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Terminating the Immune Response

Philippa Marrack[1,2], **James Scott-Browne**[2], and **Megan K. L. MacLeod**[2]

[1]Howard Hughes Medical Institute, Integrated Department of Immunology, National Jewish Health, Denver, CO, USA

[2]Integrated Department of Immunology, National Jewish Health and University of Colorado Medical Center, Denver, CO, USA

As for most things in life, turning things off in the immune system is as important as turning them on. Biologists usually like to focus on the positive, the ways in which natural processes get started. However, this is not the case for the immune system. Numerous studies have addressed the problems of resolving immune responses, perhaps because inhibition and resolution of the immune response are so important, required, as they are, to prevent autoimmunity and reduce ongoing inflammation.

The body responds to infection by inducing many processes. Often granulocytes are the first cells to appear at sites of infection. Later, antigen and danger signals from the infected area arrive in draining lymph nodes, either free from cellular carriers or on migrating dendritic cells. Together these materials activate T and B cells in the nodes, causing huge expansions in the numbers of antigen-specific lymphocytes and some increases in the numbers of nonspecific cells, carried along, by various means, for the ride. These cells migrate to the site of infection, where they either directly or indirectly, by recruiting and activating other cell types, cause the destruction, elimination, or inactivation of the invading organism. After the invader has been disposed of, however, various processes that eliminate the recruited cells are brought into play. Also, there is considerable evidence that even during the acute phase of the immune response, various feedback inhibitory pathways are induced, making sure that the huge cellular expansion and cytokine storm that accompany the immune response do not overwhelm the host. With all this in mind, it is clear that immune responses are controlled and resolved in many ways. Discussions of the results of many of these studies are included in this volume. While these studies are valuable and help us to some extent understand how immunity is controlled, it is still apparent and a major problem in the field that we do not know which of the many processes dominates in different circumstances and even why the immune response is controlled in so many ways. Some of these issues are discussed in this introduction.

There is another matter of historical interest associated with the results described in this volume. The scientists who proposed the elements of the clonal selection theory in the 1950s thought that the immune response would be driven entirely by antigen and that, when antigen disappeared, the immune response would cease (1-3). These scientists also expected that the primary immune response would create relatively small numbers of antigen-specific cells, cells that would survive more or less *in toto*, to become memory cells, when the primary infection was over. Now we know that the clonal selection theory was wrong on both these fronts. In spite of the fact that this theory accurately predicted many aspects of the immune response, it fell short in its predictions about the end of immunity, as amply

Correspondence to Philippa Marrack HHMI, Integrated Dept. of Immunology National Jewish Health 1400 Jackson St Denver, CO 80206 Tel: +1 303 398 1322 Fax: +1 303 398 1396 marrackp@njhealth.org.

demonstrated by the articles herein. For example, we now know that immune responses are accompanied by tremendous increases in the numbers of antigen-specific T cells (4-9) and to a lesser extent B cells (10). Clearly, most of these cells must be destroyed to make space, cytokines, and nutrients available for other cells and also to avoid huge amounts of inflammation were all these cells to be reactivated. Thus, biology has arranged that most of the antigen-specific cells generated during an infection disappear. The processes that control such removal are discussed at length in several articles in this volume (11-18). Nevertheless, not all antigen-induced cells die, many survive to create the memory cells (predicted by the clonal selection theorists) that protect us against reinfections (16, 19, 20).

Events causing and related to termination of the immune response

Loss of antigen

The idea that loss of antigen controls the termination of immune responses is very straightforward. However, it has been argued for many years that antigen, once introduced, never truly disappears from the body but instead is retained on the surface of follicular dendritic cells (21, 22). Clearly organisms that create chronic infections, such as Epstein Barr virus, can expose the body constantly or at intervals to their antigens. However, antigens associated with infections that are resolved seem to disappear from the body. Thus, numerous recent experiments in which antigen-specific T cells are transferred into hosts that have previously been exposed to antigen have shown that antigen is not necessarily retained in the host, at least in a form that is detectable by T cells (23-25). Moreover, continuous exposure to antigen is not needed for the survival of immunological memory, argued in this volume for B cells by Slifka (19) and elsewhere and herein for T cells (23-26).

