Reprinted from Immunology Today – *May, 1985* Vol. 6, No. 5, pp.147-148

The advantage of being a low responder

Irun R. Cohen, Daniel M. Altmann and Aharon Friedman

Immune response genes determine the magnitude of many immune responses. A low response is often ascribed to a genetic defect. Here Irun Cohen argues that a poor response instead reflects a heightened sensitivity to the conditions in which antigen is encountered. When these are optimal the response is normal. Poor responders thus have the advantage of a greater flexibility of response over individuals who respond strongly regardless of prevailing circumstances.

The cellular effects of immune response (Ir) genes have been studied with energy and ingenuity for about two decades and we can anticipate clarification of their molecular biology in the near future. However, understanding how a gene works does not tell us necessarily why a gene works. As biologists we are obliged to ask what purpose do Ir genes serve. At the level of the organism, Ir genes code for the magnitude of the immune response to particular antigens or defined epitopes within an antigen. Ir gene high responders are thus distinguished from low or non-responders. One way to ponder the purpose of Ir genes is to consider whether low or non-responsiveness is a positive attribute, or merely the absence of a high response. Is low responsiveness an entity or only a deficiency?

The state of low or non-responsiveness has often been referred to as if it were the expression of a cellular or a molecular defect[1,2]. Perhaps it was hoped that defective Ir genes, following the precedent set by gene defects in bacteria or bacteriophage, would serve as keys to the molecular mysteries of the immune response[3]. Perhaps 'more' was felt intuitively to be 'better'; 'less' to be 'defective'. Some investigators may have been led to postulate defective machinery in low responders as a consequence of choosing experimental conditions that maximize the differences between high and low responders. Psychology notwithstanding, there is still no evidence that Ir gene low or non-responders have a discrete structural defect. On the contrary, it seems clear that lack of responsiveness may be conditional and the existence of some flaw or vice in the system should not be assumed. In fact complete non-responsiveness is rare and most Ir gene low-responders can be converted into high responders by manoeuvers such as changing the mode of immunization[4], manipulating the adjuvant[5], inhibiting suppression[6] removing tolerogenic determinants[7], or priming *in vitro*[8]. By such means, antigen-presenting cells of 'low responder' mice were shown to be capable of processing antigen adequately[9] and specific antigen receptors were demonstrated on their lymphocytes[5].

A detailed picture of the low-responder phenotype has been afforded by observing the immune response to the molecule avidin. It was found that compared with mice with *H-2I*^{s} genes, mice with *H-2I*^{k} genes produced about a thousandth of the titer of antibodies *in vivo*, about a third to a tenth of antigen-driven T lymphocyte proliferation *in vitro*, and low or absent delayed-type hypersensitivity reactions after immunization with optimal doses of avidin in complete Freund's adjuvant[10]. Hapten-carrier and transfer experiments indicated that T lymphocytes played a major part in the differences between I^s and I^k mice – a normative finding in *H-2* Ir gene systems[11].

Analysis of molecular processing of avidin by antigen-presenting macrophages led to the conclusion that I^k low-responder macrophages were capable of generating a superimmunogenic form of processed avidin that was indistinguishable from that produced by I^s high-responder macrophages[9] and that an Ia-positive moiety associated with processed avidin probably imposed both *H-2* restriction and Ir phenotype[12]. Thus, there was no defect in the low responder in the handling of the antigen itself.

The phenomenology of the response to avidin in the animal was no less revealing than were the results of the molecular studies. Friedman and Cohen found that I^k low responder mice could be converted into high-responder mice simply by surgically removing the subcutaneous deposits of avidin/adjuvant on the 4th day after immunization[5]. This conversion could be compartmentalized anatomically; a lymph node draining a site of antigen excision showed a high responder phenotype while, simultaneously in the same mouse, a lymph node draining an unexcised site showed a low responder phenotype. Most striking was the long range imprinting of the conditions of priming. Mice that had been primed to avidin without excision maintained a low responder phenotype in a secondary response, whether or not the secondary site was excised. In contrast, mice that had been primed to avidin with excision exhibited a high response to a secondary immunization to avidin, even when the secondary site was not excised. The variations in response of I^k mice to avidin were specific. There was no fluctuation on the high response of these mice to the purified protein derivative (PPD) antigen present in the adjuvant. Unlike I^k mice, I^s mice showed a persistently high response to avidin, whether or not the antigen deposit was excised. Thus, I^k mice, compared with I^s mice, were not born with a defect in their potential to respond immunologically to avidin, but rather with a heightened sensitivity to the conditions of primary contact with the antigen. The I^k mice had the option of responding to a low degree, while I^s mice had a monotonously high response.

Department of Cell Biology, The Weizmann Institute of Science, Rehovot 76100, Israel.

The cellular and molecular mechanisms responsible for this *H-2* genetically controlled option are open to speculation[13,14], but whatever they may be, it is legitimate to question the selective advantage of their effects.

