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BITS AND BYTES

A network map of Interleukin-10 signaling pathway

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Abstract Interleukin-10 (IL-10) is an anti-inflammatory cytokine with important immunoregulatory functions. It is primarily secreted by antigen-presenting cells such as activated T-cells, monocytes, B-cells and macrophages. In biologically functional form, it exists as a homodimer that binds to tetrameric heterodimer IL-10 receptor and induces downstream signaling. IL-10 is associated with survival, proliferation and anti-apoptotic activities of various cancers such as Burkitt lymphoma, non-Hodgkins lymphoma and non-small scell lung cancer. In addition, it plays a central role in survival and persistence of intracellular pathogens such as *Leishmania donovani*, *Mycobacterium tuberculosis* and

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Trypanosoma cruzi inside the host. The signaling mechanisms of IL-10 cytokine are not well explored and a well annotated pathway map has been lacking. To this end, we developed a pathway resource by manually annotating the IL-10 induced signaling molecules derived from literature. The reactions were categorized under molecular associations, activation/inhibition, catalysis, transport and gene regulation. In all, 37 molecules and 76 reactions were annotated. The IL-10 signaling pathway can be freely accessed through NetPath, a resource of signal transduction pathways previously developed by our group.

Keywords Co-stimulatory molecules · Interferon-gamma (IFN-γ) · Lipopolysaccharides · Pro-inflammatory cytokines · Protein-protein interactions · Translocation · NetSlim · Systems biology markup language

Abbreviations

IL-10	Interleukin-10
CSIF	Cytokine synthesis inhibitory factor
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
HPRD	Human protein reference database

Introduction

Interleukin-10 (IL-10), also known as 'cytokine synthesis inhibitory factor' (CSIF), is a pleiotropic cytokine with important immunoregulatory functions. It has anti-inflammatory properties and influences the activity of several cell types of the immune system. IL-10 is primarily secreted by activated T-cells, monocytes, macrophages, dendritic cells, natural killer (NK) cells and B-cells (Blanco et al. 2008; Seki et al. 1998; Chomarat et al. 1993). It is released upon activation of these cells by endogenous and exogenous mediators such as lipopolysaccharides (Barsig et al. 1995; Roach et al. 1995), catecholamines and cAMP-elevating drugs (Meisel et al. 1996; Jilg et al. 1996). In response to antigens, cells of the immune system produce pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interferon -gamma (IFN-γ), interleukin-2 (IL-2) and interleukin-1 (IL-1) (de Waal et al. 1991). They are involved in rapid pathogen clearance and cell necrosis at the site of infection. Prolonged action of pro-inflammatory cytokines can lead to excessive tissue damage, fever, inflammation, and death in extreme cases (Dinarello 2000). IL-10 dampens the inflammatory effects of pro-inflammatory cytokines in overwhelming infections which otherwise can lead to potential tissue damage (Kapur et al. 1997; Wang et al. 1994; Cassatella et al. 1993).

The human *IL10* gene is 4.7 kb in size and is located on the long arm of chromosome 1. It contains five exons. Biologically functional IL-10 exists in the form of a 36 kD homodimer composed of two non-covalently bonded monomers each with 160 amino acids length (Zdanov 2010). Two disulfide bridges exist between the monomers, which are required for their biological activity and maintaining structural integrity (Windsor et al. 1993). IL-10 homodimer binds to tetrameric IL-10 receptor complex, which consists of two IL-10R-alpha and two IL-10R-beta subunits. IL-10R-alpha is known to bind to the ligand and IL-10R-beta is the accessory signaling subunit (Liu et al. 1994).

