doi:10.1006/jaut.2000.0481, available online at http://www.idealibrary.com on IDEAL® Journal of Autoimmunity (2001) **16,** 337–340

Antigenic Mimicry, Clonal Selection and Autoimmunity

Irun R. Cohen

Department of Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel

Key words: altered peptide ligands, antigenic mimicry, autoimmunity, receptors, specificity

The triggering of autoimmunity by infection or immunization is often blamed on antigenic mimicry. But the concept of antigen mimicry impinges on our understanding of adaptive immunity in general, and not only on autoimmunity. Here are some thoughts about the consequences of immune mimicry.

Pathogenic Antigenic Mimicry

Antigenic mimicry [1, 2] is an attractive concept for two reasons: it rests on a molecular truth and it seems to explain the origin of autoimmunity. The antigen receptors of T cells and B cells recognize antigens by the power of non-covalent fittings between their combining sites and epitopes on antigens. Since more than one epitope can be envisioned (and demonstrated) to fit any receptor combining site, any given antigen receptor can recognize more than one antigen; antigen receptors, like all biological receptors, are degenerate [3, 4]. Receptors are receptors because they can transduce signals into the cell; ligands alone have no intrinsic capacity to signal; no receptor, no signal. Therefore, from the cell's viewpoint ligands that activate the same receptor mimic one another biologically, no matter how the ligands may differ chemically. The immune system, like the endocrine and other signaling systems, tends not to fit to chemistry, so antigenic mimicry is a molecular fact [5, 6].

Mimicry also expresses an ideology. The classical formulation of the Clonal Selection Theory of Acquired Immunity (CST) teaches that the receptor repertoire must be purged of all antigen receptors that could possibly recognize self-antigens [7, 8]; autoimmunity is a theoretical impossibility according to the CST. Nevertheless, autoimmune diseases do occur, and they occur with regularity in the wake of certain infections, like group A strep, *Treponema pallidum, Borrelia burgdorferi*, some enteric infections, or various viruses. How can this regularity be explained? One reasonable explanation blames autoimmune disease on molecular mimicry between infectious agents and host self-antigens [9]. The host's repertoire, in keeping with the tenets of the CST, should be deleted of receptors that could be triggered by genuine self-epitopes, but an infectious agent can circumvent the deletion of anti-self clones and present the host with epitopes that mimic host epitopes. Although a natural self-epitope would never be able to find a fitting receptor on its own, the mimicking epitope selects and activates clones whose receptors are sufficiently degenerate to now see and respond to a host antigen. The immune system may not be allowed by the CST to engender self-recognition, but pseudo-self-recognition is allowed. Host-mimicry by infectious agents can explain the induction of autoimmune diseases, without seeming to violate the CST.

Altered Peptide Ligands: Medicinal Mimicry

What if pathogenic mimicry, as described above, has actually triggered pseudo-self recognition leading to an autoimmune disease; how are we to remove the offending clones? We can try to out-mimic them. Altered peptide ligands (APL) are benevolent mimics [10]. Autoimmune diseases, according to the CST, are diseases caused by self-reactive clones; whether the self-reactive clones have been activated by mimicry or arise by mutation, a reasonable cure is to inactivate the self-reactive clones by inducing tolerance or anergy, or to get them to otherwise change their behaviour. The specific key to any clone is its specific antigen. If the pathogenic clone recognizes a self-peptide, then the way to silence that clone is to tweak it with a pseudo-self-peptide that will anergize it or signal it to stop destroying the disease target. APL peptides are molecular mimics of self-epitopes that bind with an altered affinity to the clone's receptor. Varying the time the epitope spends in the T-cell receptor can greatly influence the behaviour of the T cell [11]. An APL with altered affinity might be able to neutralize the bad clone. APL peptides could thus be seen as mimicry medicine for mimicry disease.