In very general terms, the immune system may be described as a system that processes information. All systems that process information face the problem of extracting a signal from noise and so are obliged to focus attention on only part of their potential input. You cannot simultaneously read *Immunology Today* and carry on a conversation with your spouse, and do justice to either. Similarly, the immune system could not respond to all of the potentially antigenic contours of a macromolecule without being jammed. Not only must the system know what *not* to respond – the problem of autoimmunity – it must also decide to which potential epitopes a response is worthwhile. Because responding lymphocyte clones necessarily compete for space and energy, a response to all epitopes can paralyze the system doing more harm than no response at all.

The primary repertoire of lymphocyte receptors, both B-cell[15] and T-cell[16], is created by genetic recombinations and mutations and is immense. It is very unlikely that the molecular mehanisms that generate V regions could intrinsically favor one set of receptor configurations over another. Thus, the problem of choosing a dominant epitope, the problem of focus, cannot be solved by primordial holes in the repertoire. Some evidence indicates that the functional repertoire of T lymphocyte receptors may be moulded during ontogeny in the thymus[17]. However, the effects on the Ir phenotype of exposure to foreign or self-antigens in the thymus are not predictable[18]. Be that as it may, it is reasonable to suspect that interactions between antigenic molecules and particular MHC allelic products might obscure some potential epitopes while favoring the exposure of others. In this way MHC gene products could aid in limiting the focus of attention of the immune system and restrain the destructive profligacy inherent in the lymphocyte receptor repertoire. Some evidence suggests that the frequency of specific MHC alleles in a population may reflect the experience of the population with certain microbial pathogens[19]. In addition to the MHC, the decision whether or not to respond at all is influenced greatly by adjuvant signals, most prominently those generated by microbial infection such as bacterial cell walls or interferon. From any point of view, it is clear that the immune system, like any information system, operates most efficiently and effectively when it limits its field of interest – witness the relatively few portions of the lysozyme[20] or insulin molecules[21] that engage the attention of T lymphocytes even in high responders. The response to myoglobin is similarly limited. High responder mice respond to five sites on the molecule while low responder mice, using the same procedure of immunization, respond to only one of the sites. The low responders can be persuaded to respond to additional antigenic sites if primed with high doses of myoglobin[22]. However, even five is not a very large number of sites. Thus it can be argued that high responders are similar to low responders in that both express their response to limited parts of the antigen molecule. The low responders are only relatively more frugal in the magnitude and extent of their investment.

Considering the above, an individual who can exercise an option to respond more or less or not at all, would be at an advantage compared with an individual who has a strong tendency to a high response with less regard to prevailing conditions. Thus, the Ir gene low responder can be seen to reflect the fine regulatory machinery of the immune system rather than a hereditary disgrace. Perhaps we ought to seek the Ir gene defect expressed by high responders.

References

1 Sela, M. (1974) *Prog. Immunol.* 2, 179–180
2 Theze, J. (1984) *Ann. Immunol.* 135C, 379–386
3 Seman, M. (1984) *Ann. Immunol.* 135C, 397–400
4 Fierz, W., Brennan, M., Müllbacker, A., *et al.* (1982) *Immunogenetics* 15, 261–270
5 Friedman, A. and Cohen, I. R. (1984) *Immunogenetics* 19, 449–454
6 Gougeon, M.-L. and Theze, J. (1983) *J. Immunol.* 130, 1521–1526
7 Yowell, R. L., Araneo, B. A., Miller, A., *et al.* (1979) *Nature* 279, 70–71
8 Cohen, I. R., Talmon, J., Lev-Ram, V., *et al.* (1979) *Proc. Natl Acad. Sci.* 76, 4066–4070
9 Friedman, A., Zerubavel, R., Gitler, C., *et al.* (1983) *Immunogenetics* 18, 277–288
10 Friedman, A. and Cohen, I. R. (1983) *Immunogenetics* 18, 267–275
11 Klein, J. and Nagy, Z. (1982) *Adv. Cancer Res.* 37, 233–317
12 Friedman, A., Zerubavel, R., Gitler, C., *et al.* (1983) *Immunogenetics* 18, 291–302
13 Grossman, Z. and Cohen, I. R. (1980) *Eur. J. Immunol.* 10, 633–640
14 Janeway, C. A. (1983) *J. Mol. Cell. Immunol.* 1, 15–18
15 Honjo, T. (1983) *Annu. Rev. Immunol.* 1, 449–528
16 Hedrick, S. M., Cohen, D. I., Nielsen, E. A., *et al.* (1984). *Nature* 308, 149–153
17 von Boehmer, H., Haas, W. and Jerne, N. K. (1978). *Proc. Natl Acad. Sci.* 75, 2439–2442
18 Maron, R. and Cohen, I. R. (1983) *Immunogenetics* 17, 95–100
19 de Vries, R. R. P., Meera Khan, P., Bernini, L. F., *et al.* (1979) *J. Immunogenet.* 6, 271–287
20 Goodman, J. W. and Sercarz, E. E. (1983) *Annu. Rev. Immunol.* 1, 465–498
21 Talmon, J., Ranghino, G., Yonath, A. *et al.* (1983). *Immunogenetics* 18, 79–89
22 Young, C. R. and Atassi, M. Z. (1982) *J. Immunogenetics* 9, 343–351