IL-10 homodimer upon binding to its receptor IL-10R-alpha, activates JAK/STAT (Janus kinase/signal transducer and activator of transcription) and Akt (also known as protein kinase B, PKB) cascades (Riley et al. 1999). IL-10 has also been involved in proliferation, survival and anti-apoptotic activities of several cancers such as Burkitt lymphoma (Kube et al. 1995), non-Hodgkins lymphoma (Cortes and Kurzrock 1997) and non-small cell lung cancer (De Vita et al. 2000b). Studies have reported that overexpression of IL-10 promotes tumor development in certain lymphomas and melanomas by suppressing the antitumor immune response (Huang et al. 1999; Boulland et al. 1998; Kruger-Krasagakes et al. 1994). Several investigations have also suggested that serum level of IL-10 may indicate disease progression. A study in advanced solid tumors has reported that IL-10 serum level returns to normal in radically resected patients. However, in case of tumor recurrence, the IL-10 level was observed to be persistently elevated (De Vita et al. 2000a). Additionally, elevated serum level of IL-10 has also been associated with autoimmune and inflammatory diseases such as systemic lupus erythematosus (SLE) (Park et al. 1998), systemic sclerosis (Hasegawa et al. 1997) and Bullous pemphigoid (Schmidt et al. 1996). Studies have reported a protective role of IL-10 in cartilage of osteoarthritis patients (Jung et al. 2013). Recombinant human IL-10 has also been tested as a promising therapeutic agent in patients with rheumatoid arthritis (Keystone et al. 1998) and Crohn's disease (Tilg et al. 2002).

IL-10 plays a central role in survival and persistence of intracellular pathogens in vivo. Pathogens such as *Leishmania donovani* (Chandra and Naik 2008; Ghalib et al. 1993) *Mycobacterium tuberculosis* (Higgins et al. 2009), *Trypanosoma cruzi* (Holscher et al. 2000) and *Coxiella burnetii* (Ghigo et al. 2001) have evolved various mechanisms for stimulating IL-10 production in immune cells for their survival. Recent studies have indicated the correlation between IL-10 and tuberculosis (TB) susceptibility in humans and mice (Jamil et al. 2007; Bonecini-Almeida et al. 2004; Olobo et al. 2001; Verbon et al. 1999). IL-10 mediated deactivation of macrophages leads to reduced production of pro-

inflammatory cytokines and reactive oxygen species which would otherwise lead to cell damage (Fiorentino et al. 1991; de Waal et al. 1991 During *Mycobacterium tuberculosis* infection, IL-10 contributes to survival and persistence of bacteria inside macrophage by inhibiting MHC-restricted cytotoxicity against infected macrophages (de la Barrera et al. 2004). The abundance of IL-10 in TB infected individuals, and its role in downregulation of IFN-gamma and a T-cell costimulatory molecule called cytotoxic T-lymphocyte-associated protein 4 (CTLA4), suggest an altered antigen presentation in infected individuals. In addition, the $CD8^{+}$ CTL-mediated cytotoxic activity could be enhanced upon neutralization of IL-10, suggesting a direct role of IL-10 in suppressing the anti-mycobacterial response (Gong et al. 1996).

IL-10 related signaling events have been well documented in the literature. However, a well annotated pathway map for IL-10 is currently lacking in the available pathway resources. Considering their significance in immunological events with respect to disease and infection, documentation and pathway map availability in a public domain is much desired. To this end, we developed a comprehensive signaling pathway of IL-10 by manually curating the molecules associated with IL-10 signaling from published literature. The pathway map is made available through NetPath (http://www.netpath.org/reactions?path_id=NetPath_132) (Kandasamy et al. 2010), a resource for human signaling pathways. This manuscript describes the methodology of generating downstream signaling pathway by manually curating the events upon interaction of IL-10 with its cognate IL-10 receptor.

Materials and methods

Literature survey pertaining to IL-10 signaling was carried out in PubMed and Google Scholar using search terms that included - (IL-10 OR "Interleukin-10") AND (Signaling OR Pathway OR Signal OR "Signal Transduction") NOT 'Review'. Studies describing the downstream signaling events induced upon binding of IL-10 to its receptor were screened for annotation of this pathway. The information was then manually curated and cataloged using PathBuilder (Kandasamy et al. 2009), an annotation tool developed in-house for the curation of signaling pathways. Annotation criteria, previously employed for generation of RANK/RANKL (Raju et al. 2011a), Interleukin-17 (Sharma et al. 2015), CRH (Subbannayya et al. 2013), Gastrin (Subbannayya et al. 2014), BDNF (Brain derived neurotrophic factor) (Subbannayya et al. 2013) and TSLP (Thymic stromal lymphopoietin) (Zhong et al. 2014) signaling pathways, were followed for mapping IL-10 signaling molecules. Besides listing of IL-10 induced molecular events, we also annotated biological information including catalytic reactions, protein-protein interactions, gene regulation events and activation/

