Butyrophilin (BTN) family interactions

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

17/12/2022
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 83

This document contains 1 pathway and 8 reactions (see Table of Contents)
Butyrophilins (BTNs) and butyrophilin like (BTNL) molecules are regulators of immune responses that belong to the immunoglobulin (Ig) superfamily of transmembrane proteins. They are structurally related to the B7 family of co-stimulatory molecules and have similar immunomodulatory functions (Afrache et al. 2012, Arnett & Viney 2014). BTNs are implicated in T cell development, activation and inhibition, as well as in the modulation of the interactions of T cells with antigen presenting cells and epithelial cells. Certain BTNs are genetically associated with autoimmune and inflammatory diseases (Abeler Domer et al. 2014).

The human butyrophilin family includes seven members that are subdivided into three subfamilies: BTN1, BTN2 and BTN3. The BTN1 subfamily contains only the prototypic single copy BTN1A1 gene, whereas the BTN2 and BTN3 subfamilies each contain three genes BTN2A1, BTN2A2 and BTN2A3, and BTN3A1, BTN3A2 and BTN3A3, respectively (note that BTN2A3 is a pseudogene). BTN1A1 has a crucial function in the secretion of lipids into milk (Ogg et al. 2004) and collectively, BTN2 and BTN3 proteins are cell surface transmembrane glycoproteins, that act as regulators of immune responses. BTNL proteins share considerable homology to the BTN family members. The human genome contains four BTNL genes: BTNL2, 3, 8 and 9 (Abeler Domer et al. 2014).

**Literature references**


### Editions

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The B30.2 cytoplasmic domain (PRY/SPRY domain) of Butyrophilin 1A1 (BTN1A1) binds to xanthine oxidoreductase (XDH). This interaction provides scaffolding function, stabilizes the milk fat globule membrane (MFGM), and aids in milk fat globule secretion (Jeong et al. 2009).

**Literature references**


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BTN2A1 binds DC-SIGN

**Location:** Butyrophilin (BTN) family interactions

**Stable identifier:** R-HSA-8851018

**Type:** binding

**Compartments:** plasma membrane

Butyrophilin 2A1 (BTN2A1) can bind to a lectin molecule, DC-specific ICAM3-grabbing non-integrin (DC-SIGN; also known as CD209), found on monocytes and dendritic cells. Binding of DC-SIGN is dependent on the tumor- and/or tissue-specific high-mannose glycosylation of BTN2A1 (Malcherek et al. 2007). BTN2A1 may represent a susceptibility gene for metabolic syndrome and myocardial infarction through an effect on dyslipidaemia (Fujimaki et al. 2011, Hiramatsu et al. 2012, Yamada et al. 2011, Arnett & Viney 2014).

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BTN2A2 binds T cell surface

Location: Butyrophilin (BTN) family interactions

Stable identifier: R-HSA-8851988

Type: binding

Compartments: plasma membrane

BTN2A2 protein is upregulated upon T cell activation and interacts with activated T cells suggesting the presence of one or more receptors on these cells. It has been demonstrated that BTN2A2 inhibits T cell metabolism upon binding to its putative receptor on T cells (Smith et al. 2010).

Literature references

Smith, IA., Palmer, DB., Mather, IH., Rhodes, DA., Ammann, JU., Aw, D. et al. (2010). BTN1A1, the mammary gland butyrophilin, and BTN2A2 are both inhibitors of T cell activation. *J. Immunol.*, 184, 3514-25.

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BTN3A1 binds prenylated phosphoantigens

**Location:** Butyrophilin (BTN) family interactions

**Stable identifier:** R-HSA-8851038

**Type:** binding

**Compartments:** plasma membrane, extracellular region

Butyrophilin 3A1 (BTN3A1) directly binds to small pyrophosphate containing organic molecules known as prenyl pyrophosphates or phosphoantigens (pAgs). These molecules are produced either endogenously, such as isopentenyl pyrophosphate (IPP), an intermediate of the mevalonate pathway in human cells that can accumulate intracellularly during tumorigenesis, or by microbes, such as hydroxy-methylbutyl-pyrophosphate (HDMAPP, also known as HMBPP), a microbial intermediate of the 2-C-methyl-D-erythritol 4-phosphate (MEP) pathway. This interaction causes a conformational change in the extracellular domain of BTN3A1, which then leads to the activation of a specialized subset of gamma/delta T cells Vgamma9Vdelta2. The other two members of the BTN3A family, BTN3A2 and BTN3A3 may also be involved in the activation process (Sandstrom et al. 2014).

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**BTNL2 binds activated T cells surface**

**Location:** Butyrophilin (BTN) family interactions

**Stable identifier:** R-HSA-8852010

**Type:** binding

**Compartments:** plasma membrane

Butyrophilin-like 2 (BTNL2), is a butyrophilin family member with homology to the B7 costimulatory molecules. BTNL2 binds to a putative receptor on activated T cells and functions to have an inhibitory effect on CD4+ T cell proliferation (Nguyen et al. 2006). It may also bind to receptors on liver and vascular endothelium in mouse (Arnett et al. 2007). Polymorphisms in BTNL2 have been linked with various autoimmune and inflammatory diseases (Pathan et al. 2009, Mochida et al. 2009, Arnett & Viney 2014).

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BTNL8 binds resting T cell surface

**Location:** Butyrophilin (BTN) family interactions

**Stable identifier:** R-HSA-8852013

**Type:** binding

**Compartments:** plasma membrane

Human BTNL8 (butyrophilin like 8), shares characteristics of both B7 and BTN like (BTNL) proteins. BTNL8 was shown to interact with a putative receptor on the surface of resting T cells but not activated T cells, and is able to promote activation of resting T lymphocytes (Chapoval et al. 2013).

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BTNL9 binds immune cell surfaces

Location: Butyrophilin (BTN) family interactions

Stable identifier: R-HSA-8851979

Type: binding

Compartments: plasma membrane

Butyrophilin-like protein 9 (BTNL9) is expressed in a variety of tissues in humans and mice. No known function has been ascribed to BTNL9 but recombinant BTNL9-Fc has been shown to bind to many immune cells including T cells, B cells, macrophages and dendritic cells (Yamazaki et al. 2010).

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**BTN3A1 and BTN1A1 binds periplakin (PPL)**

**Location:** Butyrophilin (BTN) family interactions

**Stable identifier:** R-HSA-8938431

**Type:** binding

**Compartments:** plasma membrane, cytosol

Periplakin (PPL) is a 195-kDa cytosolic protein of the cytoskeleton-associated plakin family. BTN3A1 and BTN1A1 are shown to interact with PPL with a membrane-proximal di-leucine motif located in their cytoplasmic tail (Rhodes et al. 2015).

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