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Editorial

Dysregulating the regulators

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Two articles in this issue of *Journal of Biology* prompt a brief reflection on the regulation of adaptive immune responses. (I suspect many, if not most, non-immunological readers may find immunology impenetrable, and I cannot promise that what follows will reassure them, so they may like to click over to something else – Articles by Semple on diabetes [1], or Garfield and Wray on the evolution of development [2], *inter alia*, may interest them. Immunologically sophisticated readers will not learn anything and may also be better advised to read something else.)

Both of the articles that occasioned this excursion discuss the consequences of disrupting the regulation of the immune system. In one case the disruption is by dioxin and other aryl hydrocarbon environmental pollutants [3], in the other by helminth parasites [4]. In both cases the effect is immune suppression. Both invoke a class of cells known as regulatory T cells, although they are mentioned only peripherally in the article on helminths, the main point of which is to draw attention to recent evidence that the increasing prevalence of asthma and other allergic disorders in developed countries may reflect immune hyperresponsiveness that evolved to counter chronic immunosuppression by parasites in less salubrious times. (Readers may recognize this as the so-called hygiene hypothesis.)

Regulatory T cells are one of four known subsets of T lymphocytes all belonging to the class known as CD4 T cells after the defining (and functionally crucial) marker they all express. The three other subsets are known as T_H1, T_H2 and T_H17 cells, all of which activate other immune cells of different types and with distinct functions, defined by the distinct cytokines by which they signal to the cells they activate (this is all summarized in Figure 1 of [3], and a general account can be found in [5] and [6]). The H stands for helper (because they act on, or help, other cells). T_H1 and T_H2 cells were so named when it was first recognized that there is more than one kind of helper T cell; and T_H17 when it became clear that there is a third: the 17, with the perverse logic that so bewilders non-immunologists, stands for interleukin-17, one of the defining cytokines produced by these cells.

All of these helper T cells to some extent regulate one another: T_H17 cells seem to operate early, though they are also believed to be responsible for some chronic autoimmune diseases, and are suppressed by the later-arriving T_H1 and T_H2 cells; and T_H1 and T_H2 cells tend to suppress one another, so that one or other prevails, depending, it is thought, on the activating cytokines elicited from other immune cells by the distinct kinds of pathogens they must combat. Regulatory T cells are specialized to suppress all the other types of helper cells. They are produced at the expense of T_H17 cells, and vice versa, depending again on the prevailing cytokines, and are thought to be a major mechanism for preventing autoimmune responses. An immune cell that can specifically suppress other immune responses is clearly of practical interest.

The entire cast of characters above (and others, but enough is enough, and these will do to make the point) appears in Brigitta Stockinger's article [3] on what, exactly, aryl hydrocarbons do to immune responses, which, as she explains, is not yet clear, though the net effect is immunosuppression. All of these cells have receptors for aryl hydrocarbons, presumably to enable them to respond to a physiological signal whose exact function, so far, is unknown. The question is how the actions of these receptors lead to immunosuppression. Stockinger argues that it is not simply that they switch off immune cells, but that because they are expressed at different levels on the distinct functional classes of cells, they may differentially affect distinct subsets and this dysregulates the entire system, because all these cells interact.

In particular, she suggests that they may preferentially damage those cells on which they are more highly expressed; and this would favor the survival of regulatory T cells, which express the receptors at very low levels. An alternative interpretation is that ligand binding to the aryl hydrocarbon receptor induces the differentiation of regulatory T cells. The difference, Stockinger urges, is important, because there is, on the basis of recent research, some interest in the potential of aryl hydrocarbons to activate regulatory T cells for treatment of hitherto intractable autoimmune disease.

Regulatory T cells, as presently understood, specifically suppress other immune cells with autoimmune potential; they may also be induced in response to chronic stimulation by infectious or other foreign agents, and thus prevent tissue damage. Most immunosuppressive agents available in the clinic are relatively blunt instruments that

suppress, at best, entire classes of immune cells, and with them the protection they provide. It is thus hard to exaggerate the interest in the possibility of activating suppressive cells specifically targeted at the responses you do not want, and they are under investigation in many contexts (Rick Maizels [4], for example, mentions recent work of his indicating that induction of regulatory T cells by parasites can suppress allergic responses). Had not the holy grail of Christian mythology become the most tiresomely overused metaphor in the scientific literature, I might be tempted to deploy it here.

In practice however therapeutic intervention in the regulatory interactions of immune cells may not always be readily achieved, arguably because they are simply not well enough understood. The trial of TGN1412 in 2006 is a dramatic case in point [7]. TGN1412 is a potent antibody against CD28, a surface molecule that activates T helper cells in the presence of infection, but that has also been reported to activate regulatory T cells. In a phase 1 clinical trial aimed at developing the antibody as an immunosuppressant, six volunteers collapsed with multiorgan failure consequent on the rapid induction of inflammatory cytokines from T cells indiscriminately and powerfully activated by binding of CD28. Perhaps the most surprising thing about this trial is how unsurprising the result may seem, given the physiological function of CD28; although the commentary [8] accompanying the report on the volunteers in *The New England Journal of Medicine* persuasively explains the rationale for the expectation of immunosuppression. The aryl hydrocarbon receptor, whose physiological function is unknown, seems certain to be approached with more caution as a therapeutic target.

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