

Resolution of Inflammation: Concept and Mechanisms. Lipid mediator resolution agonists: a strategy to treat Inflammation & Implications for CNS lesions

The pro-inflammatory signalling pathways and cellular mechanisms that initiate the inflammatory response have become increasingly well characterized. However, little is known about the mediators and mechanisms that switch off inflammation. We provide data which indicate that the resolution of inflammation is an active process controlled by endogenous mediators that suppress proinflammatory gene expression and cell trafficking, as well as induce inflammatory-cell apoptosis and phagocytosis, which are crucial determinants of successful resolution. During resolution, specific omega-3 polyunsaturated fatty-acid-derived mediators are generated within resolving exudates, including resolvin E1 (RvE1), Lipoxin A4 (LX4) and protectin D1 (PD1). Here we report that RvE1 and PD1 in nanogram quantities promote phagocyte removal during acute inflammation by regulating leukocyte infiltration, increasing macrophage ingestion of apoptotic polymorphonuclear neutrophils *in vivo* and *in vitro*, and enhancing the appearance of phagocytes carrying engulfed zymosan in lymph nodes and spleen. The molecular and functional characterization of agonists based on endogenous mediators that are inherent to resolution might represent a new strategy in anti-inflammatory therapy. So far, a number of factors have been identified, such as RVE1, PD1, which although are unstable with short half-lives *in vivo*, exert powerful alleviating effects when used in their native form or, particularly, as stable analogues to treat experimental inflammatory diseases. Therefore, the development of compliant mimetics based on their structure shows great promise for clinical usage.

Refs

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