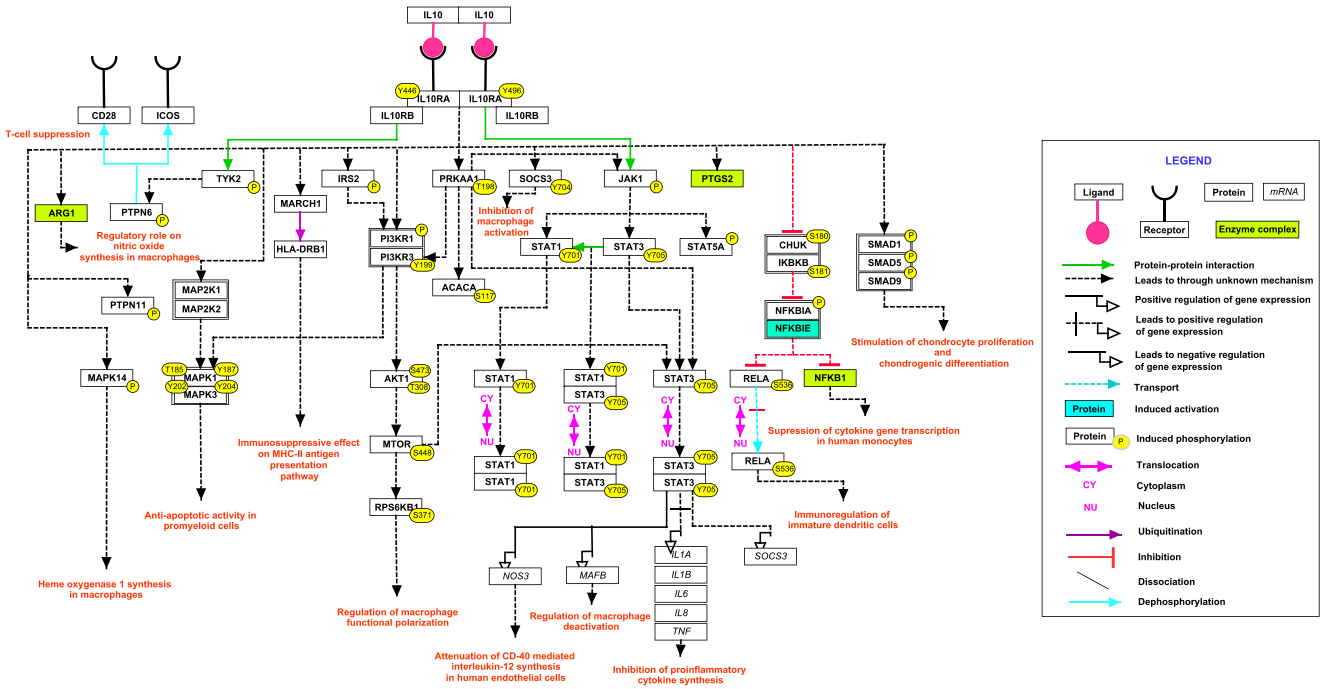

Fig. 1 A schematic representation of reactions induced by IL-10. The signaling pathway map depicts molecules involved in protein-protein interactions, catalysis, activation/inhibition and translocation events induced upon treatment with IL-10 cytokine. Information regarding site and residue of post-translational modification is also shown in the pathway. Pathway legend is provided to identify the interactions, molecular associations and gene regulations on the map

inhibition reactions corresponding to IL-10 signaling. Information such as cell lines used in experiment and experimental conditions were also documented. In case of post-translational modification (PTM), information on site and residue for PTMs were also curated. Comments on each reaction were written in brief, describing the experiment and results from which the reaction was inferred. An internal review system was followed to confirm the annotation and to avoid any error of commission. In addition, each pathway reaction was reviewed by a Pathway Authority, who has a proven expertise in the field of study (SG, co-author in this article).

IL-10 pathway map generation and visualization

The signaling events derived from manual curation are available as pathway map. We have also developed a pathway map based on the reactions by following NetSlim criteria (Raju et al. 2011b). This enabled us to shortlist high confidence reactions and develop a more stringent IL-10 pathway map. The reactions associated with IL-10 pathway can be visualized using PathVisio (van Iersel et al. 2008). The IL-10 pathway in NetSlim version can be downloaded in png, gpml and pdf formats. The pathway molecules are linked to corresponding NetPath page containing links for 'Pathway Authority," Curator's details' and 'Comments' section.

