Medical care, Regenerative therapy

Development of novel administration method to improve regenerative capacity of cell therapy in peripheral artery disease

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Abstract

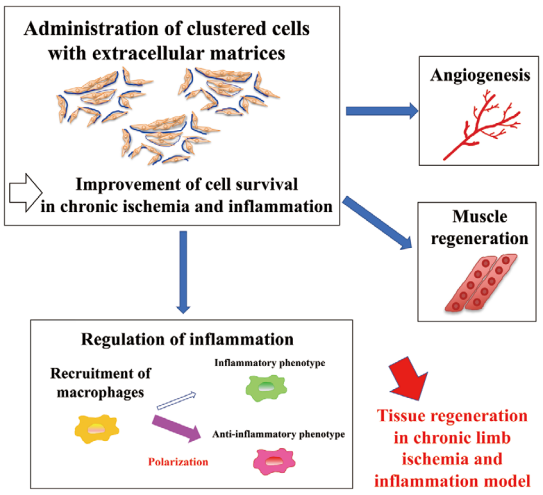
Peripheral artery disease (PAD) is a global problem because of the growing number of patients and the dreadful outcome of the disease with high major amputation rate and subsequent poor survival outcome. Although revascularization is the standard treatment for PAD, growing number of patients are difficult to treat with standard treatment, and alternative ways of treatment, including regenerative cell or gene therapy, have been pursued. However, severe ischemic and inflammatory condition of the disease limits the treatment efficacy of such regenerative treatment because administered agents cannot survive sufficient to show treatment effect in such harsh environment, and therefore current guideline does not recommend regenerative therapy for PAD due to the scarce treatment efficacy. In this study, we developed a novel administration method of cells, in which cells are combined with extracellular matrices to form "clustered cells." Clustered cells dramatically improved cell survival even in a severe ischemic and inflammatory condition, and consequently showed improved regenerative effect by controlling inflammatory condition and augmenting angiogenesis and muscle regeneration.

Background & Results

The low survival rate of administered agents due to severe ischemic and inflammatory environments limits the efficacy of the current regenerative therapy in peripheral artery disease (PAD). We previously clarified the efficacy of cell sheet technology for ischemic cardiomyopathy by improving cell retention rate. This study aimed to develop a new treatment method to enhance the efficacy of cell therapy in PAD with severe ischemic and inflammatory environments, using cell sheet technology. Clustered cells from myoblast cell sheets obtained from mice, which included various extracellular matrices, including laminin, fibronectin, and vitronectin, were administered into ischemic mouse muscles. A chronic severe limb ischemia model was developed to mimic PAD ischemic condition. Control groups were administered with single myoblast cells or saline. Compared with the single cell administration, clustered cells showed markedly improved cell survival at 7 days and 28 days after administration. Consequently, clustered cells administration alone showed markedly improved blood perfusion of the limb, angiogenesis, and muscle regeneration, along with the upregulation of associated genes. Additionally, inflammation status was well regulated by clustered cells administration. Clustered cells administration increased the number of macrophages and then induced polarization into an anti-inflammatory phenotype, along with the increased expression of genes associated with anti-inflammatory cytokines. Our findings suggested clinical potential of rescuing severely damaged limbs in PAD using clustered cells.

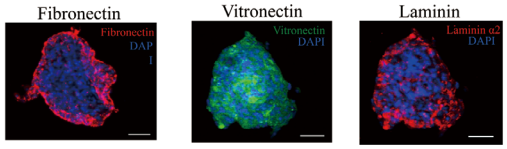
Significance of the research and Future perspective

This study showed the therapeutic effect of novel administration method of cells in the form of clustered cells. Clustered cell administration enabled to improve administered cell survival, which in turn enabled to control inflammation and to promote tissue regeneration. This study suggested that clustered cell administration would enable to bring therapeutic effects in various inflammatory and/or ischemic diseases that are refractory to cell therapy so far.

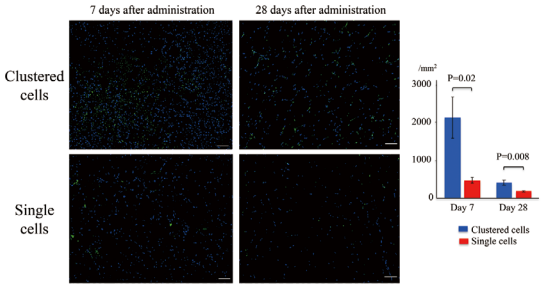


Tissue regeneration effect of clustered cells

Extracellular matrix included in clustered cells



Survival of administered cells (clustered cells vs. single cells)



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Treatise Miyake, Keisuke; Miyagawa, Shigeru; Sawa, Yoshiki et al. Engineered clustered myoblast cell injection augments angiogenesis and muscle regeneration in peripheral artery disease. Mol Ther. 2022, 30 (3), p. 1239-1251, doi: 10.1016/j.ymthe.2022.01.008

URL

Keyword cell therapy, peripheral artery disease, angiogenesis, chronic inflammation