Tel.: +972-8-934 2195. Fax: +972-8-934 4103. E-mail: Irun.Cohen@Weizmann.ac.il

0896–8411/01/030337+04 $35.00/0

The concept of the APL as a clonal anergizer has resulted in therapeutic trials designed to tolerize clones; APL trials, to neutralize every last autoimmune cell, have employed prolonged treatment with relatively high doses of APL. Unfortunately, such a therapeutic strategy can lead to undesirable side effects [12, 13]. The concept of antigen mimicry provides a way for the classical CST to explain autoimmune diseases, and antigen mimicry, through the APL, is proposed as a reasonable, CST-compatible cure. Rather than serving the CST, the concept of molecular mimicry actually undermines the CST.

Specificity Agonistes

Antigenic mimicry was thought to be primarily limited to epitopes that shared a noticeable degree of chemical similarity; one peptide could mimic another only if the two peptides did not differ too much in their amino acid sequences [14]. Indeed, arguments for mimicry are based on amino acid homologies retrievable from databases. Antigen agonists and antagonists were thought to share some familial chemistry that necessarily limited the promiscuity of antigen mimicry. But, as we mentioned above, the basic chemistry of receptors renders them ignorant of ligand chemistry; what fits, fits, irrespective of sequence and irrespective of self or not-self chemistry: affinity is the all. Sugars and peptides and nucleic acids, which share no chemical subunits, can mutually mimic, and can be seen to activate a given receptor [15].

The CST paradigm is accurate when it teaches that the adaptive repertoire is composed of a differential frequency of clones and that antigens are critical to the process by which clones, are selected. Unfortunately, the antigen receptors of clones cannot guarantee the antigen specificity required by the CST worldview. The problem for the CST is that antigen receptors are fundamentally degenerate, and this means that the specificity of the immune response is not granted automatically by an act of clonal selection. The degeneracy of antigen receptors also means that clonal selection cannot be entrusted to absolutely discriminate between self and not-self epitopes [16, 17]. The phenomenon of antigen mimicry proclaims this conclusion loud and clear, the CST notwithstanding. Clonal selection pushes the millstone of immunity, while suffering from a lack of visual acuity. Specificity is the central pillar of adaptive immunity; how does the immune system keep the edifice from crashing onto the self?

Specificity Emergent

Although individual clones can be demonstrated to be less than specific, the immune response, at the population level, is manifestly specific. Witness the exquisite specificity of an antiserum compared to the degeneracy of the individual clones that comprise the serum. Hypersensitivity reactions, immediate and delayed, can discriminate between very closely related antigens. Graft rejection is specific. Acquired resistance to infectious agents is reasonably specific. Specificity emerges in polyclonality at the level of the whole system; specificity is a collective effort. But how can a population of clones act specifically, if each of the clones are intrinsically degenerate, if specificity cannot be reduced to the individual clones underlying the response?

In principle the answer is known, but at a deeper level the answer is a mystery.

Immune specificity is not unique in its complexity or in its resistance to a simple analytical strategy. The specificity of signal transduction is even more complicated than immune specificity; the path from a specific membrane receptor to the activation of a specific gene is mediated by a bewildering network of redundant and degenerate signal transduction molecules. The specificity of signal transduction, like that of immune reactivity, emerges from a pattern of collective interactions [18]. Emergent properties are precisely those behaviours manifested by a system when it operates as a whole; an emergent property is not evident in any particular component of the system when we examine each part individually. We can therefore answer the riddle of immune specificity, despite antigen mimicry, by invoking emergence; we can say that the precision of immune specificity is an emergent property of the immune system, and not an intrinsic property of this or that degenerate clone examined on its own. The specificity of the immune response is created by the immune system downstream of the initial antigen recognition [17–19].