Persistent antigen may have in itself contradictory effects, possibly depending on the conditions, location, and time at which the T cell sees its antigen. For example, antigen-specific T cells present in the lung during influenza infection are more prone to activation-induced cell death (AICD) following restimulation than those present in the draining lymph node (18). Thus, while the loss of antigen signals the beginning of the T-cell contraction phase, continual signals via the T-cell receptor can also cause T-cell death by AICD. Likewise, in chronic infections, continual signals through the TCR result in anergy or exhaustion of the responding T cells (27).

The functions of interleukin-2 (IL-2), which is usually produced in response to antigen, are particularly difficult to understand. IL-2 is famously a tremendous promoter of T-cell survival and proliferation *in vitro*. However, *in vivo*, IL-2 can provide survival signals or induce death depending on the state of the responding T cell. IL-2 can sensitize cells to AICD (17, 18) by, for example, causing the upregulation of Fas ligand (15). Alternatively, autocrine IL-2 signals reduce cell death *in vivo* during the lymphocyte contraction phase, at least following some infections (18). IL-2 is also important during T-cell proliferation. This is not just because IL-2 stimulates the proliferation of activated cells; it also promotes expression of the glucose receptor Glut1 on the cell surface, thus helping the T cells take up glucose to use as fuel to drive proliferation (28). Glucose is a particularly important nutrient for dividing T cells, since such cells, perhaps unexpectedly, switch from an aerobic, Krebs cycle-dependent mode to a phase that is anaerobic and glycolytic.

The resolution of the immune response does not always result in a return to normality. For example, following clearance of measles virus, the host undergoes a transient state of immunosuppression that is linked to lymphopenia and a switch to T-helper 2 responses that leaves the host susceptible to other infections (29). Therefore, infections and the immune responses to them can have effects that last beyond the clearance of the pathogen.

Dampeners of ongoing immune responses

T cells are among the most miraculous dividers in the immune response. When appropriately triggered by antigen, $CD8^+$ T cells can divide every 6-8 h (6), a rate that is limited apparently by the speed at which the DNA of the cells can be replicated. Given this limitation, there is considerable opportunity for biology to control the magnitude of the immune response by controlling the speed of T-cell replication. There is evidence that this is accomplished in several ways. Limitations in the availability of antigen lead to competition between antigen-specific lymphocytes and inhibition of growth of some lymphocyte clones versus others, usually based on the relative affinities of the cells for antigen (9, 30-33). Regulatory T cells play a role, by reducing the potency of antigen-presenting dendritic cells (11, 34) or by secreting inhibitory cytokines and by other means (35-37). Lymphocytes may restrict their own expansion via expression of potentially inhibitory receptors such as cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death 1 (PD-1), and KLRG-1 (35, 38-41), which have ligands that may, like PD-ligand 1, be expressed on many tissues, attempting to protect themselves against the unleashed fury of the immune system (35).

Metabolic considerations

Like all other cells, lymphocytes, dendritic cells, and granulocytes are subject to the dictates of their metabolisms. They must have nutrients to survive and grow and must turn over toxic metabolites. The restraints placed on them by such dictates can lead to immunosuppression. Various tissues and alternatively activated macrophages and monocytes may consume essential amino acids, thus denying important nutrients to growing T cells. Among the well-publicized situations along these lines is consumption of tryptophan by the placenta/fetus and by the liver and arginine by alternatively activated macrophages (42, 43). However, as Grohmann and Bronte and Cobbold *et al.* write (34, 44), other amino acids such as phenylalanine, cysteine glutamine, and histidine may join this list. Grohmann and Bronte also point out an interesting evolutionary idea, that the requirement for these amino acids may originally have been exploited by invading bacteria and/or their hosts, to allow or limit infection. For example, mycobacteria are tryptophan auxotrophs, and this fact may be exploited under some circumstances by their host. Moreover, amino acid consumption is not just an end unto itself. The metabolites produced by amino acid breakdown may also have immune inhibitory properties. Additionally, there is evidence that, via suppression of mammalian target of rapamycin (mTOR), amino acid deprivation can induce regulatory T cells (11, 34, 44).

