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BOOK REVIEW

Arachidonate Remodeling and Inflammation

(Fonteh, A. N., and Wykle, R. L. (eds.) (2004) in *Progress in Inflammation Research* (Parnham, M. J., series editor) Birkhauser Verlag, Basel-Boston-Berlin)

Arachidonic acid (AA) and other 20- or 22-carbon polyunsaturated fatty acids (PUFAs) are precursors of signaling molecules that are critical in disease processes and in regulating normal cell function. AA level is tightly controlled in resting cells by many enzymes. In most cells, AA resides in ether-linked phospholipid subclasses. Cellular activation leads to the release of and buildup of free AA levels within cells. Free AA is converted to bioactive lipid mediators. These mediators are implicated in inflammation, analgesia, apoptosis, cell migration, and proliferation. The AA remodeling process is important in cell function, and the roles of enzymes that regulate AA homeostasis are examined in detail in this book.

The role of phospholipase A_2 (PLA_2) in remodeling in inflammatory cells is outlined in a chapter written by S. Barbour, S. Al-Darmaki, and A. D. Manguikian. The PLA_2s are typically grouped into three broad families of enzymes: the secreted or $sPLA_2$s, the cytosolic or $cPLA_2$s, and the calcium-independent or $iPLA_2$s.

Enzymatic and receptor mediated effects of secretory phospholipase A_2 from mast cells on the pathophysiology of diseases are examined in the next chapter (C. R. Marion and A. N. Fonteh). $sPLA_2$ receptor is considered as a potential target responsible for linking $sPLA_2$ to inflammatory diseases.

The role of Ca^{2+}-independent phospholipase A_2 in the control of arachidonic acid levels in resting and activated U937 phagocytic cells has been explored in recent studies and is described in the chapter written by J. Balsinde, R. Perez, Y. Saez, and M. A. Balboa. Under resting conditions, $iPLA_2$ accounts for most of PLA_2 activity of cells. Stimulation of the cells by receptor agonists results in the activation of $cPLA_2$, which then becomes the dominant PLA_2 involved in AA release. Under these conditions, the rate of AA release clearly exceeds that of reincorporated into phospholipids; hence, net accumulation of AA occurs that is followed by its conversion into different oxygenated compounds, collectively called the eicosanoids.

It was early recognized that the same stimuli, which elicit eicosanoids also elicit synthesis of platelet-activating factor (PAF). R. Wykle presents a review on arachidonate remodeling and PAF synthesis in human neutrophils. PAF and the eicosanoids have overlapping activities and act synergistically to promote cell function.

AA and 20-22 carbon PUFAs play a number of roles in mammalian physiology. These fatty acids serve as structural components of cellular membranes and as precursors of mediators of inflammation. Thus, their levels in mammalian systems are more tightly controlled than those of saturated fatty acids, which appear to primarily serve a structural role. Control of PUFA levels and the role of inhibitors of incorporation and remodeling on the biosynthesis of lipid mediators are described by M. McAlexander, B. J. Barham, M. Johnson, and A. N. Fonteh.

Remodeling of arachidonic acid in inflammatory cells of the human lung is outlined in the next chapter (M. Triggiani, G. Giannattasio, F. Granata, S. Loffredo, F. W. Rossi, S. Salzano, G. Marone). Activation of inflammatory cells, e.g., by recruitment into an inflammatory area, or their differentiation and maturation may lead to significant changes in AA distribution within intracellular pools. An interesting observation that has emerged in the last decade is that human inflammatory cells may constitutively contain or build-up a large pool of AA associated with triglycerides. This is an expandable, high-capacity pool presumably located in cytoplasmic lipid bodies. This pool is not an immediate source for AA in stimulated cells, and it may rather function as a recapture pool for AA mobilized from phospholipids.

Arachidonate remodeling is a very prevalent process in cells of the central nervous system. Although PAF was originally described as an inducer of platelet aggregation, PAF is an important modulator of neural function. Its overproduction plays a role in neural dysfunction. Arachidonate remodeling, PAF signaling and the inflammatory response in the central nervous system is reviewed in the chapter written by R. D. Saunders and N. G. Bazan.

Neurodegenerative diseases involve profound alterations in arachidonate remodeling. A. N. Fonteh and M. G. Harrigton in the next chapter summarize data on remodeling of arachidonate and other polyunsaturated fatty acids in Alzheimer's disease. A combination of dietary manipulation with enzyme inhibitors or antioxi-

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dants may be required for effective control of PUFA levels in the adult brain.

C. N. Serhan and N. Chiang wrote in the next chapter about lipoxins and resolvins as local mediators in endogenous anti-inflammation and resolution. Lipoxins are trihydroxy-tetraene-containing eicosanoids that are primarily generated by cell–cell interactions via transcellular biosynthesis. They serve as local endogenous anti-inflammatory mediators. These "stop signals" in inflammation may be involved in switching the cellular response from additional neutrophil recruitment toward monocytes that could lead to resolution of the inflammatory response and promotion of repair and healing.

In the last decade of the 20th century, two derivatives of AA, i.e., N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) were reported to be new members of the bioactive lipids. The review of Sugiura et al. focuses on anandamide and 2-AG and describes the metabolism and possible physiological significance of these molecules in mammalian tissues and cells including inflammatory cells and immune competent cells. Both anandamide and 2-AG have been shown to act as endogenous cannabinoid receptor ligands. The cannabinoid receptors and their endogenous ligands, especially 2-AG, are assumed to play essential roles in the nervous system and the immune system as addressed in this review, although subsequent intensive studies are indispensable for a comprehensive understanding.

This book is a rich resource of knowledge about AA remodeling for scientists and clinicians. Understanding remodeling will unravel better therapeutic targets for controlling inflammatory diseases.

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