Chapter 7. Non-specific components

Society is based on the assumption
that everyone is alike...
-Hugh Kingsmill
in Michael Holroyd

Specific and non-specific regulatory components

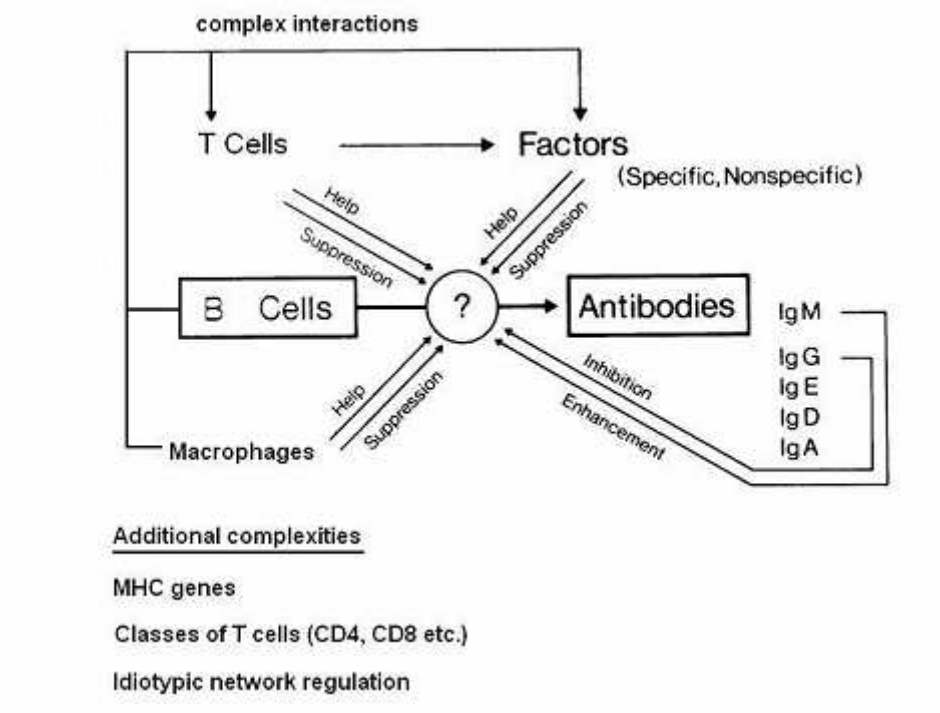
The sharp dividing line that can be drawn between components of the immune system that have V (variable) region(s) and those that don't cannot be overemphasized. Specific interactions typically take place via a V region, while non-specific interactions take place via non-variable molecules. Adaptive immunity is the ability of the immune system to learn and exhibit memory, both in terms of having an immune state with respect to an antigen, and with respect to the possibility of the system being specifically tolerant with respect to the antigen. Adaptive immunity involves V regions. Mammals share with more primitive organisms a type of immunity that does not involve learning, which is called innate immunity.

In this chapter we make a detour from our main focus on specific regulation, to briefly consider nonspecific regulatory components. Some of these play a role in both adaptive and innate immunity. Much of the following information on non-specific regulation has not yet been incorporated into immune network theory, that so far has had adaptive immunity as its prime focus. Remarkably, we are able to develop a fairly wide-ranging theory of adaptive immunity without very much reference to innate immunity.

An overview of some of the cells and molecules regulating B cell immune responses is shown in Figure 7-1. In addition to the specific interactions involving helper T cells, suppressor T cells and antibodies, non-specific cells called A cells (accessory cells) such as macrophages, monocytes and dendritic cells are typically involved, and also various non-specific molecules. The antibodies that are produced can also have potent specific enhancing or inhibiting effects on the immune response. Different classes of antibodies, in particular IgM and IgG, have different regulatory properties. If antigen-specific IgM is injected together with antigen, the response is enhanced, while if antigen-specific IgG is given with antigen, the response is inhibited relative to that seen with antigen alone. Non-specific regulatory molecules include several families, namely interleukins (that facilitate communication between leukocytes[67]), lymphokines (that are made by lymphocytes), cytokines (that are

[67] Leukocytes are blood cells.

Figure 7-1. Some of the components of the immune system that are involved in the regulation of the production of antibodies by B cells. Specific regulation is exerted by T cells and their cell-free products (antigen-specific T cell factors) and by antibodies. Non-antigen-specific regulation is exerted by macrophages and numerous non-antigen-specific lymphokines. Adapted from G. W. Hoffmann (1978) in "Theoretical Immunology", G.I. Bell, A.S. Perelson and G.H. Pimbley (eds.) Marcel Dekker, N.Y., 571-602.



made by and regulate cells generally), Fc receptors (receptors present on a cell surface that recognize the Fc part of IgG) and molecules of the CD series (an extensive series of molecules that are present on various cell surfaces).

MHC

The major histocompatability complex (MHC) is a part of the genome that encodes a small number of self cell surface molecules called "MHC class I" and "MHC class II", that in turn have a profound effect on the T cell repertoire of V region specificities. The MHC class I molecules strongly influence the cytotoxic T cell repertoire by a process of positive selection, (cells must have some affinity for MHC class I to be selected), while MHC class II molecules similarly influence the selection of helper T cells. Since T cell receptors, like antibodies, are multispecific (see chapter 5), they can also specifically recognize other (foreign) antigens, in addition to the MHC that they have been selected to recognize.