The incredible change in state of lymphocytes induced by antigen is accompanied by a dramatic change in their production of adenosine triphosphate (ATP). Given that oxidative phosphorylation creates many more ATP molecules per unit of glucose, one might have imagined that activated T cells might switch to overwhelmingly aerobic metabolism. On the contrary, however, as Michalek and Rathmell (28) mention, activated T cells switch off the aerobic metabolic pathways that dominate in resting T cells and convert to glycolytic production of ATP, a phenomenon that is permitted by the drastically increased level of glucose transport into the cells. Why would activated lymphocytes switch from aerobic to anaerobic metabolism when the latter is so much less efficient, glucose molecule for glucose molecule? Perhaps the anaerobic metabolism of activated T cells allows them to flourish in relatively oxygen and/or glucose-deprived tissues such as tumors and extra circulatory sites. The switch may also allow lymphocytes to escape damage from reactive oxygen species, the inevitable byproducts of the ramped up mitochondrial activity required by respiration.

At the end of the immune response, T cells that survive must switch back to a resting metabolic state. Only cells that are able to make this transition will be able to become memory cells. As growth factors that sustain T-cell responses decline during the time the

response wanes, the T cells must find alternative fuel. One way in which they may do this is via autophagy, but this is only a short-term option and autophagy will eventually lead to apoptosis (13, 17). An alternative source of fuel may be provided by lipids as the transition of activated T cells into memory cells requires TRAF6 [tumor necrosis factor (TNF)-associated factor 6] that somehow promotes lipid-β metabolism (28, 45)

Antibodies can tone down immune responses

The injection of immunoglobulin (Ig) molecules intravenously has been found to reduce inflammation in autoimmune patients and in mouse models of autoimmunity. While the mechanism of this action is still unclear, Nimmerjahn and Ravetch (46) argue that the presence of sugar moieties on the Ig molecules is required. The sugars can be recognized by a population of macrophages in the spleen, and these cells can then trigger an anti-inflammatory pathway. This theory suggests the intriguing idea that by altering the glycosylation state of Ig molecules, the immune system can strike a balance between inflammatory and anti-inflammatory signals.

Cell death

We are all very well aware that cells can die in several ways: apoptosis, auxotrophy, and what is now called necroptosis. A number of the articles in this volume describe these processes in detail (11, 13-15, 17, 18) and the circumstances under which they apply, not only to antigen-specific lymphocytes but also to dendritic cells and granulocytes. As many of the reviews in this volume discuss, there are two main pathways by which cells die: the extrinsic and the intrinsic. The extrinsic pathway involves the ligation of cell surface molecules that initiate a cascade of protein interactions culminating in the activation of caspase 8(47, 48). The role of these cell surface molecules, including Fas and TNF receptor, in cell death has been complicated by the finding that some components of the pathways, such as Fas itself, have been shown to have opposing roles in the immune response: both acting to increase or decrease T-cell responses in different systems. Walsh and Edinger (17) suggest that this apparent contradiction can be explained by the fact that T cells that lack Fas-associated death domain protein (FADD) undergo increased amounts of autophagy and that this leads to death by necrosis rather than the expected apoptosis following T-cell activation, a process that requires the presence of FADD.

Hedrick *et al.* (13) also discuss the confusing findings that defects in caspase 8 result in increased cell death, often by necroptosis rather than apoptosis. They suggest that in the absence of this caspase, T cells may believe they have been infected by a virus, which often express inhibitors of caspase 8. Better, therefore, to die than to survive and propagate a virus. These data suggest that experiments in which one death pathway has been blocked cannot be easily interpreted as the molecules involved in the various death pathways are sensed by the cell at all times; any alternation throws the cell out of kilter, altering this careful balance.

It's not over when it's over, immunological memory

We still do not completely understand how antigen-activated lymphocytes decide their fate, whether to survive and become some sort of memory cell or to die. For T cells, clearly the conditions under which the cell was activated determine to some extent the fate of the cell. For example, adjuvants, via stimulation of innate immunity, spare some activated T cells from death (49, 50). In this volume, Cui and Kaech (27) describe the properties characteristic of $CD8^+$ cells that will convert to functional memory and the phenomena that, in addition to inflammation, aid such a conversion. Such phenomena include antigen dose, costimulatory molecules, the presence of IL-2 and, later, IL-15, and good expression of the transcription factor Bcl-6 versus Blimp-1 (26, 27, 51).

