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The B7 family of immunoregulatory receptors: A comparative and evolutionary perspective

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ABSTRACT

In mammals, T cell activation requires specific recognition of the peptide–MHC complex by the TcR and co-stimulatory signals. Important co-stimulatory receptors expressed by T cells are the molecules of the CD28 family, that regulate T cell activation, proliferation and tolerance. These receptors recognize B7s and B7-homologous (B7H) molecules that are typically expressed by the antigen presenting cells. In teleost fish, typical T cell responses have been described and the TcR, MHC and CD28/CTLA4 genes have been characterized. In contrast, the members of the B7 gene family have only been described in mammals and birds and have yet to be addressed in lower vertebrates. To learn more about the evolution of components guiding T cell activation in vertebrates, we performed a systematic genomic survey for the B7 co-stimulatory and co-inhibitory IgSF receptors in lower vertebrates with an emphasis on teleost fish. Our search identified fish sequences that are orthologous to B7, B7-H1/B7-DC, B7-H3 and B7-H4 as defined by sequence identity, phylogeny and combinations of short or long-range syntenic relationships. However, we were unable to identify clear orthologs for B7-H2 (CD275, ICOS ligand) in bony fish, which correlates with our prior inability to find ICOS in fish. Interestingly, our results indicate that teleost fish possess a single B7.1/B7.2 (CD80/86) molecule that likely interacts with CD28/CTLA4 as the ligand-binding regions seem to be conserved in both partners. Overall, our analyses implies that gene duplication (and loss) have shaped a molecular repertoire of B7-like molecules that was recruited for the refinement of T cell activation during the evolution of the vertebrates.

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1. Introduction

The activation of T lymphocytes is finely tuned by a combination of signals delivered through the TcR–CD3 complex and accessory signals that can be either stimulatory or inhibitory. The initial signal through the MHC/peptide/TcR complex termed "signal 1" is not sufficient to induce full activation of naïve T lymphocytes and thus requires an additional co-stimulatory signal, which is antigen-independent (signal 2). This co-stimulatory signal is provided by interactions between B7.1 (CD80) and B7.2 (CD86) ligands on APCs and CD28 expressed on T cells (Freeman et al., 1993). Once receiving this confirmatory signal from the APC (signal 2), the armed T cell will only require signal 1 for future activation and effector functionality against non-self. In mammals, both B7.1 and B7.2 are required for full complete activation of the naïve T cell by providing a balance of activating and inhibitory signals. However, these two receptors display distinct expression patterns: B7.1 is inducible, while B7.2 is constitutively expressed on APCs, up-regulated upon activation in APCs (Larsen et al., 1994) and is required for the generation of mature DC repertoires. In contrast, the ligation of B7.1 and B7.2 with CTLA4 exerts an inhibitory effect on T cell activation, blocking Th2 responses and maintaining peripheral tolerance. Accordingly, comparison of B7.1-KO, B7.2-KO and B7.1/.2-KO mice and blocking antibodies suggests a complex role for these receptors in autoimmunity (Larsen et al., 1994; Lenschow et al., 1995; Poussin et al., 2003; Salomon and Bluestone, 2001). Mammalian B7.1 and B7.2 are membrane bound receptors containing one IgSF V domain, one IgSF C domain, a transmembrane region and rather divergent intracytoplasmic regions. Additionally, a splicing variant lacking the TM has also been described for B7-2, that is expressed by non-activated

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monocytes. The secretion of B7.2deltaTM induces proliferation and cytokine production by both naive and memory T cells (Greenfield et al., 1998), providing an example of additional structural complexities of B7-mediated co-stimulation. B7.1 and B7.2 genes have been found in many mammalian species and are tightly linked on human chromosome 3 and mouse chromosome 16 (Table 1).

Aside from B7.1 and B7.2, five additional receptors have been characterized and named "B7-homologs" (B7-H), owing to shared structural features with the primary B7 molecules. Three of these B7-H receptors bind members of the CD28 family, providing functional support to the notion that the B7 family mirrors the diversity of the CD28-related receptors for evoking T-cell stimulatory/inhibitory pathways in the immune system: B7-H1 (PDL-1) and B7-DC (PDL-2) bind the programmed cell death (PD-1) receptor (Keir et al., 2008), and B7-H2 (CD275) is the ligand of ICOS (inducible co-stimulator) (Wang et al., 2000).