The emergence of specificity by a degenerate and redundant central nervous system is a manifest example of the inadequacy of reductionism; any colour-sighted person can see the power of emergence with his or her own eyes. Each of us can easily discriminate thousands of different colours, yet our retinas contain only three types of colour receptors: red, green and blue. How can only three different receptors make thousands of discriminations? They can do it because each of the receptors is degenerate; each responds with high ‘affinity’ to only a few wavelengths but also with lesser ‘affinity’ to many other wavelengths. The important feature is that the degeneracy of the colour receptors overlaps from one receptor to another; different receptors can be activated by the same coloured light. This redundant and degenerate arrangement allows the three receptors to generate complex patterns of signals, which are sent to the brain. The brain, in turn, discriminates between thousands of different patterns (all emanating from different combinations of the three colour receptors) and interprets the different patterns as different colours [18]. Obviously, the immune system does not have a brain to read different clonal patterns, and that is the mystery. We simply don’t know how the emergence of immune specificity works in molecular terms. But this lack of understanding does not justify a blind insistence on clonal specificity as the only basis for antigen discrimination; antigen mimicry proves

otherwise. The challenge to immunology is to explain mechanistically how antigen specificity is created by the system despite the degeneracy of the individual clones that constitute the repertoire.

Autoimmunity, Mimicry and Disease

Let us return to the theme of the symposium: autoimmune disease and its induction by infection. What does infection contribute to autoimmunity and to autoimmune disease? Despite the tenets of the CST, we don't need pseudo-self antigen mimics to generate self-recognizing clones of lymphocytes; the healthy immune system is filled with them at the outset [20, 21]. Autoimmunity is built into the system, and natural autoimmunity appears to serve the individual. Inflammatory molecules and signals are essential for wound healing, angiogenesis, regeneration, neuroprotection and other maintenance functions, and the adaptive, as well as the innate arm of the immune system, is involved in regulating the physiological inflammation required for body maintenance [17, 18, 22]. The adaptive arm of the immune system maintains the body by way of physiological autoimmunity to certain key self-antigens, what has been called the immunological homunculus [20, 21].

Infectious agents can trigger the transition from benign autoimmunity to autoimmune disease by providing accessory or adjuvant signals along with the self-antigens that may be intrinsic to the infected tissue, or supplied by the agent as self-antigen mimics. It is not the self-antigen that causes the disease, but the adjuvant signals produced by the infectious agent that get appended to a key self-antigen [23]. This is clearly evident in many experimental autoimmune diseases. Immunizing experimental animals with myelin basic protein alone will not usually induce experimental autoimmune encephalomyelitis (EAE); the self-antigen is most dangerous when injected along with the complete Freund's adjuvant that mimics an accompanying infection [24]. A real infection can also supply an adjuvant and trigger an inappropriate autoimmune response.

The difficulty in understanding autoimmune disease is to sort out the factors responsible for the persistence or recurrence of the disease. An episode of EAE is often self-limited and cannot be induced a second time [24]. The immune system of the experimental animal contains pre-formed regulatory cells that control the disease [25, 26]. These regulatory networks include anti-idiotypic [25–27] and anti-ergotypic T cells [28]. The induction of the experimental autoimmune disease activates the regulatory cells, and these cells shut off the disease and prevent its re-induction. Human patients suffering from exacerbating or chronic autoimmune diseases may be expressing a failure or weakness of natural autoimmune regulation. Thus, the transition of natural autoimmunity to autoimmune disease involves at least two factors: the activation of the disease process by adjuvant signals (supplied by an infectious agent or by tissue injury), and the perpetuation of the state of activation by a failure of physiological regulation. Perhaps the adjuvant signal of infectious agents can dys-regulate regulation as well as activate pro-inflammatory autoimmunity; but we don't know how this might happen.

Specific Immune Therapy

If natural regulation of autoimmunity exists in humans as it does in experimental animals, then the most reasonable approach to the treatment of an autoimmune disease ought to be the induction or enhancement of physiological regulation. Physiological mechanisms are likely to be grounded on natural ligands and not on the mimics of natural ligands. Therefore, if we attempt to activate specific immune modulation of an autoimmune disease, we might be more successful and cause fewer side effects if we don't use APL mimics. The self-antigen, or a peptide of the self-antigen, might be more effective and safer [29]. The critical factor is to provide the self-epitope in a suitable adjuvant context, a context that does not feature the accessory signals of an infection or of an infectious agent. My colleagues and I are currently carrying out clinical trials in recent onset type 1 diabetes mellitus using a peptide of the hsp60 molecule, p277, which does not function as an APL [29, 30]. Since we aim to activate physiological regulation (and not to anergize or tolerize autoimmune clones), we are using a limited dose schedule modeled on vaccination: a priming injection followed by a few booster injections.