While there has been considerable attention paid to the transition of effector T cells into memory cells, we still have little understanding of the transition of activated B cells into the memory or plasma cell pool. The transcription factors that determine B-cell fate have been studied. It is thought that the presence of Bcl-6 induces memory cell generation, while the opposing transcription factor Blimp-1 sends B cells down the plasma cell route (52-54). However, less well appreciated is what signals tell the B cells to upregulate or downregulate these two critical transcription factors and of course what signals regulate whether the activated B cell dies or not. On the whole, it seems that mature B cells and their various memory descendants are controlled by TNF- related cytokines, BAFF (B-cell activating factor belonging to the TNF family), CD40L, and APRIL (a proliferation-inducing ligand) (20), whereas T cells of course remain, like their precursors, addicted to cytokines related to IL-2 (26, 27). The induction of long-lived plasma cells in the bone marrow is a universally important consideration, as these are the cells that provide the protection mediated by almost all of the current human vaccines (55). Ammana and Slifka (19) argue that the lifespan of the plasma cell is determined by the signals that the precursor B cell received during activation. For example, an antigen with a repetitive structure supplemented with T-cell help will lead to the generation of long-lived plasma cells, perhaps because these antigens are often found on the surface of microorganisms such as viruses. Certainly it is clear that the lifespan of plasma cells varies from several years to a whole lifetime, and there must be factors that determine which cells survive in the finite space in the bone marrow.

Apologia

The authors apologize for the fact that in their list of references they have concentrated on the articles in this volume. Surely the contributors deserve a nod for putting in the work. More importantly, we also apologize for the fact that some issues related to resolution of the immune response are inadequately discussed herein. We are thinking particularly of the processes that mop up dead cells and get rid of inflammatory mediators such as the cytokines, chemokines, and various arachidonic acid derivatives. Defects in these processes certainly lead to prolonged inflammation and, in some cases, to autoimmune disease (56-59). Some discussion of desensitization as it relates to chemokine and cytokine receptors might also have been useful. Thinking that the subject has already been well and frequently reviewed, we deliberately did not include an article on regulatory T cells, though, as the reader can easily notice, they have showed up all over the place in the articles in this volume anyway. There is also the problem that we may not have distinguished well between circumstances that prevent the immune response from getting off the ground in the first place versus circumstances that resolve the immune response once it is over.

The great conundrum

Clearly the immune response is limited in many ways, both during the actual response and later as the response resolves. One of the major problems facing us immunologists today is, therefore, if the response is limited in so many ways and if each cell actually contains the seeds of more than one of these processes, why is it that interruption of even just one of these systems leads to autoimmunity? For example, lymphocyte death can be mediated by both the intrinsic and extrinsic apoptotic pathways, yet inhibition of either of these leads to autoattack. Admittedly, hosts that are knocked out for both apoptotic pathways suffer more severe and rapid autoimmune disease; however, the redundant aspects of these and other pathways are nevertheless apparently not complete.

Why not? Is it that some cells that, even though appear identical to their fellows, can only be destroyed or inactivated by one route? Is this controlled by the type of cell, the structure and persistence of the antigen, and/or the nature of costimulation to which the cell is exposed, or is the issue entirely stochastic, by chance a few cells escape one mechanism and are

normally mopped up by another? Thus, they are allowed to survive if one or other controlling process is missing. Along perhaps related lines, why is the autoimmune response that results so frequently lupus-like, regardless of the nature of the mutation that allowed the response? Is this because researchers most frequently measure anti-nuclear antibodies, or is it that the escape mechanisms allow recognition of antigens that are widely available, sparing attack on antigens located in immune privileged sites? Whichever, it is clear that the resolution of the immune response plays a critical role in the prevention of ongoing inflammation that can lead to autoinflammatory or autoimmune diseases. Understanding how to control the cells and molecules that themselves control the immune response is as important as understanding their initial activation.

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