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Opinion Article

OPINION ARTICLE

What Mediates the Inflammation Resolution?

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The concept of specialized proresolving lipid mediators (SPMs) is such a perfect model: Different enzymes of the arachidonic acid cascade lead to formation of specific multiply hydroxylated PUFAs. These SPM stop inflammation at high potency through the binding to G-protein-coupled receptors (GPCRs).[1]

A year ago we showed, based on own data and current literature, that neither the formation routes of trihydroxylated specialized proresolving lipid mediators such as lipoxins and resolvins via lipoxygenases are convincing nor the signaling through particular GPCRs has been conclusively demonstrated.[2] This challenges the biological role of these SPMs. However, most attention focused on the finding that analytical methods to demonstrate their formation and occurrence in biological samples are inappropriate, while methods validated according to internationally agreed standards largely fail to detect the molecules.[2–4]

Although this started an intense discussion, our questions regarding the formation route, the signaling, and the validity of detection methods have not yet been addressed. Meanwhile, many SPM papers, which show "illustrations" of LC–MS chromatograms instead of original data are marked in PubPeer but the authors are yet to provide original data to prove the existence of SPMs in their samples. Instead, arguments such as the testing of SPM in clinical trials, the own *h*-index or the number of SPM papers were used to substantiate the SPM concept.[3,4] The lack of answers regarding formation and signaling, and the refusal to show raw data, but also the nonscientific character and intensity of the debate raise serious doubts about substantial parts of the SPM concept.

In this discussion, it should be noted that the concept of active resolution of inflammation has not been challenged. But if not through these SPMs, research next needs to address how this process is regulated.

Indeed, the differentiation from a proinflammatory macrophage (M1) to a more inflammation resolving M2 type leads to a shift in the expression of the enzymes of the AA cascade and a change in the pattern of oxidized fatty acids, that is, oxylipins.[5] Thus, also the hypothesis that oxylipins play a key role in the regulation of both the onset as well as the resolution of inflammation is sound. Taking into account that hundreds of oxylipins are formed, current research should reevaluate which of the oxylipins may act as lipid mediators of resolution. For example, in-vitro conversion of PUFA by LOX leads to a complex pattern of oxylipins, which is so far not well characterized.[6]

A good starting point for investigation would be looking at the mono- and dihydroxy-PUFAs, some of which belong to those few SPMs, which seem to be detected using validated assays (RVD5, RVE4).[2,5] However, lipid biochemistry is much more complex:

There is not only a rapid release of (PU)FA from phospholipids by phospholipids, but also a rapid reincorporation of PUFA into phospholipids (Lands cycle). The same enzymes (lysophosphatidylcholine acyltransferases, long chain acyl-CoA synthetases) accept oxidized PUFA as substrates. Consistently, a major portion of the oxylipins occurring in biological samples are esterified in polar lipids.[7,8] The biological role of these esterified oxylipins is largely unknown. However, it is clear that this can lead to the remodeling of membranes and to orthosteric and allosteric receptor signaling.

Thus, in our view, the regulation of resolution of inflammation and other biological processes is a complex signaling network, which most likely involves many lipid mediators. However, it has to be verified that the proresolving lipid mediators are formed in the resolution phase in amounts, which are able to activate their proposed receptors.

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In summary, we are at the beginning of understanding how lipid mediators act on membranes and their receptors. Unravelling this requires a joint effort from biologists, biochemists, analytical chemists, physiologists, and pharmacologists to address these questions in appropriate models.

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Conflict of Interest Statement

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