Chapter 6

Autoimmune Inflammation and Multiple Sclerosis

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Inflammation and Multiple Sclerosis

The term inflammation was first used as a gross description of the redness of the skin observed at sites of injury. Later it was discovered that the redness was the natural result of blood vessel physiology. Now we know that the blood vessels are only one of the many factors involved in inflammation, a process in which immune cells of various types and their molecular products interact with signal molecules produced by the injured tissue.

There are different ways to view the roles of inflammation, depending much on the aspect of your view. Lord Florey quotes Ebert who proposed that "inflammation is a process that begins following a sublethal injury to tissue and ends with complete healing" [1]. Florey invoked Ebert to stress the idea that "inflammation is a process and not a state. The inflamed area undergoes continuous change." Inflammation, in Florey's view, is a process that is initiated by injury and aims at healing. What then is the role of inflammation in multiple sclerosis (MS), particularly the inflammation caused by autoimmunity?

Healing is not the traditional role assigned to inflammation in MS. On the contrary, inflammation is seen as the cause of MS; autoimmunity to myelin triggers aberrant inflammation, and this inflammation injures the white matter of the central nervous system (CNS) producing MS. Inflammation, even physiological inflammation, triggers the death of cells and the remodeling of tissue [2]. Cell death and scar formation is decidedly not good for the CNS; indeed, immune privilege may have evolved to isolate the CNS from inflammation of any kind [3]. Inflammation in the CNS, even if bent on healing, may complicate rather than cure disease. Is inflammation then the pathogenic culprit in MS, or could it be a physiological healer of MS?

We are now beginning to appreciate the molecular complexity of inflammation and its spectrum of manifestations; inflammation activates genes and makes some cells die, some cells move, and some cells proliferate and differentiate [2]. Inflammation remodels connective tissue and triggers angiogenesis and vascular adjustment. Inflammation can be critical in inducing tissue regeneration; activated macrophages can even trigger regeneration of the injured CNS [4]. Inflammation, then, is not of one type; inflammation is a manifold agent for body maintenance. If this is really the case, we ought to consider the possibility that some of the inflammatory manifestations of MS are reparative, and not all

bad. The problem, of course, is to sort out the good from the bad. In either case, blind immunosuppression is likely to disable the good along with the bad.

Autoimmunity and MS

Autoimmunity refers to a process in which the antigen receptors of lymphocytes are capable of recognizing antigens in the individual's healthy tissues [2]. Because autoimmunity requires antigen receptors, the phenomenon of autoimmunity is a property of the adaptive arm of the immune system. Inflammation, however, is the outcome of the activation of both the innate and adaptive arms of the immune system; the cytokines and other molecules that orchestrate inflammation are produced both by the adaptive T cells and B cells and by the innate leukocytes [5]. The role of autoimmunity in MS is thus related to the role of inflammation in MS.

Autoimmunity used to be equated with disease; it was inconceivable that healthy individuals might harbor autoimmune lymphocytes in their immune systems [6]. The immune system was viewed as a defense system only; a system that attacked whatever molecules it might be able to recognize. Such a system could only live in peace with the body if the system were purged of antigen receptors capable of self-recognition. Autoimmune disease, therefore, was imagined to erupt whenever an autoimmune lymphocyte accidentally appeared. Autoimmunity could never be up to any good.

This classic concept of autoimmunity is logical, but it does not comply with the facts; autoimmune B cells are common in every body housing an adaptive immune system [7, 8], yet most bodies show no evidence of autoimmune disease. Moreover, the activation of autoimmune T cells can contribute to maintenance of the body. My colleagues and I have shown that lines and clones of T cells reactive to myelin can cause the MS-like disease – experimental autoimmune encephalomelitis [9]. However, these same T cells were found to mediate neuroprotection when applied to the models of CNS white matter injury developed by Schwartz and colleagues [10-12]. Inflammatory processes involving autoimmune T cells, like those mediated by innate leukocytes [4], can promote healing [10, 11]. Moreover, autoimmune T cells that recognize myelin seem to be activated as a matter of course in CNS injury [13]. Thus we return to the questions of cause and effect; is the activation of autoimmunity observed in MS a result of the disease, or is activated autoimmunity the cause of disease?

Causality and MS

The problem with the cause-and-effect questions is that neither inflammation nor autoimmunity are intrinsically good or bad; the outcomes of inflammation and of autoimmunity depend on the circumstances. Sometimes these processes are beneficial and sometimes they are detrimental. So we cannot reduce MS to CNS white matter autoimmune inflammation. MS emerges from

inappropriate interactions, not from faulty parts [2]. MS is a basket of reaction patterns; similar reaction patterns may be triggered off by different factors, such as viral infections, traumatic injury, stress, and so forth. Autoimmunity to myelin is built into the normal immune system physiologically; myelin autoimmunity is a part of the immunological homunculus [8, 14, 15]. The disease erupts when the autoimmune process is unleashed, by whatever insult, and when the process gets stuck in a mode of recurrent or chronic activation.