Macrophages and monocytes (A cells), Fc receptors (FcR) and more about Antibody Dependent Cellular Cytotoxicity (ADCC)

Macrophages and monocytes are white blood cells that, in contrast to B cells and T cells, do not have antigen-specific receptors, but nevertheless play a pivotal role in the regulation of the immune system. Macrophages are scavenger cells. They are able to engulf foreign material that has antibodies attached to it. To this end they have receptors on their surfaces for the constant part (Fc) of antibodies. They are effector cells of the process we described in chapter 2 called antibody-dependent cellular cytotoxicity ("ADCC"); see Figure 2-7. The production of the antibodies involves of course a specific interaction between the antigen and the V region of the B cell receptor, but a nonspecific receptor on a nonspecific cell binds to a nonspecific part of the antibody to complete the job of getting rid of the antigen.

Macrophages and monocytes are functionally similar to each other, both being non-specific cells that play accessory roles in immune responses, in addition to their ADCC capabilities. Experimentally, these cells can be conveniently separated from B cells and T cells using the fact that they bind to glass surfaces, for example glass beads. They are called A cells for "accessory" cells or "adherent" cells. Macrophages and monocytes can be distinguished from each other by size and tissue distribution. Macrophages are larger than monocytes, and are found mainly in lymphoid organs such as the spleen, while monocytes are present mainly in the blood. Non-specific regulatory molecules made by macrophages and monocytes are called monokines.

Antigen-specific T cell factors were found by Evans and collaborators in the early 1970s to also bind to the surface of macrophages.[68] This finding is important in the symmetrical network theory, as discussed in chapter 10. It is postulated that the antigen-specific factors form a bridge between the antigen and A cells, which facilitates the activation of A cells to secrete cytokines (see below). These cytokines, including IL-1, give T cells a non-specific "second signal" for proliferation.

Antigen presenting cells are non-specific accessory cells

Macrophages, monocytes and dendritic cells are non-specific accessory cells that express MHC class II, and interact with helper T cells during the induction of immune responses. T cells that recognize both an antigen and the MHC class II that is present on the A cell surface are selected to proliferate in preference to cells that recognize antigen alone. Non-specific accessory cells are activated to provide T cells a second signal for proliferation (in addition to the signal via the V region bearing T cell receptor), for example the interleukin IL-1. They have also been ascribed a role in providing B cells with a second signal for differentiation from being dividing small lymphocytes to large, antibody secreting plasma B cells (chapter 10).

pH

There are many antigen non-specific substances that can influence (and hence non-specifically "regulate") the size of an immune response. These include the amount of water to which an animal has access, and the pH of its blood. These examples are extreme cases of non-specificity, since they influence not only immune responses but also many other metabolic processes.

Complement

Antibody by itself does not kill cells to which the antibody binds, or remove foreign substances from the system. A set of eleven serum proteins called complement, together with antibodies, does this, in a way that permits the antibodies to specifically direct the process. It was discovered already late in the 1800s that antibody and complement are both needed to kill cells. Complement components are non-specific; they interact with the constant part of the antibody molecules. Hence complement components are unable to participate in distinguishing between self and non-self. Target cells may thus be

[68] R. Evans, C. K. Grant, H. Cox, K. Steele, and P. Alexander (1972) Thymus-derived lymphocytes produce an immunologically specific macrophage-arming factor. J. Exp. Med., 136, 1318-1322.

something foreign or the body's own cells, providing the corresponding antibodies have been produced. The IgM and IgG classes of antibody play roles in complement mediated killing in different ways; see chapter 2.

Cytokines, interleukins and lymphokines

Cytokines, interleukins and lymphokines were sometimes called "factors", especially when they were still poorly characterized. Cytokines are protein molecules that mediate signalling between cells. Interleukins (a slightly less generic term) are protein molecules that mediate signalling between leukocytes (white blood cells). Lymphokines are protein molecules that mediate signalling between lymphocytes, and include both specific factors (antigen-specific and antiidiotypic) and proteins that are not specific for the antigen, such as IL-1 and IL-2 (below).

Much has been learnt about the network of regulatory interactions involving these molecules. Some interleukins are made by T cells, some are made by B cells, and some are made by non-specific accessory cells such as monocytes and macrophages. Some of them act as growth factors for B cells and/or T cells. They provide signals that, together with the signal transmitted via the specific receptor of a lymphocyte, tell the cell to divide or differentiate (change) to a different state. Differentiation steps include transitions between different stages of the cell cycle, such as changing from being a resting cell to being a dividing cell, or going from being a non-secreting cell to an antibody secreting cell, or switching from the production of one antibody isotype to another. Some of the better known non-specific lymphokines include the interleukins IL-1, IL-2, IL-4, IL-6 and IL-10, migration inhibition factor (MIF), gamma interferon (IFN-γ), tumor necrosis factor-β (TNF-β), granulocyte-macrophage colony stimulating factor (GM-CSF) and lymphotoxin.

