Hypoxia, Oxidative Stress and Inflammation

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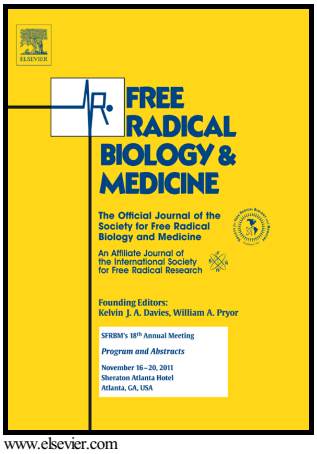

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Abstract

Inflammatory Arthritis is characterized by synovial proliferation, neovascularization and leukocyte extravasation leading to joint destruction and functional disability. Efficiency of oxygen supply to the synovium is poor due to the highly dysregulated synovial microvasculature. This along with the increased energy demands of activated infiltrating immune cells and inflamed resident cells leads to an hypoxic microenvironment and mitochondrial dysfunction. This favors an increase of reactive oxygen species, leading to oxidative damage which further promotes inflammation. In this adverse microenvironment synovial cells adapt to generate energy and switch their cell metabolism from a resting regulatory state to a highly metabolically active state which allows them to produce essential building blocks to support their proliferation. This metabolic shift results in the accumulation of metabolic intermediates which act as signaling molecules that further dictate the inflammatory response. Understanding the complex interplay between hypoxia-induced signaling pathways, oxidative stress and mitochondrial function will provide better insight into the underlying mechanisms of disease pathogenesis.

Keywords
Inflammatory Arthritis; Hypoxia; Dysregulated Angiogenesis; Oxidative stress; Mitochondrial Dysfunction; Altered Cellular Metabolism

Key Points

- The inflamed joint is profoundly hypoxic, and promotes activation, proliferation and survival of synovial cells.