Treatment for MS

MS is a complex disease because both the brain and the immune system are complex systems. Indeed, inflammation and autoimmunity are complex manifestations of the immune system. So how are we to deal with MS? Ideally, it is usually more efficient and less costly in side-effects to go with nature, than against nature. If autoimmune inflammation has the capacity to heal, as well as harm, it might be useful to enlist the immune system itself to regulate the type, timing, site, and strength of inflammation that takes place in the patient. β-interferon is a modulator of immune inflammation and Copaxone also exerts multiple effects on the autoimmune response. T-cell vaccination was thought to work primarily by inducing anti-idiotypic regulation, but now we are discovering that T-cell vaccination actually affects the nature of the cytokines generated by the autoimmune response [16, 17 18, 19]. T-cell vaccination, thus, influences the nature of autoimmune inflammation.

Modulation of autoimmune inflammation, by whatever means, is likely to be more successful if it is instituted as early as possible in the course of the disease, before detrimental feed-back loops become entrenched. Moreover, we need convenient methods to monitor the state of the immune system and its response to treatment. Each patient, because of individual genetics and individual immune history, is likely to need different forms of treatment, doses, and dose scheduling to obtain an optimal therapeutic effect. The new bioinformatics might be deployed to stage the immune system and its response to therapy in MS and in other autoimmune diseases [2].

Acknowledgements. I am the incumbent of the Mauerberger Chair of Immunology and the Director of the Robert Koch-Minerva Centre for Research of Autoimmune Diseases. I thank Ms. Danielle Sabah-Israel for her help in preparing this manuscript.

References

1. Florey HW (1970) General pathology, 4th ed Lloyd-Luke, London, pp 22-39
2. Cohen IR (2000) Tending Adam's garden: evolving the cognative immune self. Academic Press, London

3. Schwartz M, Moalem G, Leibowitz-Amit, Cohen IR (1999) Innate and adaptive immune responses can be beneficial for CNS repair. Trends Neurosci 22:295-299
4. Schwartz M, Lazarov-Speigler O (1998) The role of immune system in central nervous system recovery: an evolutionary perspective. Curr Top Neurochem 1:123-132
5. Cohen IR (2000) Discrimination and dialogue in the immune system. Semin Immunol 12:215-219
6. Burnel M (1959) Self and not self. Cambridge University Press, Cambridge
7. Avarameas S (1991) Natural autoantibodies from "Horro Autotoxicus" to "Gnothi Seauton". Immunol Today 12:154-159
8. Cohen IR (1992) The cognitive paradigm and the immunological homunculus. Immunol Today 13:490-494
9. Ben-Nun A, Wekerle H, Cohen IR (1981) The rapid isolation of clonable antigen-specific T lymphocyte lines capable of mediating autoimmune encephalomyelitis. Eur J Immunol 11:195-199
10. Moalem G et al (1999) Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. Nat Med 5:49-55
11. Hauben E et al (2000) Autoimmune T cells as potential neuroprotective therapy for spinal cord injury. Lancet 355:286-287
12. Schwartz M, Cohen IR (2000) Autoimmunity can benefit self-maintenance. Immunol Today 21:265-268
13. Yoles E et al (2001) Protective autoimmunity is a physiological response to CNS trauma. J Neurosci 21:3740-3748
14. Cohen IR, Young DB (1991) Autoimmunity, microbial immunity and the immunological homunculus. Immunol Today 12:105-110
15. Cohen IR (1992) The cognitive principle challenges clonal selection. Immunol Today 13:441-444
16. Elias D, Tikochinski Y, Frankel G, Cohen IR (1999) Regulation of NOD mouse autoimmune diabetes by T cells that recognize a TCR CDR3 peptide. Int Immunol 11:957-966
17. Waisman A et al (1996) Suppressive vaccination with DNA encoding a variable region gene of the T-cell receptor prevents autoimmune encephalomyelitis and activates Th2 immunity. Nat Med 2:899-905
18. Zang YC, Hong J, Tejada-Simon MV, Li S, Rivera VM, Killian JM, Zhang JZ (2000) Th2 immune regulation induced by T cell vaccination in patients with multiple sclerosis. Eur J Immunol 30:908-913
19. Zang YC, Hong J, Rivera VM, Killian J, Zhang JZ (2000) Preferential recognition of TCR hypervariable regions by human anti-idiotipic T cells induced by T cell vaccination. J Immunol 164:4011-4017