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Initiating immunity: Antigen presentation by dendritic cells

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Abstract

Most if not all antigen-specific immune responses are initiated by dendritic cells (DCs), among the most efficient of all antigen presenting cells, and one with an exceptional capacity to stimulate even naive T lymphocytes. DCs can not only elicit both MHC class I and class II-restricted T-cell responses, but can polarize T cells to develop along specific pathways (e.g. Th1 vs Th2 cells). Another feature of DCs is their ability to mediate "cross presentation", i.e. the presentation of exogenous antigens on MHC class I molecules. Cross presentation is thought to play a critical role in triggering anti-viral and perhaps anti-tumor immune responses while, at the same time, ensuring tolerance to self antigens. Thus, DCs appear to be important both for initiating and for controlling T-cell responses to antigen.

The DC's remarkable capacity for antigen presentation is currently the subject of intense investigation. It is a problem of interest because of its fundamental cell biology but also because understanding the mechanisms of antigen presentation by DCs will greatly assist mobilizing their activities for the purposes of aiding the development of rational vaccine strategies or for intervening in chronic inflammatory reactions. Indeed, recent work from our group as well as other groups have demonstrated that DCs exhibit a range of specializations that combine to enhance their antigen presenting abilities. Central to these specializations is the fact that DCs developmentally and spatially compartmentalize their abilities for antigen accumulation and antigen presentation by a process termed "maturation". In peripheral tissues, highly endocytic immature DCs reside as sentinels awaiting the arrival of foreign antigen. As immature cells, antigen is internalized, delivered to lysosomes which are also rich in MHC class II molecules, but reside there undegraded and are thus unable to be used to generate peptide-MHC class II complexes.

Shortly after encountering any of a variety of activating stimuli, however, the immature DCs initiate a dramatic alteration both in morphology and function. Endocytosis and thus antigen accumulation is down regulated, newly synthesized MHC class II molecules are now transported to the plasma membrane, and lysosomes are turned on. This latter event involves an activation of lysosomal enzymes that had been quiescent in immature DC lysosomes. This, in turn, leads to the proteolysis of previously internalized antigen and the subsequent production of peptide-MHC class II complexes. The activation of proteolysis also enhances the rate of invariant chain degradation, probably responsible for the redirection of newly synthesized molecules. Finally, the lysosomes themselves begin to exhibit unique tubular extensions, which break off and serve as carriers of the newly formed MHC-peptide complexes to the DC surface. This last event has most recently been observed by live cell video imaging of DCs expressing GFP-tagged MHC class II molecules.

Similarly, cross presentation of exogenous antigens on MHC class I molecules becomes activated concomitant with DC maturation. Interestingly, however, not all maturation signals are capable of triggering cross presentation. Thus far, we have found this to occur only following the ligation of surface CD40 molecules or the disruption of E-cadherin-mediated cell-cell contacts.

It is likely that a variety of specializations also occur at the DC plasma membrane. DCs appear to interact with T cells in a highly dynamic fashion, most typically "embracing" them closely but only for finite periods of time (<90 min) even in the presence of antigen. MHC molecules may also be clustered in a unique fashion at the DC surface, perhaps increasing the opportunity for recognition events by T cells.

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