Another approach to the physiological modulation of autoimmune disease is T-cell vaccination [31]. Here, the subject is vaccinated with attenuated clones of autoimmune T cells involved in the disease process. The regulatory mechanisms are stimulated by the cells to be regulated [32]. T-cell vaccination also uses the agents of the disease, not their mimics.

In summary, it seems that self-antigen mimicry by infectious agents is probably not the critical factor in the triggering of autoimmune disease; the addition of adjuvant signals to self-antigens by the infection would seem to be more decisive. Restoration of regulation might best be achieved using the natural self-antigen in a salutary setting of anti-inflammatory accessory signals [33].

Acknowledgements

I am the Director of the Robert Koch-Minerva Center for the Study of Autoimmune Disease, and the Director of the Center for the Study of Emerging Diseases.

References

1. Rowley D., Jenkin C.R. 1962. Antigenic cross-reaction between host and parasite as a possible cause of pathogenicity. *Nature* **193:** 151–154

2. Damian R.T. 1964. Molecular mimicry: antigen sharing by parasite and host and its consequences. *The American Naturalist* **98:** 129–149
3. Klotz I.M., Hunston D.L. 1975. Protein interactions with small molecules. Relationships between stoichiometric binding constants, site binding constants, and empirical binding parameters. *J. Biol. Chem.* **250:** 3001–3009
4. Lancet D., Sadovsky E., Seidemann E. 1993. Probability model for molecular recognition in biological receptor repertoires: significance to the olfactory system. *Proc. Natl. Acad. Sci. USA* **90:** 3715–3719
5. Nanda N.K., Arzoo K.K., Geysen H.M., Sercarz E.E. 1995. Recognition of multiple peptide cores by a single T cell receptor. *J. Exp. Med.* **182:** 531–539
6. Mason D. 1998. A very high level of crossreactivity is an essential feature of the T-cell receptor. *Immunol. Today* **19:** 395–404
7. Burnet F.M. 1959. *The Clonal Selection Theory of Acquired Immunity*. Cambridge University Press, Cambridge
8. Burnet F.M. 1969. *Self and Not-Self*. Cambridge University Press, Cambridge
9. Oldstone M.B.A. 1998. Molecular mimicry and immune-mediated diseases. *FASEB J* **12:** 1255–1265
10. Ruiz P.J., Garren H., Hirschberg D.L., Langer-Gould A.M., Levite M., Karpuj M.V., Southwood S., Sette A., Conlon P., Steinman L. 1999. Microbial epitopes act as altered peptide ligands to prevent experimental autoimmune encephalomyelitis. *J. Exp. Med.* **189**(8): 1275–1284
11. Kersh E., Shaw A.S., Allen P.M. 1998. Fidelity of T Cell Activation through Multistep T Cell Receptor zeta Phosphorylation. *Science* **281:** 571–575
12. Kappos L., Comi G., Panitch H., Oger J., Antel J., Conlon P., Steinman L., Comi G., Kappos L., Oger J., Panitch H., Rae-Grant A., Castaldo J., Eckert N., Guarnaccia J.B., Mills P., Johnson G., Calabresi P.A., Pozzilli C., Bastianello S., Giugni E., Witjas T., Cozzone P., Pelletier J., Pohlau D., Przuntek H. 2000. Induction of a non-encephalitogenic type 2 T helper-cell autoimmune response in multiple sclerosis after administration of an altered peptide ligand in a placebo-controlled, randomized phase II trial. *Nat. Med.* **10:** 1176–1182
13. Bielekova B., Goodwin B., Richert N., Cortese I., Kondo T., Afshar G., Gran B., Eaton J., Antel J., Frank J.A., McFarland H.F., Martin R. 2000. Encephalitogenic potential of the myelin basic protein peptide (amino acids 83-99) in multiple sclerosis: results of a phase II clinical trial with an altered peptide ligand. *Nat. Med.* **10:** 1167–1175
