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“Macrophage miR-21, Yin Yang in Cancer and Atherosclerosis”

Atherosclerosis and cancer are chronic diseases considered two of the main causes of death all over the world. Both diseases are multifactorial as they share several important molecular pathways and many etiological and mechanistical processes from the very early stages of development up to their advanced forms. Factors involved in their progression comprise of genetic alterations, dysregulated proliferation and inflammatory processes among others that can alter the behavior of the different cell types that are involved in the pathophysiology of both diseases. Since miRNAs have been found to regulate the development of atherosclerosis and cancer, it becomes of importance to investigate if similar therapeutic strategies involving miRNAs could apply to both diseases. We recently became interested in studying the participation of miR-21 in regulating tumor progression and atherosclerosis. miR-21 is among the most highly studied microRNAs in cancer cells but as well in cells of the vascular system and involved in the regulation of inflammatory, angiogenic and differentiation responses. We first analyzed the function of miR-21 in non-cancer cells of the tumor microenvironment to determine its contribution to tumor progression. We found that the expression of miR-21 in cells of the tumor immune infiltrate, and in particular in macrophages, but not in the stroma cells, is responsible for promoting tumor growth. Absence of miR-21 expression in tumor associated macrophages (TAMs) causes a global rewiring of their transcriptional regulatory network that is skewed towards a pro-inflammatory angiostatic phenotype. This promotes an antitumoral immune response characterized by a macrophage-mediated improvement of cytotoxic T cell responses trough the induction of cytokines and chemokines including IL12 and CXCL10. These effects translate to reduction of tumor neovascularization and an induction of tumor cell death that lead to a decrease in tumor growth. Based on these findings, we then aimed to the contribution of miR-21 expression in macrophages, during atherogenesis. We found that the absence of the most abundant miRNA in macrophages results in accelerated atherosclerosis, plaque necrosis, and vascular inflammation. miR-21 expression influences foam cell formation, sensitivity to ER-stress-induced apoptosis, and phagocytic clearance capacity. Mechanistically, we discovered that the absence of miR-21 in macrophages increases the expression of the miR-21 target gene, MKK3, promoting the induction of p38-CHOP and JNK signaling. Both pathways enhance macrophage apoptosis and promote the post-translational degradation of ABCG1, a transporter that regulates cholesterol efflux in macrophages. Altogether, these findings reveal a major role for miR-21 in atherogenesis. Consequently, our work demonstrates that differential modulation of miR-21 in macrophages could provide effective approaches to both directly impact tumor cell growth and atherogenesis.

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