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AUTOIMMUNITY, AUTOIMMUNE DISEASES AND LYMPHOPROLIFERATIVE DISORDERS

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The existence of close relationships between autoimmunity, autoimmune diseases and lymphoproliferative disorders is a recurrent *leitmotiv* in both hematology and immunology. Recent developments in the pathophysiology of B cells make now timely to revisit the connections between autoreactive and transformed B lymphocytes.

The normal B cells that are *at risk* for malignant transformation have at least one of three features:[1,2] 1) high proliferative activity; 2) important DNA remodelling including immunoglobulin (Ig) and T cell receptor rearrangement, Ig switch and somatic mutations; 3) extended survival, i.e. lack of or reduced apoptosis. Virtually all normal B cells are *at risk* of becoming autoreactive, i.e. capable of making pathogenic high affinity autoantibodies (Abs). The risk is inherent in the mechanisms that lead to the generation of Ab diversity.[3,5] Suffices to a B cell producing polyreactive, low affinity Abs to self antigens (Ag) to undergo the process of somatic hypermutation that occurs in germinal centers (GC) of secondary follicles to generate anti-self high affinity autoAbs.[6] Immunoregulatory mechanisms must be continuously operating to prevent the generation of high affinity anti-self B cells.

What are epidemiology and clinics teaching us?

It is reasonable to start by addressing three clinical questions: 1) do lymphoproliferative disorders occur with increased frequency in autoimmune diseases? 2) do autoimmune diseases occur with increased frequency in lymphoproliferative disorders? 3) does autoAb production, irrespective of the development of autoimmune diseases, occur with increased frequency in lymphoproliferative disorders?

Epidemiological surveys are muddled by differences in median follow-up of the patients and frequently also by differences in accuracy of diagnosis. Taking into account the methodological difficulties, it is fair to state that monoclonal gammopathy of undetermined origin (MGUS), multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL) are the most frequent lymphoproliferative disorders encountered in autoimmune diseases and that Sjögren's syndrome (SS), rheumatoid arthritis (RA), chronic active hepatitis and thyroiditis are the autoimmune diseases where these lymphoproliferative disorders occur with increased frequency.[7,10] The relative risk of NHL in SS is increased up to 30-40× and the frequency rises to 300× after neck irradiation for parotide swelling.[10] The increased risk of NHL, MGUS and myeloma is 2-3× in RA.[7] Again, the accuracy and extent of diagnosis is essential: 6% of RA patients have a MGUS if monoclonal paraproteins are assessed by immunofixation.[11]

Surprisingly, while lymphoproliferative disorders have a frequency that ranges from appreciable to significant in RA and SS, there is no evidence for an association with systemic lupus erythematosus (SLE), the prototypic systemic autoimmune disease. Although several anedoctical cases of NHL have been reported,[12] controlled studies in large series fail to reveal a statistically significant association;[13,14] SLE is usually clinically quiescent at the time of diagnosis, and may antedate, follow or be coincidental with the diagnosis.

A number of factors are advocated to explain the development of lymphoproliferative disorders in autoimmune diseases. First, it is possible that viral infections associated with immunodeficiency may play a causative role as in

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mixed cryoglobulinemia-HCV related[15] and in HIV infection, where vasculitis, Sjögren's syndrome, NHL and also MM are frequently observed.[16] The quest for a hidden retrovirus in SS (reviewed in ref. 17) has provided a number of indirect evidences, but no formal proof has been insofar obtained. Second, the continuous use of immunosuppressive and cytotoxic drugs may explain some cases, even if it remains to be clarified why this should happen in selected autoimmune diseases and spare SLE. Third, it is not unreasonable to postulate that chronic antigenic stimulation may favour the development of lymphoproliferative disorders as witnessed by the natural history of plasma cell tumors which are known to occur in association with chronic infections.

The case of B-chronic lymphocytic leukemia

If epidemiological data are taken to explore the other side of the coin, i.e. which autoimmune diseases most commonly occur and in which lymphoproliferative disorders, it clearly emerges that the lymphoproliferative disorder characterized by the development of autoimmune diseases is B-chronic lymphocytic leukemia (B-CLL).[18,19] Over the course of the disease, 20-25% of the patients develop either autoimmune hemolytic anemia (AHA) or autoimmune thrombocytopenia (ATA).

