Editorial

Metalloproteininas and specific inhibitors in multiple sclerosis: from blood to brain or vice versa?

During the last two decades the understanding of the molecular basis of antigen capture, processing, presentation and recognition has grown enormously, and it is everyone’s hope that the knowledge of specific tolerance induction, molecular mimicry, epitope spreading and auto-antibody formation will be translated into better treatments for autoimmune diseases. However, if one examines current treatments with proven usefulness in multiple sclerosis e.g. corticosteroids, β-interferon and copolymer-1, it can be seen that these are all indirectly linked to the above concepts and are nonspecific immunologically. This observation is important for the multiple sclerosis society because it should not only catalyse further research into developing immunologically specific treatments, but also stimulate those who envisage that inducible cytokines, chemokines and enzymes might constitute important nonspecific targets for treatment.

Inflammatory reactions, including those observed in autoimmune diseases such as multiple sclerosis, are triggered. The interplay between possible aetiological agents, the immune system and the genetic constitution of the host has been evaluated in prototypic studies and in animal models of autoimmune diseases. For example, many researchers attempted to associate viral or other microbial infections with multiple sclerosis, to define elements of the specific arm of immunity, i.e. autoreactive T-cell clones or antibody specificities, to decipher the role of disease-promoting or disease-limiting cytokines and to determine by genome scanning studies the genes involved in multiple sclerosis. None of these single elements can explain fully the pathogenesis of multiple sclerosis, but it is increasingly appreciated that the interplay between these different factors is crucial in vivo and might be a suitable target in the fight against multiple sclerosis. The interactions between nonspecific effector molecules of leucocytes and other cells involved in immune reactions, namely cytokines, chemokines, proteases, inhibitors and antigenic peptides, were viewed as being likely to have practical consequences for the multiple sclerosis patients (Opdenakker and Van Damme, 1994). This issue of Brain contains such an application-oriented report (Lee et al., 1998). These authors combined clinical, MRI-data and laboratory findings, tackled the issue of the balances between proteases and inhibitors (the ‘protease-load’) and described relevant means for patient stratification.

In vivo veritas

Basic aspects of the biochemistry and biology of matrix metalloproteinases (MMPs) (Yong et al., 1998) and in particular gelatinase B (MMP-9) (Collier and Goldberg, 1998) have recently been summarized. The involvement of gelatinase B in human diseases has been suggested by association studies (for example, see Lee et al., 1998). This enzyme has also been studied in animal models of experimental autoimmune encephalomyelitis (Gijbels et al., 1993; Matyszak and Perry, 1996). In addition, EAE inhibition studies with aselective inhibitors of serine proteases (Brosnan et al., 1980) or metalloproteases (Gijbels et al., 1994; Hewson et al., 1995) generated hope for the therapy of multiple sclerosis. However, it remains crucial to think of Claude Bernard’s milieu interieur, which warns us that nature often provides intrinsic compensatory mechanisms (feedback control, balances between proteases and inhibitors). Indeed, the spatiotemporal evolution of both proteases (tissue plasminogen activator, collagenase, stromelysin-1, gelatinase A and B) and the inhibitors (PAI-1, and TIMP-1) has been documented in multiple sclerosis lesions (Cuzner et al., 1996). These findings are now complemented by Lee and co-workers, who illustrate on a quantitative basis that dysregulation of gelatinase B and TIMPs (measurable in the circulation) may play a role in multiple sclerosis. However, more details about the TIMP species and larger population studies with quantitative data (on serum and CSF enzyme and inhibitor levels) in disease evolution are needed before embarking on clinical trials for multiple sclerosis with, for instance, a specific form of recombinant TIMP. Indeed, what would be the benefit of injecting exogenous TIMP if the host already produces large amounts of this inhibitor?

L’union fait la force

Unification always constitutes a bonus in science. Bringing together data on a protease and its inhibitor is such an example. The report by Lee et al. contains another bonus: it brings laboratory technology to the clinic. The establishment of sensitive assay systems to detect disease markers in serum (even when nonspecific) yields compliance for the patient and enhances clinical research possibilities. However, every researcher acknowledges that a scientific work is never perfect. Also many questions remain unanswered in this study and constitute challenges for future work. For instance,
from the methodological standpoint, immunotests do not yield information about enzyme and inhibitor net bioactivity, and might capture inactive degradation fragments and latent pro-enzymes as well as activated enzyme forms. Gelatin substrate zymography has a sensitivity for gelatinases in the picogram range and furthermore gives insights about the activation status of the enzymes. Specific probes that discriminate between active and latent enzymes and TIMP–enzyme complexes will further delineate the role of this enzyme–inhibitor pair in multiple sclerosis. Alternatively, sensitive assays that measure the net activity of gelatinases may be used (St Pierre et al., 1996). From the biological viewpoint it is important to evaluate in the future the prognostic value of the immunotests by correlating them with the clinical manifestations. For example, patients with rheumatoid arthritis will presumably also have increased net gelatinase B levels (and a trend towards decreased TIMP) in the circulation during the active stage of the disease. In other words, the disease-specificities of the described tests are predictably low, but obviously within a patient population they remain relevant.

Another question relates to the cell types producing serum gelatinases and TIMPs. Analysis of paired samples of CSF and serum might yield information on whether the molecules are originating in the blood or the CNS and eventually whether the blood brain barrier plays a role. Different leucocyte types, including T cells (Weeks et al., 1993), produce gelatinase B variants with discrete biochemical differences (truncation, glycosylation, complex formation under non-denaturing and denaturing conditions). The biochemical analysis of such purified enzyme variants will help to define the producer cell types. As illustrated in the study by Lee et al., driving technology, critical evaluation of patient populations and assembly of the pieces of the multiple sclerosis autoimmunity puzzle into a coherent picture is crucial to the development of new treatment strategies against multiple sclerosis.

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References


