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Commentary

Leukotrienes are proinflammatory lipid mediators that have been shown to be upregulated in several diseases, including asthma, aspirin-exacerbated respiratory disease (AERD), inflammatory bowel disease, and acute respiratory distress syndrome. Leukotrienes have been explored as therapeutic targets for these diseases and others; however, leukotriene inhibitors have had limited success in the clinic. There are noted differences in the incidence of leukotriene-mediated diseases in males and females, but sex as a factor in the response to leukotriene inhibitors has not been fully explored. In this issue of the *JCI*, Pace and colleagues present evidence that there are sex-specific differences in the effectiveness of certain leukotriene inhibitors and link the differences in response to the presence of androgens. The results of this study indicate that sex needs to be taken into consideration in the future evaluation of leukotriene inhibitors to treat disease.

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Leukotrienes and sex: strange bedfellows?

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Leukotrienes and disease

Leukotrienes are bioactive mediators that were initially identified in the 1970s, and the biosynthetic pathways involved in leukotriene formation were elucidated around the same time (1). The major leukotrienes were designated as leukotriene B₄ (LTB₄) and as the cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄). Subsequently, several leukotriene receptors (BLT₁, BLT₂, CysLT₁, CysLT₂) were discovered, and small molecules were developed that inhibited leukotriene synthesis either by targeting 5-lipoxygenase (5-LO), 5-LO-activating protein (FLAP), cytosolic phospholipase A₂ (cPLA₂), or molecules, such as leukotriene receptor antagonists, that interfere with the ability of leukotrienes to mediate their effects. Increased leukotriene production has been linked to several inflammatory diseases through a series of animal, *in vitro*, and human studies in which leukotriene levels were measured under basal and stimulated conditions and in which the newly developed leukotriene modifiers were administered to various animal species, healthy individuals, and

patients with disease. Specifically, leukotriene expression has been associated with asthma (2, 3), aspirin-exacerbated respiratory disease (AERD) (4), allergic rhinitis (5), inflammatory bowel disease (6), and acute respiratory distress syndrome (7). However, with rare exceptions, such as AERD (8), leukotriene modifiers have shown only a modest beneficial effect on diseases in which leukotrienes would be expected to play an important role. Several explanations, including differences in leukotriene levels in individual patients, the heterogeneity of disease phenotypes, and differences in drug pharmacokinetics, pharmacodynamics, and pharmacogenomics, have been proposed for why targeting leukotrienes does not benefit leukotriene-related diseases (9); however, there has not been a clear explanation for why antileukotriene drugs have not worked as expected.

Sex and the response to leukotriene inhibition

One possible explanation comes from the study of diseases associated with elevat-

ed leukotriene levels and the response of these conditions to antileukotriene drugs. Several of these diseases have a female predominance and have been associated with sex hormone levels (e.g., asthma in adults, AERD) (8, 10). Based on these data, it is possible that leukotriene modifiers would have a greater effect in those with the highest leukotriene levels. In this issue, Pace and colleagues build on their previous work and address a potential mechanism that may be responsible for the relatively limited response to leukotriene modifiers in several disease states (11). Pace et al. exposed male and female mice and rats as well as peripheral blood cells from male and female human volunteers to inflammatory stimuli and administered different leukotriene synthesis inhibitors. The results from this study confirmed their previous findings that there are sex-dependent differences in leukotriene biosynthesis and the effects of leukotriene modifiers and that these differences are mediated at least in part by androgens (12). Pace and colleagues also note that females are more likely than males to have 5-LO/FLAP complex assembly at the nuclear membrane, the site where this complex mediates its effects. Additionally, androgens inhibited the tight assembly, and drugs that directly interfered with FLAP and 5-LO/FLAP assembly were most likely to result in a sex-specific effect. One area that Pace and colleagues did not explore is how androgens may alter the interaction between 5-LO and FLAP. Nonetheless, their experiments highlight the complexity of trying to understand the role of sex in the differences in leukotriene synthesis and response to leukotriene-targeting drugs, as the results were influenced by the specific stimulus and model system, the type of inflammatory cell (human peripheral blood neutrophils and monocytes and mouse and rat peritoneal macrophages), and the leukotriene modifier selected. Even the use of structurally dissimilar 5-LO inhibitors showed different effects.

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Conclusions and future directions

This report by Pace and colleagues provides new insights into the influence of sex (and sex hormones) on leukotriene synthesis and its inhibition. While the potential of these results to be of clinical relevance is exciting, additional preclinical and clinical studies are needed to define the true clinical impact, which is likely to be complex. For example, Pace et al. focus primarily on inflammatory processes and leukocytes that predominantly generate LTB_4 . Although a number of inflammatory diseases, including scleroderma lung disease (13), inflammatory bowel disease (6), sickle cell disease (14), and cardiovascular disease (15), are reported to be associated with increased LTB_4 levels, there are few, if any, examples in which treatment of these diseases with leukotriene synthesis inhibitors has shown benefit. The diseases in which there is the most information relevant to leukotriene biology are asthma, AERD, and allergic rhinitis, to which cysteinyl leukotrienes are known to contribute. For example, well-characterized mouse models of asthma have been used to study the role of leukotrienes and leukotriene modifiers, including cysteinyl leukotriene receptor blockers, which have become widely used in clinical practice (16, 17). Experiments with disease models that have a demonstrated response to leukotriene modification could be used to further explore sex-dependent differences in cysteinyl leukotriene synthesis and the response to leukotriene synthesis inhibitors and receptor blockers. Additionally, sufficient numbers of human peripheral blood eosinophils could be obtained from individuals with elevated eosinophils counts and used to determine whether or not there are sex-specific differences in stimulus-generated cysteinyl leukotriene levels in vitro and/or in the ability of leukotriene modifiers to block these effects.

Retrospective analyses of databases from studies performed in the 1990s, which tested leukotriene synthesis inhibitors and receptor antagonists in patients with asth-

ma, may also provide further information on the role of sex and the response to leukotriene modification. These studies, which enrolled males and females, were of sufficient size to identify sex-specific differences. It is a bit surprising that a sex-dependent effect on response was not noted, considering the extensive post hoc analyses that are typically performed on such clinical trials. It is possible that earlier studies of leukotriene modifiers used doses that did not fully inhibit leukotriene synthesis. There is a recent interest in using higher doses of leukotriene modifiers and in delivering these inhibitors directly to the organ of interest so that high local concentrations are achieved. These approaches have the potential to be taken advantage of for possible identification of sex-dependent effects that have not previously been seen. For any new study, the influence of sex should be a predefined variable and the statistical analysis powered to identify such an effect. If the clinical studies identify a sex-specific effect on leukotriene synthesis inhibitors, it would validate the results of Pace and colleagues, expand the number of drugs whose effects are influenced by sex (18), and possibly lead to sex-specific therapy of a disease that affects large numbers of men and women.

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