellent antigen presenters, it is the job of mature DCs to instruct and activate T-cells. When immature DCs present antigen to native T-cells, normally these T-cells become deleted or anergic.

This is an important pathway for the development of clinical tolerance. Under normal conditions, activation of T-cells by mature DCs results either in desired and wanted immunity or in autoimmunity

This depends on the level and strength of cross-reactivity of the presented antigen with

self. If the presented antigen does not cross-react with self, immunity results as a consequence of T-cell activation and these T-cells can then develop into normal TH-1 or TH-2 effector T-cells. In contrast, if the presented antigen shows cross-reactivity with self proteins, then the result would be autoimmunity. Dependent on the level of cross-reactivity, these autoimmune responses are either transient or stable. What type of antigens is potentially cross-reactive with self? In this regard, two concepts have been independently developed. On the one hand side, molecular mimicry in the case of an infectious disease seems to be important. On the other hand, bystander activation might be an at least as important mechanism to induce an autoimmune response. Such bystander activation can occur when an immature DC recognizes microbial patterns through their toll-like receptors. When this immature DC presents a self peptide, no further T-cell activation occurs. In contrast, if the immature DC receives additional activation signals through toll-like receptors (viral or microbial components), unwanted activation of such an autoactive T-cell might follow.

This novel concept may explain why autoaggression can be induced and triggered in the presence of microbial antigens.

The development of regulatory T-cells is absolutely necessary in order to control and prevent the development of chronic inflammatory conditions. These T-cells play an important role in the development of "clinical tolerance". It is well known that the development of clinical tolerance is an active immune mechanism, requiring antigen contact. This process starts already prenatally through the presentation of antigens via the placental barrier to the foetal immune system. However, this is a life-long process which must be maintained at any time. Clinical tolerance is strictly T-cell dependent, and a variety of molecular mechanisms are involved. One major mechanism already starts in the thymus, where potentially autoreactive T-cells are being deleted (Figure 5).
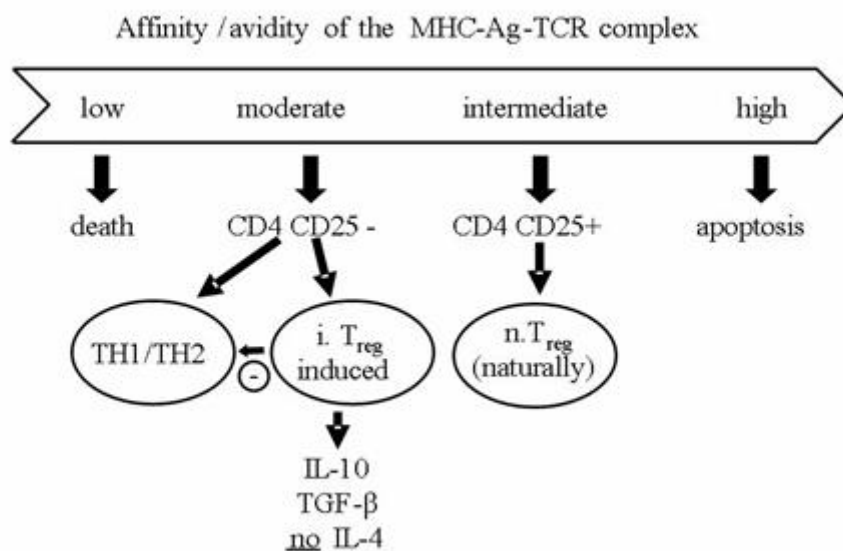

Figure 5. Thymic derived T-cell subsets

However, this process of central deletion is not complete and allows the escape of some autoreactive T-cells into the peripheral immune system (Figure 6). Here in the periphery, the fate of these T-cells strongly depends on the presence of mature or immature DCs, triggering these cells in a wanted or unwanted fashion.

nat. T_{reg} (naturally occurring)

- CD4 CD25+
- ca. 10 –12 % of CD4 CD25+ in blood/LN
- expression of CD38 (~50%); CTLA -4 (~50%)
  Fox p3
  CD62L (L-Selectin)
  CD45RB^{low}
- absence of   IL-2, CD40L
  CD28, CD80(86)
  Stat5a - /-
- supression depends on activation of T-cells through CD3

Figure 6. Characteristics of naturally occurring regulatory T-cells

In this regard, the presence of regulatory T-cells is absolutely essential. One experiment of Nature, where patients lack regulatory T-cells due to mutations in critical genes, illustrates the importance of this T-cell population. These immuno-deficiency syndromes are either termed as the x-linked autoimmunity-allergic dysregulation syndrome (XLAAD) or as the immune dysregulation polyendocrinopathy, enteropathy and x-linked inheritance syndrome (IPEX). In both diseases, patients developed simultaneously severe autoimmune phenotypes, together with allergies.

It will be important for the future to design new modes of immuno-intervention and immuno-prevention, based on this novel concept of immuno-regulation in chronic inflammatory disease. There might be several avenues to strengthen the development of regulatory T-cells and, therefore, the development of "clinical tolerance". Particularly early in life, the exposure to a variety of microbial compounds seems to be necessary for shaping the tolerance programming. This concept receives currently some support through clinical and experimental studies, investigating the potential of so termed "probiotics". However, until now it is too early to utilize this knowledge for clinical interference. Major research is currently under way to design and to develop new modes of prevention and treatment of autoimmunity based on this concept.

Literature

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