A difficulty that has emerged in the study of lymphokines is that most if not all of them are made by multiple cell types, and most if not all act on multiple cellular targets.[69] Hence in addition to the idiotypic regulatory network there is a complex lymphokine regulatory network. Lymphokines do not have the exquisite specificity of enzymes. For enzymes we have the rule "one enzyme, one substrate", which is valid to a good approximation, *in vivo*), and this rule makes it possible to analyse and make sense of biochemical pathways. The promiscuity of lymphokines makes the analysis of the lymphokine network more difficult. The V region network is simpler conceptually, in the sense that each V region can functionally interact with all of the V regions to which it has complementarity.

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[69] S. K. Durum and J. J. Oppenheim in W. E. Paul (Ed.) (1989) Fundamental Immunology, 2nd Ed., Raven Press, p. 655.

IL-1

IL-1 is one of the best characterized interleukins. It is a macrophage derived factor that was formerly known as "lymphocyte activating factor" (LAF) and is stimulatory for the proliferation of T cells. IL-1 can also stimulate the production of another interleukin, IL-2.

IL-2

IL-2 was formerly known as T cell growth factor. IL-2 interacts with T cells via a receptor (the "IL-2 receptor") that is expressed on some activated T cells. This interleukin is used to support the continuous growth of T cell lines in vitro.

IL-6

IL-6 can be produced by monocytes and macrophages. It acts as a differentiation factor on B cells to secrete antibodies. While IL-6 has a broad spectrum of effects on various target cells, its properties include those postulated in the symmetrical network theory[70] (see chapter 10) for a non-specific second signal differentiation factor for B cells.

Th1, Th2, TH1 and TH2 cells

In 1978 two classes of helper T cells were described by Tada and his colleagues, which they called Th1 and Th2.[71] These Th1 and Th2 cells were defined in *in vivo* experiments, that will be described in chapter 17. They differ from each other in the expression of a serologically defined marker called I-J. Then in 1986 Mosmann and his colleagues studied clones of helper T cells, and showed that they can be roughly classified into two groups, that I will call TH1 and TH2. TH1 and TH2 cells are defined according to the cytokines the cells secrete, with TH1 cells tending to secrete IL-2, IFN-γ and TNF-β and TH2 cells tending to secrete IL-4, IL-5, IL-6, IL-10 and IL-13[72]. Both types

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[70] G. W. Hoffmann (1978) Incorporation of a Non-specific T Cell Dependent Helper Factor into a Network Theory of the Regulation of the Immune Response, in "Theoretical Immunology", G.I. Bell, A.S. Perelson and G.H. Pimbley (eds.) Marcel Dekker, N.Y., 571-602.

[71] Tada, T., Takemori, T., Okumura, K., Nonaka, M. & Tokuhisa, T. (1978) Two distinct types of helper T cells involved in the secondary antibody response: Independent and synergistic effect of Ia- and Ia+ helper T cells. J. Exp. Med. 147, 446-458.

[72] T. R. Mosmann, H. Cherwinski, M. W. Bond, M. A. Giedlin, and R. L. Coffman. (1986) Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J. Immunol. 136, 2348-2357.

produce TNF-β, IL-3 and GM-CSF. The boundaries between TH1 and TH2 categories are not sharply defined.[73] In the development of network theory I will be focusing on the Th1 and Th2 discovered by Tada et al. rather than on the distinction between TH1 and TH2 cells.

CD molecules

CD molecules distinguish cells with various functions. For example, CD4 is present on helper T cells while CD8 is present on some suppressor T cells and cytotoxic T cells. (The different function of these cells is believed to result from the fact that CD4 binds to MHC class II and CD8 binds to MHC class I; see chapter 12). There are a total of more than 100 different CD molecules.

Some of the CD molecules are cell surface receptors for interleukins. For example, there is a receptor for IL-2 that consists of two polypeptide chains, an α chain and a β chain. The α chain of the IL-2 receptor is the CD25 molecule.

Combinations of CD molecules can also define populations of T cells with particular functions. For example, the suppression of immunity against self antigens (autoimmunity) has been found to include a role for cells that express CD4 and CD25[74]. In the recent literature these cells have been called "regulatory T cells"[75].

Rheumatoid factor

The immune response to many antigens includes the production of anti-IgG antibodies. These antibodies are called rheumatoid factor. Some rheumatoid factors are specific for the Fc part of IgG. In rheumatoid arthritis, an autoimmune disease, complexes of IgG and rheumatoid factor are deposited in the joints.

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[73] A. Kelso (1995) Th1 and Th2 subsets: paradigms lost? Immunology Today, 16, 374-379.

[74] S. Sakaguchi, N. Sakaguchi, M. Asano, M. Itoh and M. Toda (1995) Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor a chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J. Immunol., 155, 1151-1164.

[75] McGeachy M. J., L. A. Stephens, and S. M. Anderton (2005) Natural recovery and protection from autoimmune encephalomyelitis: contribution of $CD4^+CD25^+$ regulatory cells within the central nervous system. J. Immunol., 175, 3025-3032.