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IJAE
Vol. 121, n. 1 (Supplement): 132, 2016
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Macrophage polarization by the microenvironment of atherosclerotic plaques

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Macrophages are key cellular mediators of innate immunity: they are positionally and transcriptionally programmed to respond to pathogens and environmental challenges. When activated by inflammatory signals in their microenvironment they develop into functionally and phenotypically distinct polarized subpopulations: classically activated macrophages, M1, characterized by cytotoxix/proinflammatory activity; alternatively activated macrophages, M2, characterized by anti-inflammatory/wound repair activity. M1 pro-inflammatory macrophages drive atherosclerotic plaques progression towards instability, cap fragilization and rupture. Our study provide new informations about the role exherted by IL-23 and its receptor in human carotid atherosclerotic plaque progression. We show the presence of IL-23 immunoreactivity, mRNA and protein in macrophages infiltrating human carotid atherosclerotic plaques. Our immunohistochemical analysis demonstrated a strong IL-23 immunoreactivity within the inflammatory infiltrate at the shoulder of the plaques, and at the level of cells lining the fibrous cap. FISH analysis confirmed the expression of IL-23 detected by immunohistochemistry. Immunofluorescence, followed by FISH analysis, showed that cells positive for IL-23 mRNA bind anti-CD68 mAb, thus indicating that these cells belong to the macrophage components of the inflammatory infiltrate. This result was further confirmed by double labelling experiments. IL-23 immunoreactivity was detected within the fibrous layer and co-localized with cells belonging to the monocyte-macrophage lineage as shown by their strong CD68- and CD14-related reaction. Clusters of double-positive cells were found at the border of the plaque, as well as in the subendothelial space. Immunohistochemistry and immunofluorescence showed a strong immunoreactivity for IL-23R at the level of inflammatory mononuclear cells accumulated within the plaque. In vitro, only M1 pro-inflammatory, but not M2 anti-inflammatory macrophages produced IL-23, upon stimulation with zymosan or bacterial lipopolysaccharide. Our results suggests that a hyperactive and highly pathogenic IL-23-IL-23R system drives chronic inflammation in atherosclerosis, while the presence of IL-23 proximal to the fibrous cap may contribute to the atherosclerotic plaque instability.

Keywords

IL-23; macrophages; human carotid atherosclerosis; immunohistochemistry.

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