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# Distinguishing the Mechanism of IL-6 in the Diabetic Kidney and Normal Kidney

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## Mechanism of IL-6 signaling in normal kidney:

- Studies suggest that IL-6 signaling is mediated through gp130-STAT3 dependent mechanisms that functions locally for tissue remodeling and immune cell infiltration.
- Two functional membrane proteins involved are ligand binding- Interleukin-6 receptor (IL-6 R) of 80kDa and signal transducing chain gp130 of 130kDa.
- IL-6R is expressed in specific cell populations such as leukocytes, hepatocytes, megakaryocytes. In cells that do not express IL-6R, IL-6 exerts its function by binding to SIL-6R (trans-signaling pathway).
- The expressed IL-6 activates the IL-6R receptors that lead to trans-phosphorylation and activation of JAK protein that in turn leads to phosphorylation of gp-130.
- The phosphorylated gp-130 recruits STAT3 protein. The STAT3 enters into the nucleus and results in the transcription of many genes that are associated with the growth and proliferation of mesangial cells.
- This SIL-6R is derived via two ways 1) proteolysis of IL-6R that involves cleavage by a disintegrin and metalloproteinase domain containing protein (ADAM10 and ADAM17). 2) Alternative splicing of IL-6 mRNA.
- The presence of SIL-6R increases the potency of IL-6 signaling as it prolongs the Half-life of IL-6.
- Circulating IL6-SIL6-R complex after reaching the cells that expresses only pleiotropic cell surface receptor gp130 can form the gp130 containing ligand receptor complex. As expression of gp130 is ubiquitous, all cells respond to IL-6 receptor hexameric complex.
- Hexameric complex that is capable of activating different intracellular signaling pathways including JAK/STAT pathway, p13/AKT pathway and SHP-2/JAK dependent Ras-Raf-Mapk pathway.
- The tyrosine phosphatase SHP2 and adapter proteins that activates MAPK pathway, also phosphorylates docking protein Gab1.
- These phosphorylated Gab1 protein moves to plasma membrane and activates MAPK and P13K pathway.
- The target genes of IL-6 are suppressors of cytokine signaling 1 and 3 (SOCS1 and SOCS3) that negatively regulate IL6 signaling.

## Mechanism of IL-6 Signaling In Diabetic Kidney:

- The characteristic features of Diabetic nephropathy involves thickening of glomerular basement membrane, glomerular hypertrophy, mesangial cell proliferation, matrix overproduction, and podocyte injury.
- The studies on animal models made a conclusion that the IL-6 is involved in inflammation of mesangial and tubular cells.
- The hyperglycemic condition of diabetes makes the podocytes to produce IL-6 and even increase the expression of gp130 and IL-6R. The activation of IL-6R results in increased phosphorylated JAK2 recruitment to gp130 and therefore leads to enhanced STAT3 phosphorylation.
- Further worsening of disease leads to increased glomerular capillary pressure and deregulated RAAS that leads to higher production of Angiotensin II. The hormonal increase stimulates mesangial cells to secrete large amounts of IL-6 that stimulates podocytes which up regulates gp130 and IL-6R. Increased IL-6 levels induce podocyte hypertrophy and leads to cell cycle arrest.
- The accumulation of neutrophil infiltrate increases the inflammatory response by activating IL-6 trans-signaling pathways. The SIL-6R promotes the differentiation of pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages there by enhancing the anti-inflammatory effects.

