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REVIEW

The CD300 molecules regulate monocyte and dendritic cell functions

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Abstract

The CD300 glycoproteins are a family of related leucocyte surface molecules that modulate a diverse array of cell processes via their paired triggering and inhibitory receptor functions. All family members have a single Ig-V like domain and they share a common evolutionary pathway. At least one member of the family has undergone significant positive selection (ranked second in the top 50) indicating a need to maintain some crucial function. Here we have reviewed the CD300 family members, and their expression on cells of the monocyte and dendritic cell lineages. The consequences of CD300 molecule expression by these leucocyte lineages are only now beginning to be understood. The ability to fine tune monocyte and dendritic cell function and immune responses highlights several potential options to exploit these molecules as therapeutic targets in chronic inflammatory diseases, allergy and other disease states.

Keywords: CD300; Ig superfamily; Immune receptors; Myeloid lineage

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The regulation of monocyte and dendritic cell (DC) responses is essential to maintain the host's well-being. Whilst providing appropriate responses to pathogens when required, if not kept in check, these cellular responses can result in chronic inflammation. For example, the plasmacytoid DC (pDC) IFNα response needs to be self-limited to prevent the inappropriate responses seen in chronic inflammatory and autoimmune diseases such as psoriasis, systemic lupus erythematosus and Sjogren's syndrome (Bave et al. 2005; Farkas et al. 2001; Gilliet et al. 2004; Gottenberg et al. 2006; Ito et al. 2007; Nestle et al. 2005; Toukap et al. 2007). Constitutively expressed membrane molecules are well placed to sense changes in the environment and provide a level of control to regulate responses. The

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Table 1. Summary of the human CD300 family members.

Molecule	Haematopoietic expression	Immunoregulatory function	Family member with most similar Ig domain sequence
CD300a	Most leucocytes expect B cells and a subpopulation of T cells.	ITIM sequences	CD300c
CD300b	Monocytes, blood DC	Associates with DAP12, Grb2	CD300f
CD300c	Most leucocytes expect B cells and a subpopulation of T cells.	Human CD300c has not been demonstrated to associate with an adaptor molecule.	
CD300d	Monocytes, blood DC	?	CD300e
CD300e	Mature myeloid cells, not blood $Lin^{-}HLA\text{-}DR^{+}$ DC	Associates with DAP12	
CD300f	Mature myeloid cells and $CD16^{+}$ blood DC	ITIM sequences interacts with p85 PI3K	
CD300g	Not expressed on leucocytes		

CD300 family is one such group of leucocyte membrane molecules with the capacity to regulate DC and monocyte function. It consists of a cluster of seven genes located on human chromosome 17q25.1 named CD300a, CD300b, CD300c, CD300d, CD300e, CD300f and CD300g, (Table 1) (Clark et al. 2009). Each family member has a single Ig-V like domain. Two members, CD300a and CD300f, contain consensus immuno tyrosine based inhibitory motifs (ITIMs) in addition to other tyrosine residues in their cytoplasmic domain, whilst CD300b–e all have a charged amino acid in their transmembrane domain indicating a likely association with adaptor molecules. This molecular structure supports the view that CD300 molecules trigger or inhibit immune responses. This review discusses the role for the family in modulating human monocyte and DC responses.

Similarities between CD300 family members

The amino acid sequence similarity of the CD300 Ig domain ranges from 40% to 80% between the human family members. Cluster analysis suggests that the human family members have evolved in pairs; CD300a is most similar to CD300c, CD300b is most similar to CD300f and CD300d is most similar to CD300e. The CD300 Ig domain has evolved from an ancient Ig-like domain and related domains can be traced back to ancient vertebrates (Cannon et al. 2006; Stet et al. 2005). Orthologues for different CD300 genes have been found in mammals, birds and fish (Stet et al. 2005; Viertlboeck et al. 2006). CD300 molecules show the closest sequence similarity of any mammalian proteins to Modular Domain Immune type Receptors (MDIR) found in the clear nose skate (*Raja eglanteria*) (Cannon et al. 2006). CD300g bears a close relationship with MDIR1 and the remaining MDIR2–4 molecules show greater similarity to CD300a–f. Despite conservation in the CD300 domain from early times, at least one member of the family has undergone significant positive selection (Nielsen et al. 2005). CD300a is ranked second in the top 50 of positively selected genes in a comparison between chimpanzees and humans, indicating a critical need to adapt and maintain a crucial function (Bustamante et al. 2005). The presence of a CD300-like molecule in ancient vertebrates and the maintenance of its function predicts for a fundamental role in innate immunity.

Expression of the CD300 molecules

Transcripts for CD300 molecules are found in most tissues. PCR analysis has shown that CD300d and CD300f are transcribed in high amounts in the lung. High CD300c transcript levels are found in the spleen and thymus, whilst low levels of CD300b transcripts are found in these locations. At a cellular level, the human CD300 family has four expression patterns; CD300a and CD300c are expressed broadly on most leucocyte lineages, CD300b, CD300d and CD300f are restricted to the myeloid/DC lineages, CD300e is restricted to mature myeloid cells and CD300g is restricted to epithelial and endothelial cells. Only CD300g is not expressed by myeloid/DC lineages (Takatsu et al. 2006) so it is not discussed here further.

Flow cytometric analysis of monocyte and DC subpopulations demonstrated differential expression of the CD300 family members on these cells (Fig. 1) {Ju et al. 2008; MacDonald et al. 2002}. CD300e is restricted to mature $CD14^{+}$ monocytes, $CD14^{dim}$ cells (sometimes classed as DC) (Aguilar et al. 2004; Clark et al. 2007a) but is absent on lineage $^{-}HLA\text{-}DR^{+}$ peripheral blood DC. CD300a and CD300c are expressed by $CD14^{+}$ monocytes and all $lineage^{-}HLA\text{-}DR^{+}$ DC. Cell surface CD300f is found on a subpopulation of $CD14^{+}$ monocytes and is restricted