A still unexplained observation is that, in the vast majority of cases, the autoAbs are polyclonal and are thus not secreted by the malignant clone.[19] The assumption is that these pathogenic autoAbs are produced by bystander B cells as a consequence of the immune dysregulation that occurs in B-CLL patients. The speculation is that they are produced against self-Ag processed by the malignant B cells. Every explanation has to cope with the fact that the pathogenic autoAbs observed in CLL have a striking predilection for hematopoietic Ag.[18,19] Indeed, the vast majority of autoimmune diseases which occur in lymphoproliferative disorders, including the sporadic cases observed in NHL and HL, are blood-cell organ-specific diseases. Two relevant exceptions are HCL, where in about 5% of the cases panarteritis nodosa (PAN) may develop[20] and hematologic neoplasms after the administration of α-interferon (α-IFN). In these patients α-IFN may lead to the appearance of anti-DNA autoAbs and even clinical manifestations of SLE have been recorded.[21] It has still to be elucidated whether these events reflect the modifications of the immune system induced by α-IFN or the fact that CD21, the Epstein-Barr virus/complement C3d receptor (R), is also an α-IFN R.[22]

In several B-CLL patients circulating monoclonal paraproteins with rheumatoid factor (RF) activity are found and the monoclonal Ig on the cell surface may have either a RF activity or a specificity for a variety of autoAg.[23] Further, in more than half of the CLL patients the leukemic cells can be stimulated to secrete polyreactive Abs.[24] These autoAbs do not cause autoimmune manifestations.

The paraproteins of 10-15% of patients with monoclonal gammapathy have autoreactive Ab activity.[25,26] RF activity, DNA-binding properties and a whole variety of autoAbs have been described in MM and Waldenström macroglobulinemia (WM).[27] In WM, autoAbs to myelin-associated glycoprotein, gastric parietal cells and red blood cells may lead respectively to peripheral neuropathy,[28] macrocytic anaemia or AHA. The vast majority of autoAbs in monoclonal gammopathies, nevertheless, do not cause apparent autoimmune clinical manifestations and, of interest, they are frequently polyclonal.

No chromosomal, nor oncogene abnormalities have been insofar detected in autoimmune diseases. Still, the susceptibility to develop B cell malignancies or autoimmune diseases is genetically associated: 18 cases of autoimmune diseases (pernicious anaemia, RA, SLE) have been recorded among 320 relatives of 28 B-CLL patients.[29] Also, the incidence of autoAbs, irrespective of the development of autoimmune diseases, in first-degree relatives of patients with WM, CLL, MM and MGUS is greater than in the control populations.[30]

The problem of CD5+ B cells

As B-CLL is regarded as a malignancy of $CD5^+$ B cells,[31] recently renamed B1 cells,[32] $CD5^+$ B cells emerge as a crossroad between

malignant and autoreactive B cells.

A monoclonal expansion of $CD5^+$ B cell subset is a feature of B-CLL, mantle zone (MZ) lymphoma and WM.[31,33] A polyclonal expansion is observed in systemic autoimmune diseases like RA, SS, systemic sclerosis and, occasionally, also SLE.[31,33] There are not yet enough data to establish whether this increase is of pathogenetic significance or whether it reflects the polyclonal B cell activation that occurs in systemic autoimmune disorders and might thus also affect the $CD5^+$ B cell subset. Were this the case, the role of $CD5^+$ B cells in the development of autoimmune diseases would be ancillary. A genetic influence has been shown to exist on the levels of circulating normal $CD5^+$ B lymphocytes,[34] but it has not yet been established whether high levels of normal circulating $CD5^+$ B cells may be a *predisposing* factor to the development of $CD5^+$ B cell malignancies or of systemic autoimmune diseases.

Normal $CD5^+$ B cells produce low avidity, polyreactive autoAbs predominantly of the IgM class (naturally occurring autoAbs), while the pathogenic autoAbs are usually of IgG class, monoreactive and of high affinity.[33, 35-37] The precise role of naturally occurring autoAbs is yet undefined: they might be a first line of defence against offending microorganisms (and perhaps also against self Ag?) and/or involved in the clearance of cell debris and/or involved in the organization of an idiotypic network.[33,35-37] Likewise unclear is the fate of normal $CD5^+$ B cells that produce natural autoAbs. As $CD5^+$ B cell VH and VL genes are mainly in germ-line configuration, it is not unreasonable to postulate that they might act in primary responses with little GC formation and restricted somatic mutations. It is nevertheless possible that a proportion of these cells enter GC, switch from IgM^+ to IgG^+ B cells and undergo the somatic mutations that lead to the production of high affinity Abs.[6,33,37]

The cytokines that regulate the size of the $CD5^+$ B cell pool have been partially explored. IL-1 and IL-2 are able to downregulate CD5 expression in purified $CD5^+$ B cells[38] and a number of stimuli can induce the surface expression of CD5 by $CD5^-$ B cells.[39] A potentially relevant cytokine is IL-10, which has a role in the development of murine $CD5^+$ B cells.[40] Contradictory data have been obtained in humans, where IL-10 in vitro appears to induce apoptotic death of B-CLL cells,[41] to prevent the spontaneous death of GC cells[42] and is spontaneously produced by B lymphocytes and monocytes in SLE.[43]

