Estrogen accelerates the resolution of inflammation in macrophagic cells

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The incidence of chronic inflammatory diseases differs significantly between sexes, with female mammals less prone than males to morbidity resulting from chronic inflammation, and a significant rise in the incidence of these diseases as a hallmark of the cessation of ovarian functions. The anti-inflammatory properties of estrogen, the primary female sex hormone, have been extensively described; nonetheless the underlying mechanism is still unclear. In particular, the influence of estrogen on the resolution phase of the inflammatory process is still largely unexplored. Aim of the present study was to evaluate the extent to which estrogens promote the intrinsic or the T-cell-regulated resolution of inflammation in macrophages. To this purpose we subjected the mouse leukaemic cell line RAW 264.7 to combined treatments of pro-inflammatory or anti-inflammatory stimuli with physiological concentration of 17β-estradiol, and we evaluated specific markers of the different phenotypes involved in the progression of the inflammatory process. We identified a previously unreported, ERα mediated, effect of estrogen on the inflammatory machinery. We provide evidence that the activation of the intracellular estrogen receptor shortens the pro-inflammatory phase by influencing the intrinsic and extrinsic programs that trigger the resolution of inflammation in macrophages. Moreover, estrogen fosters the progression towards the IL10-dependent 'acquired deactivation' phase, responsible for immunomodulation and tissue remodeling. The described putative mechanism, involving the regulation of SOCS3 and of the STAT3 signaling pathway, paves the way to novel, more efficacious anti-inflammatory therapies, aimed to the promotion of the natural resolution of inflammation.