# Pro-resolving Mediators— the Future Treatment in Inflammatory Eye Disease?



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***Key points:***

- Maresin 1, maresin 2, and annexin A1 increase Ca2+ and stimulate mucin secretion in rat conjunctival goblet cells.
- The pro-resolving mediator annexin A1 is present in rat conjunctival goblet cells.
- Maresin 1, maresin 2, and annexin A1 block the effect of histamine on goblet cells.

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Resolution of inflammation is an active process involving pro-resolving mediators derived from fatty acids and proteins. Maresin 1 and maresin 2 are examples of specialized pro-resolving mediators, and are derived from the omega-3 fatty acid DHA. DHA has been detected in tears of individuals with chronic inflammatory eye disease, indicating a potential role in the resolution of ocular surface disease. Annexin A1 is a protein with both anti-inflammatory and pro-resolving abilities, and plays a role in the anti-inflammatory effect of glucocorticoids.

Mucins are produced and secreted by conjunctival goblet cells, and are an important component of the protective tear film. Inflammatory ocular surface diseases are associated with alterations in mucin secretion, which contribute to destabilization of the protective tear film.

In this study, we examined which intracellular pathways and receptors are used by maresin 1, maresin 2, and annexin A1 in rat conjunctival goblet cells and how these mediators influence mucin secretion. In addition, we investigated the presence of annexin A1 in these cells, and the effect of these mediators on histamine, an important driver of diseases such as allergic conjunctivitis.

To examine intracellular pathways, cultured rat conjunctival goblet cells were preincubated with specific inhibitors before adding a mediator. Alterations in intracellular calcium concentration were measured using a ratio-imaging system with Fura2, while changes in mucin secretion were measured using an enzyme-linked lectin essay. The presence of annexin A1 was explored using PCR.

We found that maresin 1 and annexin A1 utilize the ALX/FPR2 receptor to stimulate the phospholipase C pathway to increase $Ca^{2+}$ and to stimulate mucin secretion, while maresin 2 uses an unknown receptor to activate protein kinase A to increase mucin secretion. Annexin A1 is present in rat conjunctival goblet cells. Regarding the role of the mediators in resolution of inflammation, we found that all three mediators blocked the effect of histamine. Thus, our results support a role of maresin 1, maresin 2, and annexin A1 in resolution of inflammation on the ocular surface.

***Remaining questions:***

- How will pro-resolving mediators influence human conjunctival goblet cells?
- Will pro-resolving mediators such as maresin 1, maresin 2, and annexin A1 be future treatment alternatives in inflammatory diseases?

***References***

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