CYTOKINE MEDIATED CONTROL OF MICROBIOTA AND INFLAMMATION IN ATHEROSCLEROSIS

Ekaterina K. Koltsova*[1], Iuliia Peshkova[1], Amiran Dzutsev[2], Turan Aghayaev[1], Giorgio Trinchieri[2] and Aliia Fatkhullina[1]

[1]*Blood Cell Development and Function Program, Fox Chase Cancer Center, Philadelphia, PA, USA*
[2] *Cancer and Inflammation Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA*

Ekaterina.Koltsova@fccc.edu

Abstract

Atherosclerosis is lipid-driven, chronic inflammatory disease of the arterial wall. While commensal microbiota is involved in the distal regulation of systemic immune responses, how this distant connection influences the development of atherosclerosis and what are the underlying mechanisms remains largely unknown. In a mouse model of atherosclerosis, we found that disease was augmented when expression of the otherwise inflammatory cytokine IL23 was ablated. IL23 and its immediate downstream target IL22 restrict atherosclerosis by preventing outgrowth of microbiota, as inactivation of IL23/IL22 signaling led to dysbiosis and expansion of bacteria with pro-atherogenic properties, due to defective production of antimicrobial peptides in the intestine. These pro-atherogenic bacteria contributed to elevated serum levels of several pro-atherogenic metabolites, which in turn induced osteopontin (OPN) expression by subsets of myeloid cells including aortic macrophages. Microbiota transfer from IL23 deficient mice accelerated atherosclerosis, while microbial depletion or IL22 administration reduced aortic osteopontin expression and ameliorated the disease. Overall, our work uncovers the innate inflammatory IL23-IL22 cytokine signaling axis as a key regulator of atherosclerosis that controls diet-induced expansion of pro-atherogenic microbiota, and argues for informed usage of cytokine blockers with regard to cardiovascular side effects driven by microbiota and inflammation.

Keywords

Atherosclerosis, cytokines, inflammation, microbiota, myeloid cells