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Reversal of Renal Fibrosis by inhibiting smad3 pathway via Mesenchymal Stem Cells

**Introduction**

Lupus Nephritis (LN) is an autoimmune disease progresses from Lupus, and affects about 50% of patients that have Lupus. The immune system attacks the kidney due to a series of complicated interactions amongst immune cells such as T cells and B cells (Lamagna et al, 2014). These interactions create autoantibodies that attack kidney tissue. The basic structure of the kidney is composed of nephrons that filters blood and eliminates waste from the body. The function of the nephron is vital to kidney function and is an indicator of LN, and over time becomes inflamed from the autoimmune attack and leads to fibrosis(the growth of excess connective tissue on an organ) overtime which also inhibits kidney function.

The treatment for LN focus’s on relieving the symptoms of inflammation and suppressing the immune system so it stops attacking the kidneys. Recently, regenerating the kidney has been a focus of treatment via stem cells. Mesenchymal stem cells (MSC) have been used to treat LN because they are known for the immune modulating, anti inflammatory effects, and ability to differentiate into other types of cells like myocytes and osteoblasts. (Chou et al, 2014) Kidney regeneration focuses on renal repair and growth of the partial and whole nephron. Reversal of fibrosis in the kidneys help retain function fo the kidney. In autoimmune attacks, cells that modulate fibrosis are activated and expedite the growth of connective tissue on the kidney.

The transforming growth factor- beta(TGF-b) is a regulator of inflammation, apoptosis(programed cell death, cellular transitions, and are positive regulators of fibrosis. TGF-b’s signal from the cell membrane to the nucleus through smad proteins modulates the transcription of target genes. Within the smad family, each individual protein has its own function. It has been found that smad3 is a mediator of fibrotic response by regulating the transcription of the collagen I gene. Then there is smad7; it has been observed that smad7 has reversal fibrosis effects because it blocks TGF-b signaling by inhibiting smad3 phosphorylation. This interaction helps prevent the overexpression of smad3 that leads to the over production of collagen gene transcription.

To understand how MSC regenerate kidneys, the interactions between smad3 phosphorylation and collagen 1 gene transcription while being treated with MSC will be observed by deleting the smad7 gene.

**Experiment**

To test the effects of smad7 and MSC’s, the smad7 protein will be knocked out in a murine model. The mouse model used by Ma et al will be used for the experiment. There will be 3 test models: control with LN, smad7 present, and no MSC- smad7 deleted, LN, and MSC- and smad7 present, MSC, and LN. As Ma et al, Murphy Roth Large/ lymphoproliferation spontaneous mutation (MRL/lpr) mice will be used for experiment. The MRL/lpr mice can develop LN that is similar to that of LN in human. MSC would be harvested from balb/c mice femurs and tibias and then grown in a plastic dish.

**Discussion**

The results I would expect to see is that the phosphorylation of smad3 would be reduced in all the groups, but have the lowest levels in the group with smad7 present. These results would suggest the gene therapy with smad7 with MSC would be more beneficial the reverse fibrosis. Reduced levels of smad3 phosphorylation would indicate if it is being activated and signaling to TGF-b, which in turn would inhibit collagen 1 gene from being transcribed.

Although research has shown that MSC treatment is effective in many types of diseases, it is important to understand how the MSC interact with pathways and cellular mechanisms to potentially improve treatment.

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