J. Cell Commun. Signal. (2015) 9:291–296
DOI 10.1007/s12079-015-0297-3

NUTS AND BOLTS

A knowledgebase resource for interleukin-17 family mediated signaling

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Received: 9 May 2015 / Accepted: 26 May 2015 / Published online: 16 June 2015

Abstract Interleukin-17 (IL-17) belongs to a relatively new family of cytokines that has garnered attention as the signature cytokine of Th17 cells. This cytokine family consists of 6 ligands, which bind to 5 receptor subtypes and induce downstream signaling. Although the receptors are ubiquitously expressed, cellular responses to ligands vary across tissues. The cytokine family is associated with various autoimmune disorders including rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, asthma and psoriasis in addition to being implicated in the pathogenesis of cancer. In addition, this family plays a role in host defense against bacterial and fungal infections. The signaling mechanisms of the IL-17 family of proinflammatory cytokines are not well explored. In this study, we present a resource of literature-annotated reactions induced by IL-17. The reactions are catalogued under 5 categories, namely; molecular association, catalysis,

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transport, activation/inhibition and gene regulation. A total of 93 molecules and 122 reactions have been annotated. The IL-17 pathway is freely available through NetPath, a resource of signal transduction pathways previously developed by our group.

Keywords Activation · Differential expression · Inhibition · NetPath · Post-translational modifications · Protein-protein interaction · Translocation

Abbreviations

IL-17	Interleukin- 17
IL-25	Interleukin- 25
IL-17R	Interleukin- 17 receptor
PPIs	Protein-protein interactions
PTMs	Post-translational modifications
BioPAX	Biological Pathway Exchange
SBML	Systems Biology Markup Language
PSI-MI	Proteomics Standards Initiative for Molecular Interaction

Introduction

Cytokines are small proteins that mediate intercellular communication. Interleukin-17 (IL-17 also known as IL17A or CTLA8) was first identified from murine T cell hybridoma cDNA library as a virus-captured cellular gene related to the immune system (Rouvier et al. 1993). While the majority of the cytokines belong to the Th1/Th2 paradigm, IL-17 served as a signature cytokine which led to the identification of a new subset of T helper cells, Th17 cells (Rouvier et al. 1993; Yao et al. 1995b; Korn et al. 2009; Weaver et al. 2007). Based on the amino acid sequence homology, five other members of this family IL-17B, IL-17C (Li et al. 2000), IL-17D (Starnes et al. 2002), IL-17E (also known as IL-25) (Lee et al. 2001), and IL-17F have been identified. In humans, all members of the IL-17 family show sequence similarity to IL-17A. While IL-17F is its closest homolog with 55 % identity; IL-17E is the most distant homolog with only 17 % identity (Moseley et al. 2003). IL-17A and IL-17F are expressed in NK, NKT, γδ T cells and LTi cells (Cua and Tato 2010). Expression of IL-17 and its subtypes is reported in diverse cells and tissues as listed in Table 1.

IL-17 binds to IL-17R, which is its cognate receptor. IL-17R family consists of 5 subtypes of IL-17 receptors known as IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE. IL-17RA is ubiquitously expressed in tissues with a relatively higher expression in haematopoietic tissues (Yao et al. 1995a). IL-17RB receptors are expressed in various endocrine tissues, kidney, liver and Th2 cells (Lee et al. 2001). IL-17RC is expressed in non-immune cells such as prostate, thyroid and joints (Haudenschild et al. 2002; Kuestner et al. 2007). IL-17RD is expressed in epithelial cells of breast, prostate, thyroid gland, ovarian surface (Zisman-Rozen et al. 2007) and endothelial cells (Yang et al. 2003). Expression of IL-17RE is not well defined. IL-17Rs are single pass transmembrane glycoprotein receptors. The subtypes of IL-17R contain conserved SEFIR (similar expression to FGF receptor/IL-17R) domain in the cytoplasm and an extracellular fibronectin III like domain (Yao et al. 1997). IL-17RA also has a specialized motif called the TILL (TIR-like loop) which is a crucial mediator of IL-17 family signaling (Maitra et al. 2007).

