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Meeting report

In vitro regulation of development and function of dendritic cells

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Dendritic cells (DC) are professional antigen presenting cells which are required for the initiation of immune responses. They are characterized by the expression of high levels of MHC class II products and an unusual dendritic shape. Although found in all organs, DC are present at trace level making tedious their purification and functional studies. Human DC can now be generated *in vitro* in large numbers by culturing CD34+ hematopoietic progenitors in presence of GM-CSF+TNFalfa during 12 days [Caux et al (1992) Nature 360 : 258].

In vitro generated DC are characterized by a typical dendritic morphology (lobulated nucleus, villous surface), the expression of CD1a antigen and the presence, in 20% of CD1a+ DC, of Birbeck granules that are characteristic of epidermal Langerhans cells. CD1a+ DC induce strong stimulation of alloreactive T lymphocytes including CD4+ T cells and cytotoxic CD8+ T cells. Furthermore, they can capture a soluble antigen, process it, and present it to established T cell clones. The strong antigen presenting capacity of DC is suppressed by IL-10 and is related to the expression of CD80 (B7-BB1) and mainly CD86 (B70) which represents the major functional ligand for CD28. As all antigen presenting cell, DC express CD40 which triggering induces survival, morphological changes, expression of accessory molecules (CD58, CD80, CD86), CD25 expression and cytokine secretion (TNFalpha, IL-8, MIp1alpha). As DC activated T cells upregulate CD40-Ligand (CD40-L), it is likely that CD40 activation of DC mimics physiological interactions between DC and T cells occurring during the early phase of T cell activation.

As T cell activation is followed by B cell recruitment, we wondered whether DC might directly interact with B cells. In a system where CD40-L transfected L cells were used as surrogate activated T cells, DC were found to considerably modulate all stages of B cell growth and differentiation. In particular, DC induce 1) a 3 to 6 fold enhancement of CD40-L dependent B cell proliferation, 2) a 10 to 100 fold increase of IgG, IgA and IgM secretion by CD40-activated memory B cells, 3) the stimulation of IgM secretion by CD40-activated naive B cells in presence of IL-2, 4) the induction of surface IgA expression and the secretion of large amounts of IgA by CD40-activated naive B cells in presence of IL-10. Thus, DC may play a major role in the extrafollicular IgM plasma cell formation occurring during primary humoral responses and in the induction of mucosal-type humoral responses.

Two subsets of DC progenitors could be identified, at early time points (day 5-7) during the culture, according to CD1a and CD14 expression. CD1a+ progenitors give rise to Langerhans cells characterized by the expression of Birbeck granules and E-cadherin, a molecule involved in homophilic interactions between keratinocytes and Langerhans cells in the epidermis. In contrast, the CD14+ progenitors mature into CD1a+ dendritic cells lacking Birbeck granules and E-cadherin but expressing CD68 and the coagulation factor XIIIa described in dermal dendritic cells (dendrocytes). The CD14+ derived DC are probably related to DC

derived from monocytes cultured in presence of GM-CSF+IL-4, with regard to their phenotype and lack of Birbeck granules. Both subsets express high levels of accessory molecules (CD80, CD83, CD86, CD58) and demonstrate a strong capacity to stimulate allogeneic naive T cells. In contrast, only the CD14+ derived DC can induce CD40-activated naive B cells to produce IgM in presence of Il-2.

Altogether, those results demonstrate that different DC subpopulations can be generated *in vitro* that correspond to DC populations that have been identified earlier *in vivo*. The *in vitro* generation of those DC and the understanding of their physiological role should make it feasible to explore the immunogenic potential of those cells in clinical situations, such as the presentation of antigens in resistance to infections and tumors.

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