

An Innate Sense of Danger

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KEYWORDS: self and non-self; immune system

For three quarters of a century, immunologists have based their theories and experiments on the fundamental belief that the immune system discriminates between self and non-self and that, if the system were perfect, it would attack everything that is non-self and be totally tolerant of anything that is self. I have abandoned this belief. Over the years there have accumulated too many immunological findings that don't fit with and too many questions that are not answered by this paradigm.

For example, if each individual's immune system learns "self" at an early age, then why are new antigens that appear at puberty not considered "foreign" and destroyed. How can normal individuals contain both T and B cells capable of reacting to self antigens like DNA, keratin, and myelin basic protein, yet not have destructive autoimmunity. Why are liver transplants rejected less vigorously than hearts? Why is a newly lactating breast not rejected when it begins to make new proteins? Why is the immune system so bad at dealing with tumors, even when they demonstrably express new, "non-self" antigens? Why do we need adjuvant? Why do we not normally respond to all the foreign antigens in food, to our commensal intestinal bacteria, or to our fetuses or to the sperm that begot them?

The answers to these questions are not easily found when we approach the immune system from a self–non-self viewpoint, although they fall easily into place when approached from the perspective that the immune system is more concerned with danger and potential destruction than with the distinction between self and non-self.

The danger model is based on the idea that the driving force for the immune system is the need to recognize danger. The model starts with the idea that the immune system defines "danger" as anything that causes tissue stress or destruction. Under this model, antigen-presenting cells are activated by alarm signals from stressed or damaged tissues. Without this activation, no primary immune response can occur. Some of the recent evidence in its favor has been shown and its implications for all of the questions above discussed.

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Ann. N.Y. Acad. Sci. 961: 341–342 (2002). © 2002 New York Academy of Sciences.

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