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Diverse functions of LILRA3 through interaction with multiple ligands

Presented by

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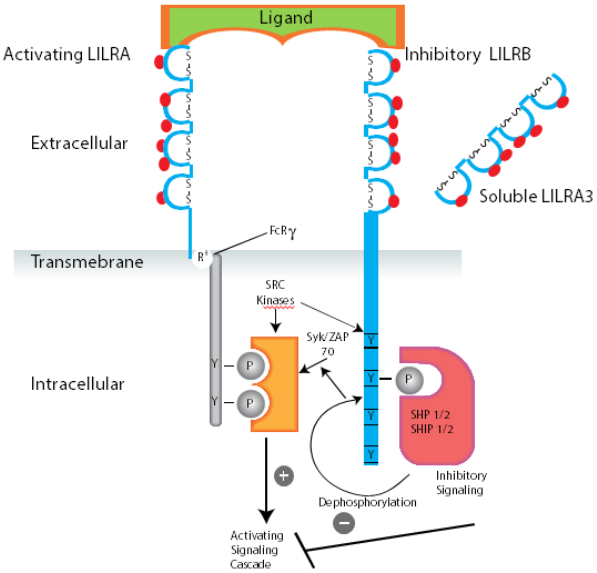
Abstract

LILRA3 belongs to a family of homologous receptors, known as Leukocyte Immunoglobulin-like Receptors (LILRs). LILRs are primarily expressed on innate immune cells and are critical regulators of innate immune activation by transducing activating or inhibitory signals (Fig). LILRA3 is a secreted protein with no transmembrane and intracellular domains, hence cannot transduce intracellular signals but may act as a soluble antagonist to the membrane bound LILRs. However, LILRA3 functions are unknown, despite its ubiquitous presence in normal sera and its strong clinical association with various inflammatory diseases. This is primarily due lack of known ligands, an absence of rodent homologues and difficulties in producing functional protein.

We produced full-length rLILRA3 protein typical of the native protein and used it as a bait to identify two novel ligands: LAMR1 and Nogo 66, and one known ligand, HLA-B27, which bound to LILRA3 with varying affinities of 9.1 pmol, 22 pmol and 0.2µM respectively. LAMR1 is highly expressed in airway epithelial cells and is involved in regulation of LPS-induced innate immune activation, Nogo 66 is a potent inhibitor of neurite outgrowth in the CNS and HLA-B27 is MHC-class I molecule involved in antigen presentation and has strong clinical association to autoimmune arthritis.



We proposed that LILRA3 may display tissue specific functions through interaction with these multiple ligands. Using *in vitro* and *in vivo* models we discovered that LILRA3 displays dual anti-inflammatory and neuro-regenerative functions via interaction with LAMR1 and Nogo 66 respectively. Recombinant LILRA3 peptide is therefore a potential new class of biological anti-inflammatory agent in the treatment of deleterious inflammation, particularly post sepsis acute lung injury and post-ischemia reperfusion cerebral injury. These diseases are common killers in Australia and worldwide with limited treatment options.

Biography

Prof Tedla gained his MD in 1987 from Addis Ababa University, Ethiopia (*summa cum laude*), followed by a 2 year training in Trauma by Prof Wolfgang Arnold at Leipzig University, Germany and worked as a frontline surgeon with the Ethiopian Armed Forces until 1992. He arrived in Australia in 1993 as a recipent of overseas postgraduate scholarship and undertook a PhD in immunopathology of HIV lymphadenopathy between 1993-1997 at UNSW under supervision of Prof John Dwyer and Dr Andrew Lloyd. Upon completion of his PhD, he was awarded a 3 year UNSW Vice Chancellor postdoctoral fellowship to study trafficking of lympocytes to lymph nodes during antigenic challenges. In December 1999, he accepted an offer for a postdoctoral position in Prof Frank Austen's lab at Brigham and Women's Hospital, Harvard Medical School to investigate mechanisms that regulate innate immune cell activation, particularly mast cells, eosinophils and basophils under supervision of Prof Jonathan Arm. He returned to Austalia at the end of 2001 with American Arthritis Foundation Fellowship and established internationally recognised Innate Immune Regulation Research Group at SoMS, UNSW. The group pioneered research on the role of a novel family of proteins, the Leukocyte Immunoglobulin like Receptors, has published >80 papers and supervised 16 PhD completions. Prof Tedla is also a multi-award-winning educational innovator and is nationally recognised for his teaching excellence of undergraduate medical students, medical science students and students from diverse programs.

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