

DCs, FcγRs, Internalisation & Presentation

Dendritic cells (DCs) comprise a family of professional antigen presenting cells that are crucial in the initiation of primary CD4+ and CD8+ T cell responses (Banchereau and Steinman 1998). Immature DCs are well equipped to capture antigens but they lack the co-stimulatory signals for efficient T cell activation. In mature DCs, antigen uptake capacity is decreased, whereas expression of co stimulatory molecules and MHC molecules is increased, and concomitantly T cell activation is enhanced.

DCs internalise exogenous antigens by fluid-phase pinocytosis or by receptor-mediated endocytosis (Banchereau and Steinman 1998; Colaco 1998). DCs express receptors (FcγRs) for the Fc portion of IgG, which mediate internalisation of antigen-IgG complexes. FcγR-mediated internalisation of these complexes by DCs is associated with enhanced presentation of peptides derived from the antigen (Regnault *et al.* 1999). In addition, FcγR engagement also induces the maturation of DCs (Schuurhuis *et al.* 2002). MHC class II-restricted antigen presentation is 1,000 to 10,000-fold more efficient than fluid phase pinocytosis and FcγR-mediated endocytosis can efficiently cross-present the internalised antigens on MHC class I (Amigorena 2002; den Haan and Bevan 2002).

Therefore FcγRs represent a privileged antigen and internalisation route for the efficient MHC class I- and II-restricted antigen presentation by DCs to both CD4 and CD8 T-cells (Nimmerjahn and Ravetch 2008).

Immune Complexes

At the end of the primary immune responses and in the course of secondary responses, the production of specific antibodies induces formation of immune complexes (ICs) between antigens and specific IgGs. The rapid rise in the specific antibody response enables the neutralisation and/or opsonisation of pathogens as well as the formation of ICs that binding and cross link the FcγRs on DCs leading to efficient antigen uptake and presentation to specific T-cells (Amigorena 2002; Colaco 1998; Nimmerjahn and Ravetch 2008). Furthermore immunisation with ICs has been shown to correct the age-associated deficiency in the germinal centre response (Zeng *et al.* 2007).

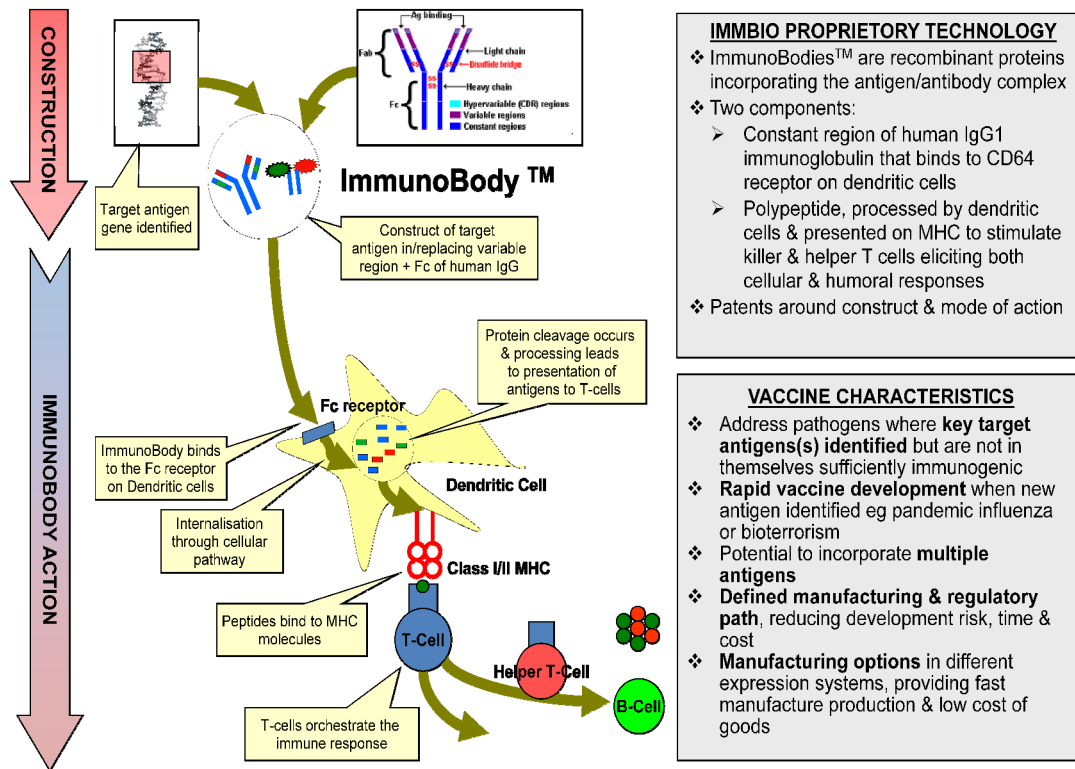
FcγRs

Three subtypes of FcγRs have been described in mice and humans: FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) (Nimmerjahn *et al.* 2005; Nimmerjahn and Ravetch 2008; Bruhns *et al.* 2009). Structurally, the FcγRs are all members of the immunoglobulin superfamily, having an IgG-binding α-chain with an extracellular portion composed of two (FcγRII and FcγRIII) or three (FcγRI) Ig-like domains. FcγRI is a high affinity FcγR, which binds monomeric and multimeric IgG. It is also an activating receptor. FcγRIIA, FcγRIIB and FcγRIII are low affinity FcγRs which bind multimeric IgG only. FcγRIIA and FcγRIII are activating but FcγRIIB is inhibitory.

The low affinity of most FcγRs has an important function: preventing binding to monomeric antibody molecules that are always present at high levels in the serum and thereby avoiding the potential non-specific activation of pro-inflammatory responses. By contrast, the high affinity FcγRI is constantly saturated with ligand; however activation only ensues after the receptors have been cross-linked by antigen (Nimmerjahn and Ravetch 2008; Bruhns *et al.* 2009).

ImmunoBodies™

ImmunoBodies are recombinant proteins that mimic ICs and incorporate the antigen-antibody complex in a single molecule. They comprise two components: the Fc region of human IgG1 that binds to the FcγRI (CD64) on DCs, and the antigen that is processed by DCs and presented on both MHC class I and class II molecules. ImmunoBodies are thus designed to target recombinant antigens directly to DCs and enable the stimulation of both CD4 and CD8 T-cell responses.



ImmunoBodies References

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