

Human mast cells as antigen-presenting cells: When is this role important *in vivo*?

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In this issue of the *Journal*, Lotfi-Emran et al.¹ report that IFN- γ -primed human skin-derived mast cells can take up and process antigens and act as antigen-presenting cells (APCs) *in vitro*. Such APC function was demonstrated with the Jurkat T-cell line and, more importantly, with autologous CD4⁺ T cells. In addition to inducing *Staphylococcus aureus* superantigen-dependent T-cell responses, IFN- γ -primed mast cells from CMV-seropositive donors took up CMV antigen and activated recall responses and IFN- γ production in autologous CMV-specific CXCR3⁺CD4⁺ T cells, thereby pointing to a potential “feed-forward loop of T_H1 cell–mast cell cross-activation.” Finally, the authors provided evidence that mast cells can take up soluble or particulate antigens in an IFN- γ – and IgG opsonization-independent manner and that mast cells could “co-opt” their protease-containing secretory granules for antigen processing and presentation.

The idea that mast cells can function as APCs in addition to being versatile effector cells of innate and adaptive immune responses is not new and initially generated some skepticism.² It is well established that a “professional APC” must be able to deliver 3 signals needed to activate CD4⁺ T cells: (1) presentation of peptide–MHC class II complexes to specific T-cell receptors (after internalization of soluble or particulate antigens and processing and loading of antigen-derived peptides onto MHC class II to create complexes, which are then translocated to the APC surface), (2) expression of certain costimulatory molecules, and (3) production of “instructional” cytokines.² Professional APCs also must be able to respond to local signals through pattern recognition receptors, migrate to the draining lymph nodes, and activate both naive and memory CD4⁺ T cells.

Mast cells appear to satisfy many of these criteria. Koch et al³ reported in 1984 that treatment with IFN- γ induced the expression of MHC class II molecules on the surfaces of mouse bone marrow-derived mast cell lines *in vitro*. Subsequent work

confirmed that mouse and human mast cells can express MHC class II molecules, especially after exposure to IFN- γ or during immune responses likely to include increased levels of that cytokine.² Mouse^{2,4} and human² mast cells also can express various costimulatory molecules, but as with MHC class II expression, such expression can vary according to the type of mast cell and the setting.^{2,4-7} For example, Lotfi-Emran et al¹ showed that IFN- γ can induce expression of HLA class II and HLA-DM, as well as the costimulatory molecules CD40 and CD80 (but not CD86) on human skin-derived cultured mast cells. Both mouse and human mast cells also represent a potential source of a large array of cytokines, including those that are instructive to T cells, such as IL-4, IL-12, and IL-13 and IL-18.^{7,8} Finally, mast cells can respond to local signals through pattern recognition receptors, and there are reports that, under some circumstances, mast cells can migrate to local lymph nodes.^{2,7}

Although these findings indicate that mast cells have the potential to fulfill many of the criteria necessary to be considered a professional APC, we are not aware of convincing evidence that mast cells actually can induce activation of naive T cells, especially *in vivo*. Perhaps, unlike professional APCs, mast cells do not properly coordinate, in time, space, or both, provision of the 3 signals needed to activate naive T cells in time, space, or both. Or perhaps we have not identified or properly examined the setting or settings in which mast cells can function as true professional APCs.

Although mast cells might not qualify as professional APCs, the findings of Lotfi-Emran et al¹ add to a growing body of evidence indicating that mast cells can indeed function as nonprofessional or atypical APCs. Early studies evaluating whether mast cells can present antigen yielded conflicting findings, raising the concern that small numbers of professional APCs contaminating the tested mast cell populations might have influenced the “positive” results.² However, as noted by Lotfi-Emran et al,¹ subsequent work,^{5,6} including that using imaging approaches to analyze antigen presentation at single-cell resolution,⁶ provided unambiguous evidence that mouse mast cells can take up, process, and present antigen to preactivated antigen-specific CD4⁺ T cells through formation of immunologic synapses and that such findings can be observed both *in vitro*^{5,6} and *ex vivo*.⁶ Lotfi-Emran et al¹ also pointed out that some of their findings are consistent with those of an earlier study,⁹ which reported that IFN- γ -primed *in vitro*-derived human mast cells can fine tune T-cell cytokine profiles by inducing concomitant production of IFN- γ and IL-22 from circulating memory CD4⁺ T cells in a system of superantigen stimulation. Gaudenzio et al also provided evidence that this process can occur in the skin *in vivo* in patients with psoriasis.⁹

Perhaps the most provocative findings of Lotfi-Emran et al¹ are those that suggest that mast cells can differ importantly from other APCs in being able to use different proteolytic pathways to

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process antigens for presentation to T cells. Professional APCs process antigens through an acidic phagolysosomal pathway involving lysosomal proteases (eg, cathepsins).² Lotfi-Emran et al¹ show that human mast cells can be activated to degranulate on antigen presentation to CD4⁺ T cells, albeit to a relatively small extent. Although it remains to be determined whether this finding is related to the observation that mast cells exhibit a lower threshold of activation through FcεRI on antigen presentation to CD4⁺ T cells,⁶ both studies indicate that some mast cells can be activated to secrete mediators while also functioning as APCs. Notably, Lotfi-Emran et al¹ also report structured illumination microscopy findings indicating that antigen can be transiently colocalized with HLA-DR and tryptase within the cytoplasmic granules in mast cells stimulated with IFN-γ, and they suggest that one of the consequences of antigen trafficking through mast cell cytoplasmic granules might be the generation of novel antigen-derived peptides that could in turn extend further the repertoire of activated CD4⁺ T cells. This is a very interesting possibility that, as noted by the authors, deserves further study.

Beyond functioning as nonprofessional APCs, mast cells can help to shape the nature of adaptive immune responses through other mechanisms. For example, mast cells can take up soluble antigens recognized by their bound IgE and then transfer such antigens to dendritic cells that then present the antigens to T cells.² Mast cells also can transport IgE-bound particulate antigens into a secretory compartment and then release them on subsequent mast cell activation.¹⁰ Certain cultured mast cells also can produce immunologically active exosomes.^{2,7} Finally, by representing a source of diverse cytokines and other mediators, mast cells have the potential to modulate the phenotype and function of other nonprofessional and professional APCs in ways that can both influence the APC functions of such cells and modulate the development of adaptive immunity.⁷

In summary, in light of the data reported by Lotfi-Emran et al,¹ it is quite clear that cultured human skin mast cells can function as nonprofessional APCs. Mast cells might even have some arguably unique tricks to offer when serving as APCs, such as the ability to

modify T-cell cytokine profiles or process antigens in part through their cytoplasmic granule proteases. However, the group of nonprofessional APCs is a large one,² which supports the notion that many individual types of APCs can provide functions that are largely redundant with those of other APCs also active in that setting. Accordingly, it will now be important to determine under which circumstances, if any, mast cells provide nonredundant APC functions that are critical for shaping particular adaptive immune responses *in vivo* and whether such APC functions are provided by mast cells in draining lymph nodes, tertiary lymphoid structures, and/or locally in tissues where mast cells normally reside.

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