

LETTER TO THE EDITOR

The Dual Recognition Systems of T Lymphocytes: A Model

A mature T lymphocyte shows double specificities: one (anti-X R_1 receptor) against a foreign antigen, and the other (anti-H2 R_0 receptor) for an H2 antigen of the host in which the T cell differentiates (Bevan, 1977; Zinkernagel *et al.*, 1978; Waldmann *et al.*, 1978). Zinkernagel *et al.* (1978) have found that the anti-H2 R_0 receptors are determined by the thymus epithelium, and that these R_0 receptors recognize H2 antigens of the thymus—under normal circumstances, the thymic H2 antigens would be identical to the rest of the self H2 antigens of an individual—in which the T lymphocytes are allowed to mature. These results have been interpreted by von Boehmer, Haas & Jerne (1978) within the framework of the selection theory. According to this interpretation, which is an augmented version of Jerne's earlier hypothesis (1971), a precursor T cell possesses two receptors, R_0 and R_1 , with identical specificities directed against a certain H2 antigen. In a given individual, the precursor T cells that can recognize the corresponding H2 antigens on the thymus epithelium undergo extensive proliferation, leading to the selection of T cells which express an unaltered R_0 (anti-H2 R_0 receptor) together with a mutant R_1 (anti-X R_1 receptor). There are several other hypotheses (Cohn & Epstein, 1978; Blanden & Ada, 1978; Talmage, 1979; Williamson, 1980) to explain the specific role of the thymus in determining anti-H2 R_0 receptors. However, all these interpretations, like the hypothesis of von Boehmer *et al.* (1978), invoke the notion of thymic selection. Such interpretations impose a constraint on the process of selection; that is, according to all these explanations, only thymic H2 antigens can bring about the selection process despite the fact that H2 antigens are also present on nonthymic tissues. In contrast with the idea of thymic selection, I propose here an hypothesis of thymic induction to explain the role of the thymus in determining T cell receptors which will recognize its own H2 antigens. The suggestion is made that H2-specific regulatory molecules, which are distinct from H2 antigens and which are postulated to be present on the thymic epithelial cells, induce expression of the genes encoding receptors to the corresponding self H2 antigens. On the other side of T cell differentiation, both thymic as well as nonthymic H2 antigens can select the precursor T cells which have the corresponding anti-H2 R_1 receptors and drive the generation of anti-X R_1 receptors.

In what follows, first I would present my ideas about the nature of R_0 receptors; then I would discuss how the expression of these receptors is brought about.

1. The R_0 Receptors of T Lymphocytes are Encoded by Non-V Genes

The hypothesis of von Boehmer *et al.* (1978) states that both R_0 and R_1 are encoded by V genes. The antigen-specific R_1 receptors of T cells are immunoglobulins (Roelants *et al.*, 1974). There is, however, no evidence to show that R_0 receptors are also immunoglobulins. Furthermore, the condition that one of the two receptors with specificities directed against the same H2 antigen to get mutated and the other to remain unaltered requires that they be different in their structural genes. The R_0 and R_1 receptors may have identical specificities, yet they can be encoded by altogether different structural genes. In other words, two polypeptide chains, even though they have identical amino acid sequences, can be coded for by two different DNA sequences. Degeneracy of the genetic code would permit such a situation. Hence, I would suggest that R_0 receptors are encoded by non-V genes, a separate set of genetic elements, to be called R_0 genes. For reasons to be discussed below, I would consider that the R_0 and R_1 receptors to a given H2 antigen are not only encoded by different structural genes but may also show different combining specificities.

2. Idiotypically Speaking, the R_0 and R_1 Receptors to a Given H2 Antigen are not Identical

The hypothesis of von Boehmer *et al.* (1978) assumes that the R_0 and R_1 receptors to a given H2 antigen have identical specificities. However, consider the experimental models of DA and Lewis rats. If one assumes that an anti-DA R_0 and anti-DA R_1 receptors have identical specificities, the anti-DA R_0 and anti-DA R_1 receptors would possess identical idiotypes. In F_1 hybrids (Lewis \times DA), the differentiating lymphocytes are constantly exposed to the (DA thymus-determined) anti-DA R_0 receptors, and therefore, the F_1 rats should be tolerant to the anti-DA R_0 idiotypes. Since, according to the assumption of von Boehmer *et al.*, the anti-DA R_1 receptors have the same idiotypes as those of anti-DA R_0 receptors, the F_1 hybrids should also be tolerant to the R_1 idiotypes and hence should not be able to produce antiserum against R_1 idiotypes. However, this conclusion is inconsistent with the experimental observation that antibodies against R_1 receptors are produced in F_1 individuals upon injection of parental T cells (Binz & Wigzell, 1975). Consequently, it would suggest

that the R_0 and R_1 receptors to a given H2 antigen may not have identical idiotypes. This would not be surprising if one considers that the R_0 and R_1 receptors to have evolved for mediating very contrasting phenomena of "pro-self" recognition and "anti-foreign" recognition respectively.

3. Generation of Anti-H2 R_0 Receptors is Mediated by H2-Specific Thymic Effector Molecules that would Derepress the Corresponding R_0 Genes

Before we could proceed further, let us contrast two different cell types, such as a liver cell and a white blood cell. The liver cell is geared for synthesizing albumin whereas a white blood cell is not normally known for producing albumin. However, this does not mean that the white blood cell cannot produce albumin. It has clearly been shown that the albumin gene is also present in a white blood cell, and the white blood cell, under appropriate conditions, can indeed be made to produce albumin. It would suggest that the albumin gene is only not expressed in a white blood cell (Ruddle & Kucherlapati, 1974). Therefore, it is the distinct portion of the genome that is expressed in a liver cell which distinguishes the liver cell, for example, from the white blood cell. I cite this precedence to show how thymus tissue-specific expression of the effector genes could similarly be possible. This, I believe, is what makes the thymic epithelium characteristically distinct from nonthymic tissues.

I suggest that every individual has a set of effector genes corresponding to a complete set of the H2 antigens of the species. In a given thymus epithelium, however, the H2 antigens along with an H2-nonspecific intracellular thymic cofactor, would bind to the regulatory sequences of only the corresponding effector genes. Consequently, the H2 antigens would derepress only the H2-specific effector genes. The postulated H2-nonspecific thymic cofactor, being an intracellular regulatory molecule, would not be available in nonthymic tissues, and therefore the effector genes would not be expressed on nonthymic tissues. The effector-gene products, that is the H2-specific thymus factors expressed on its epithelial cells, interact with the differentiating T lymphocytes and derepress the corresponding R_0 genes. To facilitate the action of a thymic effector molecule, a pre-T cell would have specific effector-accepting molecules (acceptors) on its surface, encoded by a set of genetic elements, to be called acceptor genes. As a result of a specific effector-acceptor interaction between a thymus epithelial cell and a pre-T cell, a specific R_0 gene is expressed on the T cell. This is how the proposed hypothesis of thymic induction accounts for the specific role of the thymus. In contrast, on models

involving the notion of thymic selection, the generation of R_0 receptors is mediated directly by the H2 antigens which, however, are also present, in fact more so, on nonthymic tissues (Klein, 1975). Recent findings that the serum thymic factor (Kato *et al.*, 1981) and the thymosin (Hannappel *et al.*, 1982) also are present on nonthymic tissues would further support my thinking about the special role of thymus. In summary, H2 antigens cause the expression of effector genes on thymus epithelium; the effector gene products, in turn, induce expression of the specific R_0 genes on T lymphocytes. A discussion on how the invoked H2-parallel gene families could have evolved is beyond the scope of this letter.

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