B7-H1 and B7-DC deliver negative co-stimulatory signals through PD1. B7-H1 is constitutively expressed on multiple cell types in mice including activated B, T, myeloid and DC and also on endothelial cells. In contrast, B7-DC is restricted to DC and macrophages and is induced by IL4 while B7-H1 is primarily regulated by IFNγ. Both genes are up-regulated during T cell activation and B7-DC has a higher affinity for PD-1 than B7-H1. Surprisingly, expression cloning revealed that B7-H1 not only interacts with PD-1 but also with B7.1 (but not with B7.2). The exact function of B7-H1 expressed by T cells is still unknown, but the large distribution of these receptors has to be compared to the broad expression pattern for their main ligand, PD-1. Overall, the PD1:PD-ligand pathway is critical for peripheral tolerance (Fife et al., 2006; Keir et al., 2008) and elicits an essential role in chronic viral infections by balancing immune responses to pathogens and subsequent CMI mediated tissue damage (Barber et al., 2006; Petrovas et al., 2006). The delivery of an inhibitory signal through B7-H1 and B7-DC has been well documented in the context of anti-tumor immunity since many tumors express B7-H1 and thus down-regulate specific T cell responses.

In contrast, B7-H2 delivers positive co-stimulatory signals through ICOS, a member of the CD28 family. It is constitutively expressed on the surface of a broad range of cell types including B cells, macrophages, DC, some T-cell subsets and on certain epithelial and endothelial cells. ICOS is induced on $CD4^+$ and $CD8^+$ T cells during T cell activation and the ICOS/B7-H2 pathway is critical for the delivery of T-cell help to B cells to promote humoral immunity. The B7-H2 knockout mice demonstrated that B7-H2 is required for T helper cell activation, differentiation, and the expression of effector cytokines as well as for the development of NKT cells (Chung et al., 2008; Nurieva et al., 2003).

The ligands of the last two members of the B7 family (B7-H3 and B7-H4) have yet to be identified, but their domain composition, sequence similarities and functional properties group them with the B7/B7H receptors. Mammalian B7-H3 has been detected on the surface of T cells, B cells, DC, macrophages and on specific carcinoma cells. B7-H3 transcripts are up-regulated upon *in vitro* IFNγ stimulation (in Th1 responses), but are down-regulated during Th2 responses (Suh et al., 2003). The functional properties of the B7-H3 receptor seem to be rather complex. A B7-H3Ig fusion protein binding to activated T cells provided a positive co-stimulatory response leading to T-cell proliferation, cytotoxicity and IFNγ production, suggesting a positive co-stimulatory function (Chapoval et al., 2001; Sun et al., 2002). Soluble versions of B7-H3 are also released from monocytes, DC and activated T cells via proteolytic processing resulting in the binding and activation of T cells by the soluble receptor (Zhang et al., 2008). However, B7-H3 KO mice (Suh et al., 2003) showed increased T cell responses, accelerated EAE and severe hyperinflammatory response, supporting an inhibitory function. The last member of the B7 family, B7-H4, has the same

Table 1
Properties of the B7 family in mammals.

B7 receptor	B7.1	B7.2	B7-H2	B7-H1	B7-DC	B7-H3	B7-H4
Other names	CD80	CD86	CD275, B7RP-1, LICOS, GL50, Icosl, GL50-B, ICOS-L, B7h, MGI:1354701, Ly115l	CD274, PD-L1, B7-H, PDCD1LG1, PDL1	CD273, PD-L2, PDL2, Btdc, bA574F11.2, 18731, PDCD1LG2	CD276, B7-H3	B7X, B7S1, FLJ22418, VTCN1
Location in human genome	3q13	3q21	21q22	9p24	9p24	15p24	1p13.1
Ligand and outcome of interaction	CD28, CTLA4 CS/CI	CD28, CTLA4 CS/CI	ICOS CS	PD-1 and B7.1 CI	PD-1 CI	? CS/CI	? CI
Surface expression	Induced on B, T, DC and monocytes lineages	Constitutive on B, DC, monocytes and T cells (upon induction). Up-regulated during activation	B, DC, mono lineage and some T-cell subsets	Constitutive on B, DC, monocytes and T cell (upon induction). Up-regulated during activation	Induced upon activation in DC and monocyte lineages	Induced upon activation on B, T, DC and monocyte lineages	Induced on B, T, DC, some NKs and monocyte lineages

CS, co-stimulatory; CI, co-inhibitory.