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DISCUSSION FORUM

Introduction to the Series

Seven years ago, I published the first version of the Danger model, suggesting that the immune system is more concerned with damage and destruction than with foreignness [1]. Though it explained a lot of things, it was new, untested, and covered only a small fraction of immunological phenomena. Since then, several of its predictions have been tested, and I have discussed the model hundreds of times and presented it to thousands of people. Their questions, criticisms, suggestions and feedback (both positive and negative) have helped to round out the 7 year old skeleton and make me realize that it is far more powerful than I had anticipated. I am very grateful therefore that the *Scandinavian Journal of Immunology* has extended the invitation to offer an update, and a generous format with space enough to put in some of the details that give the model life.

This will be the first of a series of essays describing the Danger model of immunity. In this first essay, I will describe the model itself and the historical context in which it sits. Later essays will show how the model deals with a wide variety of immunological phenomena, covering aspects in which the immune system seems to do things right (like responses to infections and nonresponses to foetuses) as well as some in which it appears to get it wrong (like the lack of response to most tumours and the occasional presence of responses to self components that result in autoimmune disease). Along the way, we will cover such topics as transplantation immunity, tumour immunity, the need for adjuvants, the maternal/foetal relationship, self tolerance during puberty and metamorphosis, graft versus host disease, autoimmune disease versus 'useful' autorecognition, responses to parasites, and the control of effector class.

There are also some things I will not cover, such as T- and B-cell development, and the maintenance of memory. Although these are important areas of immunological study, they are not in the realm of the Danger model, which is concerned with the initiation of immune responses. The developmental events that prepare the immune system to see a universe of antigens, or that help it maintain memory of past encounters, belong to a different domain of questions, and their details do not impinge much on the Danger model. I have written somewhat about these issues in the past [2, 3, 4] and will leave most future thoughts about them for other essays in other venues, except for those cases where they directly affect the immune system's decision of whether to respond or not.

These are essays of unabashed advocacy. The model certainly has limitations, and I will attempt to point those out as we go along. But it also has strengths. Firstly, it has made predictions that, when tested, were found to hold. Secondly, time and time again, as I wandered the world talking about the model, listening to other people's comments, and thus learning new details of the immune system from immunologists, virologists, parasitologists, physicians, students and taxi drivers that I encountered, I discovered that the Danger model offered surprising new explanations for old phenomena. For example, why unmatched kidney transplants from living donors often do better than major histocompatibility complex (MHC) matched kidneys from cadavers [5], why women seem to be more susceptible than men to certain autoimmune diseases, why graft versus host disease is less severe in gnotobiotic animals or in recipients that have had gentle rather than harsh preconditioning treatment [6, 7], why Rh disease of the newborn is much more often a problem in the second pregnancy than in the first, etc. Surprisingly these new explanations required no special new assumptions but followed clearly from the basic assumptions that have stood since the model's inception.

Although there is some power in a model that continues to explain new and (previously unexplained old) phenomena, that explains both those cases where the immune system functions appropriately and where it seems to malfunction, and that does all this with a few simple assumptions, for me, the greatest benefit from the model didn't stem from the details of the model itself but from a shift in point of view that occurred to me slowly as I worked with it. This was a shift towards the view that neither the adaptive nor the innate immune systems have the ultimate say in things. That power lies with the tissues. Once I started looking at the immune system from the point of view that it is controlled by the bodily tissues, the Danger model expanded to cover areas that I had not expected. Originally conceived as an answer to the first question the immune system must ask when faced with a potential threat, namely 'shall I respond?', it suddenly expanded to also cover the next question 'if I have decided to respond, what sort of response shall I make?'. How does the immune system know whether to generate killers to catch a virus, or immunoglobulin (Ig)E to catch a worm? How does it discriminate between virus, intra- or extra-cellular bacterium, and worm? In short, how does it determine what effector classes to produce? I believe that this decision too is controlled in some measure by the tissues, and the last essay of this series will be an attempt to describe the mechanisms by which tissues might exert this level of control.

At the website of the *Scandinavian Journal of Immunology*

(URL http://www.blackwell-science.com/sji), there will be a section for comments to each essay. I hope that readers with criticisms, comments, data that fit or don't fit with the model, suggestions for experiments, critiques of previous experiments, etc. will find it interesting, worthwhile and fun to converse there with me and other readers. In the past, it has often been the accumulated knowledge of minute details that led to the understanding of a complex system, but no one of us can possibly know all the details of the immune system's wondrously complex machinations. Perhaps, by pooling our collective wisdom and our collective knowledge of the details, we will uncover connections that would otherwise remain hidden

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