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Immunological Memory

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Preface

Although immunologists know rather a lot about the manifestation of immunological memory, an understanding of the mechanism of memory at cellular and biochemical levels eludes us. Indeed, as we shall see, it is not even clear which of the several models used to explain the working of memory approximates to the truth. It is in order to report on approaches to this problem and on recent experimental advances in the field of memory cells that this volume has been put together.

In the past 4–5 years cell surface molecules that may enable us to define memory B and T cells have been identified. It may now be possible to ask how memory cells are generated and to define what signals are required during or after antigenic encounter for a cell to enter the memory cell pool rather than to terminally differentiate into an effector cell. The transition from virgin cell to memory cell is clearly accompanied by several biochemical changes. For B cells, isotype switching and somatic mutations (leading to affinity maturation) are well-defined phenomena, although the molecular mechanisms remain mysterious. Both have received attention in many excellent reviews of late and so are not considered in detail in this book. Neither switching nor somatic mutation is a feature of peripheral T-cell maturation; biochemical differences between virgin and memory T cells may only relate to differing activation requirements and possibly changes in the expression of accessory molecules.

A complete understanding of immunological memory, however, will come not only from the phenotypic definition of memory cells but also from studying how these cells maintain memory over months and years. The conventional model of memory has been that it is carried by a cell that lives for a very long time. If this is true, then one is faced with two questions. First, given that the majority of lymphocytes in peripheral lymphoid tissues have an intermitotic lifespan of only 4-6 weeks, how do memory cells alter their lifespan? Secondly, how do memory cells remove themselves from the selection pressures which shape the peripheral lymphocyte pool? One solution to

the first problem is to postulate that memory cells themselves are not long-lived, but rather they self-renew to form long-lived clones.

There is still the problem of clonal selection: in a dynamic immune system self-renewal will require a stimulus. So, the corollary to the tenet that memory cells have the same lifespan as other lymphocytes but self-renew is that that they receive continual stimulation. If this model is taken to its logical conclusion, then we have to say that enhanced memory responses may be due not to the action of specialised cells but to the increased frequency of specific cells maintained by continual stimulation.

This model still has a problem; that is, what provides the continual stimulation? Two possibilities suggest themselves—antigen and idiotypic interactions. While even inert antigens can be stored over very long periods on specialised dendritic cells (follicular dendritic cells), the generation of anti-idiotypic antibodies or T cells may stimulate clones of cells long after antigen has decayed. Unfortunately the question of idiotypic interactions in long-term memory has received scant attention experimentally and so is not represented here.

The lack of experimental data, however, has not inhibited people from proposing rather different models for immunological memory. In its extreme form, the idiotype network theory predicts that memory need not be a function of single cells or clones but rather a property of the system as a whole (global memory). Thus, perturbing the network results in the formation of novel connections; these new circuits representing a "memory" of the experience. This is reminiscent of the theories of neural memory in which circuits of firing nerve cells called "cell assemblies" are seen as the basis of short-term memory. Long-term memory, however, would require continual electrical activity in the cell assemblies, just as idiotype–anti-idiotype interactions should persist if they are the basis of memory. It has been suggested that repetitive firing within the assembly causes alteration of the synapse, such that it becomes more efficient and enables a signal arriving at just one cell to trigger the whole assembly. Interesting though these parallels are, it is difficult to see how reinforced circuits could be formed in a disperse and dynamic lymphoid system. Indeed, there is little, if any, firm evidence for network involvement in immunological memory.

We have stressed in this short overview the importance of establishing how memory is maintained. The contributions collected in this volume address this question but also provide information about new markers for memory cells and the

functional properties of subpopulations expressing these molecules. It is clearly not only important from a theoretical point of view to distinguish between the models of immune memory: finding a "solution" to memory might have profound consequences on the design of new vaccination programmes.

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(Their addresses can be found at the beginning of their respective chapters)