

COMMENTARY

A lipid mediator controls neutrophil recruitment in acute lung injury - should we really be surprised?

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Abstract

New therapeutic approaches are sorely needed for acute lung injury. Neutrophil recruitment is a pathological hallmark of this syndrome, and is mainly regulated by CXC chemokine receptor 2 and its ligand CXC ligand 1. Rossaint and colleagues have described a new mechanism for regulation of this axis by 12/15-lipoxygenase products. This work opens the door for new therapeutic approaches and highlights the crucial interplay between lipid mediators and chemokines, a time-honored but often-ignored concept.

Acute lung injury (ALI) is a major cause of morbidity and mortality and exacts an enormous health care burden. Current treatment is merely supportive, and the lack of pathophysiologically targeted strategies is conspicuous. Neutrophil recruitment is a crucial component of ALI, with the CXC chemokine receptor 2 (CXCR2)/CXC ligand 1 (CXCL1) axis being a critical determinant of that process in murine models of ALI. Rossaint and coworkers [1] have employed both genetic and pharmacological methods to show that reducing the generation of 12/15-lipoxygenase (12/15-LO) metabolites of arachidonate can inhibit neutrophil recruitment by attenuating CXCR2 expression, with concomitant improvement in clinically meaningful parameters of edema formation and gas exchange.

One important lesson from this study was the authors' perseverance in the face of 'unexpected' data. Although mice lacking the 12/15-LO gene had reduced neutrophil recruitment, they surprisingly exhibited higher levels of CXCL1 in the serum and lung lavage fluid [1]. This apparent paradox was explained by examining the

expression of CXCR2 by flow cytometry. A modest but apparently biologically significant decrease in surface expression of CXCR2 was identified in mice lacking 12/15-LO. This decrease in CXCR2 expression was associated with desensitization of receptor signaling to an extent sufficient to reduce the response of neutrophils to CXCL1. Data such as these have the potential to challenge conventional thinking about the magnitude of changes in receptor expression that may be biologically significant.

A crucial role for 12/15-LO metabolite(s) in regulating chemokine-dependent neutrophil trafficking may have substantial therapeutic implications in ALI and other forms of acute inflammatory tissue injury. However, translating these findings first requires that the specific metabolite promoting chemokine action, its cognate receptor, or the enzyme responsible for its synthesis be definitively identified. This is a greater challenge in the case of 12/15-LO than may be apparent. First, the mouse genome contains one gene coding for the dual lipoxygenase 12/15-LO, while in the human there are two separate genes encoding each of these lipoxygenase enzymes. To complicate matters further, products of these two enzymes may have opposite actions, with 12-HETE generally possessing pro-inflammatory properties, and 15-HETE and lipoxins typically described as being anti-inflammatory. This same research group has previously reported that 12-HETE regulates vascular permeability through a CXCR2 mechanism [2] and this product is therefore a potential candidate for the metabolite likewise responsible for enhancing neutrophil recruitment. Studies by others in a model of atherosclerosis [3] or asthma [4] also suggested that 12/15-LO products have net pro-inflammatory properties. There are, however, examples where 12/15-LO products have net anti-inflammatory features [5,6]. Rossaint and colleagues also employed a pharmacological inhibitor of 12/15-LO [1], cinnamyl-3,4-dihydroxy- α -cyanocinnamate (CDC), but this too is insufficient to clarify the lipid mediator(s) responsible for promoting chemokine action owing to a lack of specificity. In fact, CDC has recently been reported to be a more potent inhibitor for 5-LO than for 12-LO *in vitro* in

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human neutrophils and *in vivo* in a rat model [7]. A final factor contributing to uncertainty about the pertinent metabolite(s) derived from 12/15-LO is our ignorance about, and thus our inability to antagonize or delete, their cognate receptors. Although a receptor for 12-HETE has recently been proposed [8], its functionality has not been tested in ALI. Together, these factors have resulted in a far less comprehensive understanding of 12/15-LO products and their therapeutic targeting than has been the case with other lipid mediators, most notably prostanoids and leukotrienes. The findings presented in this manuscript provide additional motivation for investigators to identify the products of 12/15-LO and their receptors that regulate neutrophil recruitment as a prelude to a possible breakthrough in ALI research.

The concept of a lipid mediator that controls neutrophil recruitment is not new. Leukotriene B₄ (LTB₄) has long been known to regulate chemotactic activity of human neutrophils [9]. Moreover, interactions between LTB₄ and the CXCL1/CXCR2 axis in regulating neutrophil recruitment have also been recognized [10,11]. Regulation by lipid mediators of other chemokine axes has also been reported. For example, cross-talk between 12/15-LO products or LTB₄ with the monocyte chemoattractant MCP-1 (CCL2) has been described [12,13]. Unfortunately, this rich literature on the interplay between chemokines/cytokines and lipid mediators is often ignored in reviews about neutrophil recruitment.

The synthesis or actions of lipid mediators have proven far more amenable to therapeutic targeting than have those of chemokines. The work of Rossaint and colleagues provides an impetus to identify the precise mediator derived from 12/15-LO so that it or its receptor can be targeted as a potential strategy to improve outcomes of ALI.

Abbreviations

ALI, acute lung injury; CDC, cinnamyl-3,4-dihydroxy- α -cyanocinnamate; LO, lipoxygenase; LTB₄, Leukotriene B₄.

Competing interests

The authors declare that they have no competing interests.

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