IL-17 is predominantly a proinflammatory cytokine and mediates multiple cell type specific functions. It induces the expression of a number of inflammatory effectors that includes cytokines and chemokines. It may also act synergistically with other cytokines like TNF-α and IFN-γ to amplify inflammation (Onishi and Gaffen 2010). Recent studies have implicated a role for IL-17 in the development of breast (Huang et al. 2013) and colorectal (Song et al. 2014) cancers. It has been shown that IL-17 promotes the self-renewal of ovarian CD133(+) cancer stem-like cells (Xiang et al. 2015). A significant number of studies have implicated increased expression of IL-17 in inflammatory autoimmune disorders which are multifactorial. These disorders include rheumatoid arthritis (RA), psoriasis, multiple sclerosis (MS), inflammatory bowel disease and systemic lupus erythematosus (Firestein 2003; Miossec 2009; Qian et al. 2010). Significantly elevated levels of IL-17 have been observed in the synovial fluid of patients with RA (Gaffen 2009). Mouse model of RA have shown excess IL-17 in exacerbated collagen induced arthritis (CIA) (Lubberts et al. 2002) and silencing of IL-17 or IL-17R in CIA mice reduced the symptoms of CIA (Lubberts et al. 2004). Similarly, mice deficient in IL-17 were resistant to the induction of experimental autoimmune encephalomyelitis, a mouse model of MS (Yang et al. 2008). Despite such observations, the details of signaling and the intracellular changes elicited by IL-17 and its cognate receptors are not available in the public domain. In this study, we performed a literature-based survey to systematically compile the molecular reactions orchestrated by stimulation of IL-17R with IL-17.

Materials and methods

We performed an extensive search of published literature using PubMed and iHOP (Information Hyperlinked Over Proteins). The articles were screened for information pertaining to molecular association (protein-protein interactions), catalysis (post-translational modifications),

Table 1 IL-17 ligand family members and their expression

Ligand	Alternate Name(s)	Cell/tissue Expression
IL-17A	CTLA-8 IL-17	Th17, NK, NKT, γδ T cells and LTi
IL-17B	NIRF ZCYTO7 IL-20	Intestine, pancreas and neurons
IL-17C	CX2	Prostate and fetal kidney
IL-17D	IL-27	Adipose tissue, brain, heart, lung, pancreas and spleen
IL-17E	IL-25	Th2 cells, eosinophils, basophils, lung epithelial cells, mast cells, intestine, lung and uterus
IL-17F	ML-1 CANDF6	Th17, NK, NKT, γδ T cells and LTi

transport (translocation of proteins between sub-cellular compartments), activation/inhibition and gene regulation events that have been reported under stimulation by IL-17 and its subtypes. The pathway data were annotated using PathBuilder, a curation tool developed by our group (Kandasamy et al. 2009). The annotation criteria were followed as described in IL-11 (Balakrishnan et al. 2013), RANKL (Raju et al. 2011) and TSLP (Zhong et al. 2014) signaling pathways. A hyperlink has been provided for each of the PubMed identifier from which the molecular information was annotated. Further, reactions were categorized based on the ligands and ligand-specific pathway maps were generated using PathVisio, a freely available pathway drawing tool (van Iersel et al. 2008). The reactions were exported to an in-house pathway resource known as NetPath database (Kandasamy et al. 2010).

Results and discussion

IL-17 signaling pathway resource contains 93 molecules that are involved in IL-17 family signaling events. We cataloged 43 molecular associations, 73 catalytic reactions, 6 transportation events, 9 activation/inhibition reactions and 154 gene regulations. The IL-17 pathway web page in the NetPath database (http://www.netpath.org/pathways?path_id=NetPath_128) includes a description of the pathway, statistics of the number of molecules and reactions involved in the pathway. The pathway reactions are provided in various community standard data formats including Biological Pathway Exchange (BioPAX level 3) (Demir et al. 2010), Proteomics Standards Initiative for Molecular Interaction (PSI-MI version 2.5) (Orchard and Kerrien 2009) and Systems Biology Markup Language (SBML version 2.1) (Hucka et al. 2003). Users can download these files from the database to visualize