Apoptosis, B cell malignancies and autoimmunity

A number of genes and molecules that control apoptosis have been described and their role in the natural history of lymphoproliferative disorders is now appreciated.[2] A number of observations suggest that the extended survival of relevant cells by prevention of apoptosis may also be of importance in the development of autoimmune diseases. The SLE murine models lpr (lymphoproliferation) and gld (generalized lymphadenopathy), that develop a progressive SLE-like autoAb disease, have called the attention upon the Fas gene.[44] Murine Fas gene[45] and its human homologue APO-1[46] encode for a surface protein of 35kd that has a structural homology to the R for tumor necrosis factor (TNF-R), to the low-affinity R for nerve growth factor and to the B-cell surface molecule CD40 and mediates a pathway for apoptosis.[44] Mice homozygous for lpr have either a genomic deletion or a point mutation of Fas gene and fail to produce a functional protein.[44] The stimulation of Fas protein causes the apoptotic death of the target cells, while the lack of a functional Fas appears to lead to the emergence and accumulation of auto-reactive lymphocyte populations that would normally be deleted.[44-46] Even if no consistent defect in the expression or function of Fas has been detected in peripheral blood cells of SLE patients,[47] a soluble (s) form of Fas has been identified in approximately 60% of patients with SLE, but not in RA.[48] sFas has been shown to inhibit Fas-mediated apoptosis in vitro and mice injected with sFas presented altered lymphocyte development and an increased proliferation in response to self Ag.[48] The functional role of other soluble molecules like sTNF-R[49] and sCD30,[50] recently detected in SLE, is under investigation.

Bcl-2 gene[51] encodes for a 25kd intracellular

protein, whose function is to inhibit apoptosis as shown in a variety of in vitro and in vivo situations.[52,53] The Bcl-2-induced extended survival of malignant cells is central to the pathogenesis of several malignant lymphomas. The Bcl-2 gene was identified at 18q21 when the chromosomal breakpoint of t(14;18) translocation in follicular lymphomas was mapped.[51] The translocation of Bcl-2 gene from chromosome 18 to chromosome 14 gives rise to high levels of chimeric mRNA. Bcl-2 gene product is overexpressed in B-CLL cells;[54] Bcl-2 levels in these cells do not reflect a rearrangement of Bcl-2 gene, neither a gene amplification, nor a Bcl-2 mRNA prolonged half-life and are instrumental in inhibiting the apoptosis and leading to the relentless accumulation of B-CLL cells frozen in G0.[55] Bcl-2 and Fas gene expression are inversely regulated in lymphoid cells, whose propensity to apoptosis appears to be finely tuned, at least in part, by the balance between these two gene products.[56] Some, but not all, strains of transgenic mice that overexpress Bcl-2 develop a lethal SLE-like autoimmune disease.[57]

Another mechanism where apoptosis links autoreactivity to malignant B cells has been recently described in a variant CD5- B-CLL cell population that had RF activity specific for IgG and produced RF autoAbs. The in vitro addition of autoAg (aggregated human IgG) inhibited apoptosis and significantly enhanced the survival of malignant B cells.[58]

All these data suggest that the genes that control apoptosis play a significant role in the genetic background of systemic autoimmunity[59] and might affect the lymphoid cell compartment by preventing the death of autoreactive cells. They also suggest that the production of polyreactive autoAbs by malignant B cells (mostly of the CD5 lineage) might be a system that malignant cells use to survive by cheating the immunoregulatory mechanisms of defense. Malignant $CD5^+$ B cells might be a two-edged sword. On one side they would present self-Ag to bystander B cells and lead them to produce the high affinity pathogenic autoAbs responsible for autoimmune diseases. On the other side, their monocloal surface Ig may have a reactivity to self Ag: the possibility exists that the interactions between self Ag and surface autoAbs prevent the apoptosis of malignant cells and lead to their accumulation.

According to a recent observation,[60] it is not unlikely that the mechanism of apoptosis may also affect autoAg-presenting cells, by causing the clustering of potentially immunogenic cellular components in different apoptotic blebs.

Conclusions

Lymphomagenesis is a multi-step process that starts in BM progenitors and involves oncogene abnormalities and possibly also Ag stimulation. Autoimmunity is likewise a multistep process that requires the break of the tolerance and the overcome of or the sneaking trough immunoregulatory mechanisms. It is not unlikely that early BM precursors have some alterations also in autoimmune diseases. Pre-B cell lines established from fetal liver of $(NZB \times NZW)F_1$ mice and injected into SCID mice have led to the development of an SLE-like autoimmune disease[61] and a murine model of SLE has been successfully transferred by BM transplantation (T).[62] In humans, as recently reviewed,[63] autoimmune diseases have been inadvertently transferred to the recipient by BMT and resolution of pre-existing autoimmune diseases has followed allogeneic BMT.

The roads to lymphomagenesis or to systemic autoimmune disease appear to go in parallel with only occasional cross-over. There are two major exceptions: B-CLL and SS. It is likely that the investigation of the cellular origin and the immune disregulation that occur in B-CLL and of the differential mechanisms that underlie the development of SS vs. SLE may yeld important advances in the understanding of autoreactive and transformed B cells.

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