mTOR Regulates the Phenotypic Modulation of De-differentiated Mesenchymal Stem Cells in Vascular Disease

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Atherosclerosis, a form of cardiovascular disease, accounts for 17.3 million deaths/year(Mozaffarian,2014). Characterized by plaque formation in arteries, it leads to myocardial infarctions and strokes. The dysregulated growth/motility of smooth muscle cells(SMCs) is a key step in pathogenesis. However, mechanisms involved in SMC dysfunction are unknown. To address this gap, this study postulated de-differentiation potentials of SMCs to mesenchymal stem cells(SMC-MSC). Immunofluorescence studies were used to identify this potential; a positive staining for MSC markers and a decreased staining for SMC markers were observed, indicating dedifferentiation. SMC de-differentiation has not been previously shown with unequivocal support nor has it been linked to atherosclerosis, making this a novel finding. It was also proposed that the mTOR pathway mediates these SMC-MSCs. This cell-cycle regulating pathway is linked to atherosclerosis, as its inhibitor, rapamycin, is used in angioplasty to halt cell infiltration; however, mechanisms by which rapamycin functions are unknown. Rapamycin treated SMC-MSCs underwent immediate morphological changes, approaching senescence, indicating its possible mechanism of function. However, after mTOR inhibition in non-dedifferentiated MSCs, cell count increased. These results demonstrate mTOR's mediation of SMC-MSCs and its little effect on adult MSCs. These findings suggest an increased use of mTOR inhibitors in treatment, as they downregulate proliferation of plaque causing cells and protect inflammation reducing MSCs. This study also indicates that the anti-atherogenic target is SMC-MSCs, not only SMCs, thus providing a better understanding of atherosclerotic to enable specific, targeted treatment, which will in the long run, lead to a cure.

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