Results and discussion

Over 3,000 research articles were screened from PubMed and Google Scholar for curation of molecules associated with IL-10 signalling. Articles identified with the information pertaining to signalling events induced upon binding of IL-10 to its receptor were considered for curation. By manual curation, we curated 04 protein-protein interactions, 30 catalytic reactions, 87 gene regulation events, 04 activation/inhibition events and 01 protein translocation event. These pathway reactions were depicted as signalling network (Fig. 1). The reactions in the map are linked to their respective articles as listed in PubMed. The molecules are linked to their respective pages in NetPath and HPRD (Prasad et al. 2009) and the transcriptionally regulated genes are linked to their corresponding gene pages in NCBI. The data is presented in widely accepted standard formats, namely, Systems Biology Markup Language (SBML 2.1) (Hucka et al. 2003), Proteomics Standard Initiative-Molecular Interaction (PSIMI version 2.5) (Orchard and Kerrien 2010) and Biological Pathways Exchange (BioPAX level 3.0) (Demir et al. 2010). IL-10 pathway page in NetPath gives a brief description on pathway and its importance. A table is provided with pathway statistics on the NetPath page.

Overall, the pathway map depicts that immune cells upon pro-inflammatory cytokine stimulation secrete IL-10, which binds to the extracellular domain of IL-10R-alpha that leads to phosphorylation of JAK1 (Janus Kinase1) associated with IL-10R-alpha and TYK2 (tyrosine kinase2) associated with IL-10R beta (Kotenko et al. 1997). These kinases further phosphorylate tyrosine residues (Y446 and Y496) located on the intracellular domain of IL-10R-Alpha. Phosphorylated residues act as temporary docking sites for STAT3 (Signal Transducer and Activator of Transcription-3) (Donnelly et al. 1999). JAK1 further phosphorylates STAT3, which then homo/hetero dimerize and translocate into the nucleus. In the nucleus, it regulates various cell cycle progression genes such as *BCL2* (Santner-Nanan et al. 2013; Levy and Brouet 1994) along with other anti-apoptotic genes (Donnelly et al. 1999). In addition, it also upregulates v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog B (*MAFB*) which is involved in regulation of macrophage deactivation (Gemelli et al. 2014). IL-10 controls the inflammatory processes by suppressing pro-inflammatory cytokines such as tumor necrosis factor alpha (*TNF*) (van der Poll et al. 1994), interleukin-6 (*IL6*) (Wang et al. 1994) and interleukin-8 (*IL8*) (de Waal et al. 1991). Recently, it has been shown that IL-10 prevents the differentiation of monocytes into dendritic cells, which are one of the important antigen presenting cells of immune system (Buelens et al. 1997). Studies have also reported that IL-10 down regulates co-stimulatory molecules such as *CD86* (Chang et al. 1995) and intracellular adhesion molecule-1 (*ICAM1* (Spittler et al. 1995) rendering the cells incapable of presenting antigens on their surface. Recent reports have demonstrated that IL-10 induces the expression of heme oxygenase-1 (*HMOX1*) in macrophages, which is a potent anti-inflammatory agent (Koch et al. 2009; Lee and Chau 2002). Secretion of matrix metalloproteinases (*MMP1* and *MMP3*) is also enhanced under the influence of IL-10 (Reitamo et al. 1994). In addition, IL-10 stimulates chondrocytes proliferations and chondrogenic differentiation by activating (Bone Morphogenetic Protein) BMP signalling pathway through phosphorylation of SMAD1, SMAD5 and SMAD9 proteins (Jung et al. 2013).

IL-10 signaling pathway data can be used as a useful resource for understanding the complex mechanisms associated with the anti-inflammatory cytokines. The pathway map developed will also aid in understanding the mechanisms adopted by intracellular pathogens and cancerous cells to combat the immune system and establish their survival in the body. The users can further provide their comments about the pathway in NetPath through (http://www.netpath.org/comments).

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Conflict of interests The author(s) declare that they have no competing interests.

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