P11-05. Induction of CD8+ T cell mediated immune responses through skin and mucosa: identification of immunostimulatory versus tolerogenic dendritic cells

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Background

Mucosae and skin are populated with dendritic cells (DC) (epithelial Langerhans cells [LC] and conventional DC in lamina propria/dermis) and represent privileged sites for anti-infectious vaccination.

Methods

To determine which immunostimulatory DC subset needs be targeted by vaccines, we investigated the nature of DC involved in the induction or regulation of cytotoxic CD8+ T cells (CTL) in mice.

Results

We first documented (Leborgne et al. Immunity, 2006) that CD8+ CTL can be primed by intradermal immunization (in buccal mucosa or skin) with a protein Ag combined with adjuvants inducing local secretion of the chemokine CCL20. We found that *in vivo* priming of CTL responses was induced by newly recruited DC rather than skin/mucosal resident DC. These inflammatory-type DC derive from circulating Gr1+ monocytes, are recruited by a process involving CCL20 and CCR6, and directly cross-present the Ag to CD8+ T cells. Alternatively, using conditional ablation of LC in Langerin-DTR mice and the contact sensitizer DNFB (which modifies self proteins), we showed that epithelial LC are dispensable for priming CD8+ CTL mediating delayed-type hypersensitivity responses. Moreover, using a structurally related but tolerogenic hapten, DNTB, we demonstrated that LC migrate to draining lymph nodes for Ag presentation to CD8+ T cells, but were unable to prime CTL. Depletion of LC prior to hapten immunization allowed for priming of cytotoxic T cells, indicating a tolerogenic role for LC. In addition, induction of potent CTL responses is accompanied by the recruitment of inflammatory monocytes at the site of immunization and presentation of the Ag in draining lymph nodes by both LC and Langerin-DC.

Conclusion

Our data demonstrate that, while resident LC of pluristratified mucosae and skin display tolerogenic functions, adjuvants able to recruit monocyte-derived inflammatory DC into mucosae can break tolerance and allow for priming of protective cytotoxic CD8+ T cells.