SEX BIAS IN LIPID MEDIATOR BIOSYNTHESIS DURING ACUTE INFLAMMATION AND RESOLUTION

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Acute inflammation is generally a self-limited process in which lipid mediators (LM) play a pivotal role. LM, derived from the omega-6 polyunsaturated fatty acids (PUFA) like leukotrienes (LT) and prostaglandins (PG), are potent enhancers of innate and adaptive immunity during the acute phase of the inflammatory process (Medzhitov, 2008). These pro-inflammatory LM are mainly produced by the 5-lipoxygenase (5-LO) and cyclooxygenase-2 (COX-2) enzymes. However, the omega-3 PUFA-derived specialized pro-resolving mediators (SPM) such as resolvins, maresins, and protectins are LM that regulate the resolution process and are mainly products of the 12/15-lipoxygenases (12-LO, 15-LO) (Sehran, 2014).

Due to the disparity in the incidence of immune disorders between males and females, several studies were focused on the role of sex in inflammation. We have recently demonstrated superior LT biosynthesis in human neutrophils, monocytes and in mouse macrophages from femalesand we confirmed these sex differences in vivo in a model of acute inflammation such as mouse zymosan-induced peritonitis (Rossi et al., 2014).

In this study, we report sex differences in the production of a broad range of pro-inflammatory and pro-resolving LM during the acuteand the resolvingphases of inflammation. We performed a time-dependent mouse zymosan-induced peritonitis up to 24 hours to evaluate the differences in LM production in the two sexes. Significant higher amounts of LM produced by 5-LO, 12-LO, 15-LO and COX-2 were found in the peritoneal cavity of male compared to female animals under healthy conditions. Interestingly, the expression of the main enzymes involved in LM biosynthesis did not differ between the two sexes. Four hours after zymosan administration, a significantly higher production of 5-LO metabolites was found in exudates from males, whereas more 12-LO metabolites were produced in females. Note that a higher cell afflux in female peritoneal cavity was evident as compared to males after 4 hours (Rossi et al., 2014). No differences were evident at 24 hours for the LO metabolites, whereas greater activity of COX-2 was found in males, with PG formation being significantly higher compared to females. After 24 hours, the number of cells present in the peritoneal cavity was essentially similar to what observed under healthy conditions for both sexes.

Conclusively, our data clearly demonstrate that sex is an important variable in the biosynthesis of LM with consequences for the resolution and possible implication for therapies.

Medzhitov. (2008). Nature. 454, 428-435.

Sehran. (2014). Nature. 510(7503): 92–101.

Rossi et al. (2014). Pharmacol Res. 87:1-7.