In vivo differences in leukotriene biosynthesis in zymosan-induced peritonitis: role of resident peritoneal macrophages

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Leukotrienes (LTs) are lipid mediators implicated in inflammatory and autoimmune diseases, often characterized by a sex-bias in the incidence (e.g., asthma). LTs derive from arachidonic acid through the action of 5-lipoxygenase (5-LO), which is a soluble protein translocating to perinuclear membranes after activation. We have previously shown sex-differences in LT formation in human whole blood and leukocytes, due to down-regulation of 5-LO product formation by androgens. Here we show that LT synthesis is sex-biased *in vivo*, in a model of zymosan-induced peritonitis. After intraperitoneal injection of zymosan in mice, an immediate production of LTs was observed within 30 min, which was significantly higher in female then in male mice (about two times). These effects were followed by the recruitment of neutrophils into the peritoneal cavity, and both infiltrating cell numbers and myeloperoxidase activity (marker for neutrophils) were significantly higher in females than in males. Interestingly, orchidectomy of male mice resulted in a significant increase of LT levels in the peritoneal exudates, while a decrease of LTs was observed in ovariectomized female mice, thus suggesting significant effects of both male and female sex hormones. Mechanistically, we observed that *in vitro* stimulation of resident peritoneal macrophages from female mice induced higher LTC_4 formation as compared to males, which was not due to different AA release or 5-LO protein expression, but was accompanied by a different 5-LO subcellular localization. Taking together, we here demonstrate that LT biosynthesis is sex-biased *in vivo* in mouse zymosan-induced peritonitis, seemingly related to a different activation status of 5-LO in peritoneal macrophages, with profound consequences on the development of the inflammatory reaction. These data further support the evaluation of a gender-tailored therapy with anti-LTs.