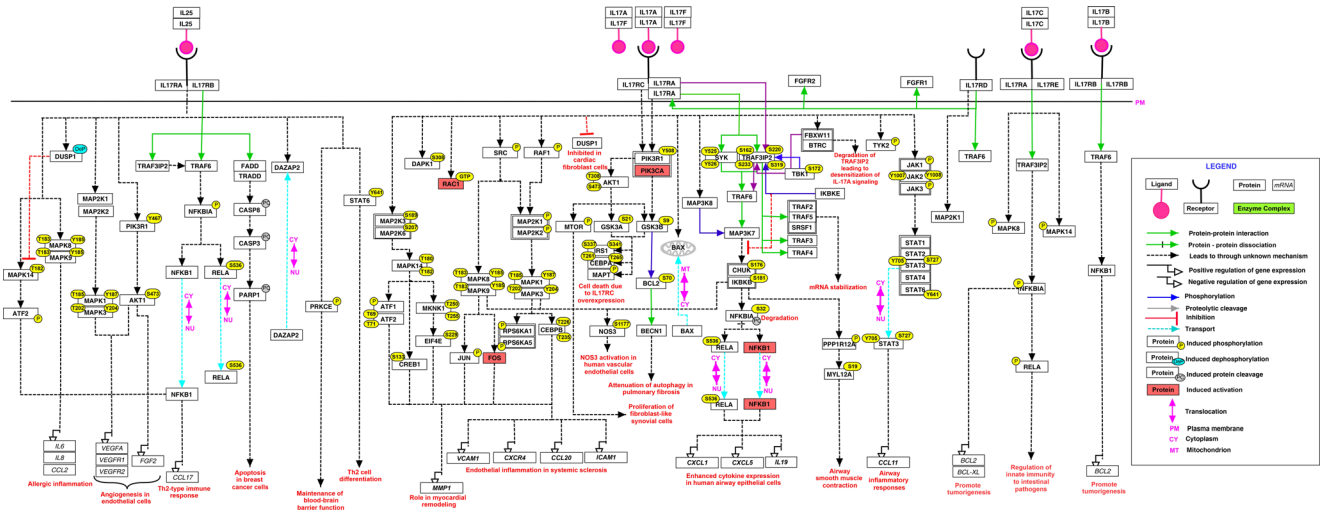

Fig. 1 A schematic representation of reactions induced by IL-17. The pathway reaction map depicts molecules involved in molecular associations, catalysis, and translocation events induced upon treatment with IL-17 ligand family. Site and residues of post-translational modifications are also mentioned, wherever available. Upon stimulation of IL-17, important signaling pathways including PI3K-AKT, Ras-MAPK, and NFκB are found to be activated

the pathway reactions using various freely available software such as Cytoscape (Shannon et al. 2003) and VISIBIOweb (Dilek et al. 2010). The data is also accessible in tab delimited and Microsoft Excel formats. The IL-17 signaling pathway will be periodically updated as and when more signaling events will be available. All the pathway reactions have been reviewed by the pathway authority (SS).

The signaling events triggered by IL-17 are shown in Fig. 1. IL-17A is the most studied member of the IL-17 family of cytokines. IL-17A and its closest homolog IL-17F, signal through a heterodimeric complex consisting of IL-17RA and IL-17RC (Toy et al. 2006). IL-17A and IL-17F can form homodimers (IL-17A/A and IL-17F/F) and heterodimer (IL17A/F) (Hymowitz et al. 2001; Wright et al. 2008). IL-17A induces TRAF6 dependent Nuclear factor kappa B (NFκB) activation, which leads to enhanced cytokine expression in human airway epithelial cells (Huang et al. 2007). Attenuation of autophagy in pulmonary fibrosis was observed through PI3K-GSK3B signaling pathway (Liu et al. 2013). The secretion of matrix metalloproteinases (*MMP1* and *MMP3*) is also enhanced under the influence of IL-17A and IL-17F (Yagi et al. 2007). IL-17B signals through an IL-17RB receptor and promotes tumorigenesis through NFκB dependent *BCL2* expression in breast cancer cells (Huang et al. 2013). IL-17C signals through a heterodimeric receptor complex consisting of IL-17RA and IL-17RE (Chang et al. 2011; Song et al. 2011). It regulates innate immunity via TRAF3IP2 dependent activation of NFκB (Song et al. 2011) as shown in Fig. 1. IL-17C also induces the phosphorylation of MAPK8/9 and MAPK14. IL-17C induces *BCL-2* and *BCL-XL* expression in intestinal epithelial cells to promote cell survival and tumorigenesis in both chemically induced and spontaneous intestinal tumor models (Song et al. 2014). The receptor of IL-17D is unknown. An orphan receptor IL-17RD interacts with IL-17RA to regulate IL-17A signaling (Mellett et al. 2012; Rong et al. 2009). It also interacts with FGFR1 and FGFR2 and is involved in cell differentiation (Xiong et al. 2003).

IL-25 is associated with Th2 responses and binds to IL-17RA and IL-17RB (Ely et al. 2009) to trigger downstream signaling events (Fig. 1). TRAF3IP2-TRAF6 dependent NFκB activation is responsible for Th2-type immune response (Maezawa et al. 2006). IL-25 induces the expression of *FGF2* through PIK3R1 (Wang et al. 2012). STAT6 is responsible for the differentiation of Th2 cells (Angkasekwinai et al. 2007) and PRKCE is involved in the maintenance of blood–brain barrier (Sonobe et al. 2009).

Conclusions

Availability of IL-17 signaling reactions in a centralized resource will accelarate the understanding of the role of various molecules in the biology of this pathway. These data have been submitted to the NetPath resource and are made available in diverse community standard data exchange formats so that they can be easily visualized and analyzed. This resource will be useful to understand IL-17 signaling in normal and disease conditions.

Acknowledgments We thank the Department of Biotechnology, Government of India for research support to the Institute of Bioinformatics, Bangalore. We thank the Infosys Foundation for research support to the Institute of Bioinformatics. JS is a recipient of Senior Research Fellowship from the Council of Scientific and Industrial Research, Government of India. KKD and AS are recipients of Junior Research Fellowship from the University Grants Commission, Government of India. AAK is a recipient of Senior Research Fellowship from Indian Council of Medical Research, Government of India. HG is a Wellcome Trust/DBT India Alliance Early Career Fellow.

Conflict of interests The authors declare no conflicts of interest.

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