14. Oldstone M.B. 1987. Molecular mimicry and autoimmune disease. *Cell* **50**(6): 819–820
15. Herkel J., Erez-Alon N., Mimran A., Wolkowicz R., Harmelin A., Ruiz P., Rotter V., Cohen I.R. 2000. Systemic lupus erythematosus in mice, spontaneous and induced, is associated with autoimmunity to the C-terminal domain of p53 that recognizes damaged DNA. *Eur. J. Immuno.* **30:** 977–984
16. Cohen I.R. 1988. The self, the world and autoimmunity. *Sci. Am.* **258:** 52–60
17. Cohen I.R. 2000. Discrimination and Dialogue in the Immune System. *Seminars in Immunology* **12:** 215–219
18. Cohen I.R. 2000. *Tending Adam's Garden: Evolving the Cognitive Immune Self*. Academic Press, London
19. Cohen I.R. 1992. The cognitive principle challenges clonal selection. *Immunol. Today* **13:** 441–444
20. Cohen I.R., Young D.B. 1991. Autoimmunity, microbial immunity and the immunological homunculus. *Immunol. Today* **12:** 105–110
21. Cohen I.R. 1992. The cognitive paradigm and the immunological homunculus. *Immunology Today* **13:** 490–494
22. Schwartz M., Cohen I.R. 2000. Autoimmunity can benefit self-maintenance. *Immunology Today* **21:** 265–268
23. Cohen I.R. 2000. Principles of Molecular Mimicry and Autoimmune Disease. In *Molecular Mimicry* M. Cummingham, R. Fujinami, eds. ASM Press, Washington, DC, pp. 17–26
24. Ben-Nun A., Cohen I.R. 1982. Spontaneous remission and acquired resistance to autoimmune encephalomyelitis (EAE) are associated with suppression of T cell reactivity: suppressed EAE effector T cells recovered as T cell lines. *J. Immunol.* **128:** 1450–1457
25. Ellias D., Tikochinsky Y., Frankel G., Cohen I.R. 1999. Regulation of NOD mouse autoimmune diabetes by T cells that recognize a T-cell receptor CDR3 peptide. *International Immunology* **11:** 957–966
26. Kumar V., Stellrecht K., Sercarz E. 1996. Inactivation of T cell receptor peptide specific CD4 regulatory T cells induces chronic experimental autoimmune encephalomyelitis (EAE). *J. Exp. Med.* **184**(5): 1609–1617
27. Lider O., Reshef T., Beraud E., Ben-Nun A., Cohen I.R. 1988. Anti-Idiotypic network induced by T cell vaccination against experimental autoimmune encephalomyelitis. *Science* **239:** 181–183
28. Lohse A.W., Mor F., Karin N., Cohen I.R. 1989. Control of Experimental Autoimmune Encephalomyelitis by T Cells Responding to Activated T Cells. *Science* **244:** 820–822
29. Elias D., Reshef T., Birk O.S., Van der See R., Walker M.D., Cohen I.R. 1991. Vaccination against autoimmune mouse diabetes with a T-cell epitope of the human 65 kDa heat shock protein. *Proc. Natl. Acad. Sci. USA* **88:** 3088–3091
30. Elias D., Cohen I.R. 1994. Peptide Therapy for diabetes in NOD mice. *The Lancet* **343:** 704–706
31. Zhang J., Medaer R., Stinissen P., Hafler D., Raus J. 1993. MHC-restricted depletion of human basic protein-reactive T cells by T cell vaccination. *Science* **261:** 1451–1454
32. Zang Y.C., Hong J., Rivera V.M., Killian J., Zhang J.Z. 2000. Preferential recognition of TCR hypervariable regions by human anti-idiotypic T cells induced by T cell vaccination. *J. Immunology* **164**(8): 4011–4017
33. Cohen I.R. 1995. Treatment of autoimmune Disease: to activate or to deactivate? *Chem. Immunology* **60:** 150–160