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Metformin Ameliorates Senescence of Adipose-Derived Mesenchymal Stem Cells and Attenuates Osteoarthritis Progression via the AMPK-Dependent Autophagy Pathway

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Abstract

Osteoarthritis (OA) is one of the most serious age-related diseases worldwide that drastically affects the quality of life of patients. Despite advancements in the treatment of arthritis, especially with adipose-derived mesenchymal stem cells (ADSCs), senescence-induced alterations in ADSCs negatively affect the treatment outcomes. This study was aimed at mechanistically exploring whether metformin could ameliorate the senescence of ADSCs and at exploring the effect of metformin-preconditioned ADSCs in an experimental OA mouse model. In this study, an H_2O_2-induced mouse ADSC senescent model was established. Cell proliferation, senescence, and autophagy were investigated in vitro. Moreover, the effects of intra-articular injection of metformin-preconditioned ADSCs were investigated in vivo. Metformin could promote autophagy and activate the AMPK/mTOR

pathway in ADSCs. The metformin-enhanced autophagy could improve the survival and reduce the senescence of ADSCs. The protective effects of metformin against senescence were partially blocked by 3-methyladenine and compound C. Injection of metformin-preconditioned ADSCs slowed OA progression and reduced OA pain in mice. The results suggest that metformin activates the AMPK/mTOR-dependent autophagy pathway in ADSCs against H_2O_2-induced senescence, while metformin-preconditioned ADSCs can potentially inhibit OA progression.

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Umbilical Cord Mesenchymal Stem Cells Ameliorate Inflammation-Related Tumorigenesis via Modulating Macrophages

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Abstract

Mesenchymal stem cells (MSCs) have been documented to be effective for the therapy of inflammation-related diseases but raised concerns on possible tumorigenic effects. Since most of the tumors are induced or promoted by chronic inflammation, one could expect that MSCs might be beneficial for the cancer therapy because of their potent roles on inhibiting inflammation. This study is aimed at performing a safety evaluation and evaluating the role of human umbilical cord mesenchymal stem cells (HUC-MSCs) on tumorigenesis. We found that HUC-MSCs cultured within 20 generations had no significant changes in proliferation, cell cycle, cellular senescence, apoptosis, and expression of

mesenchymal stem cell markers. HUC-MSCs were unable to form any tumor in immunodeficiency or normal mice with or without inflammatory stimulation. Intriguingly, we observed that HUC-MSCs inhibited tumorigenesis in B16-derived or AOM/DSS-induced colon cancer models. We reasoned that the effect of HUC-MSCs on tumorigenesis might be through regulating the inflammatory response. Indeed, HUC-MSCs dramatically ameliorated the disease symptoms and pathological changes of DSS-induced colitis mice. We deciphered the mechanism that HUC-MSCs inhibited tumorigenesis through reducing the proportion of macrophages, which were decreased in the mice suffered from AOM/DSS-induced colon cancer. Correspondingly, the expression levels of TNF-α and IL-6, which were secreted by macrophages, were significantly decreased in the plasma of colon cancer and colitis mice after injection of HUC-MSCs. This study revealed the role of inhibiting macrophages and shed light on the therapeutic application of HUC-MSCs in inflammation-induced tumorigenesis.