Lipid Signaling

Ample Opportunities for Novel Drug Targets

Lipids serve important functions as membrane constituents and also as energy storing molecules. Beside these functions certain lipid species have been recognized as signaling molecules that regulate a multitude of cellular responses, including cell growth and death, and also key aspects of important diseases. Bioactive lipids were described that are controlling inflammatory processes in one or the other way [1]. Paradigmatically, this review will highlight the present knowledge about bioactive lipids that modulate inflammatory reactions and, consequently, represent potential targets for therapeutic intervention.

Targeting Eicosanoids

Prostaglandins (PG) are the end products of the metabolism of arachidonic acid (20 C atoms) by cyclooxygenases (COX) and prostaglandin synthases (PGS), and comprise a series of classical pro-inflammatory mediators that are denoted as eicosanoids ("eicosa" is the Greek term for 20). The targeting of cyclooxygenases (COX) to interrupt the generation of PGs and reduce inflammation and pain has evolved as an efficient therapeutic approach and has culminated in the development of selective COX-2 inhibitors. An alternative target is phospholipase A₂ (PLA₂) as it represents the rate-limiting step in the generation of eicosanoids. Unfortunately, the development of PLA₂ inhibitors has been hampered by the fact that the so far developed inhibitors have insufficient bioavailability and selectivity. A promising target within the PG cascade are the PGS. Especially the inhibition of microsomal prostaglandin E-synthase (PGES-1) may relieve inflammatory symptoms. In addition, thromboxane synthase inhibitors and thromboxane receptor antagonists are now available for the treatment of disorders like asthma and thrombosis. Leukotrienes are end products of the metabolism of arachidonic acid by 5-lipoxygenase (5-LOX). Alternatively, the combined action of 5-LOX and 12-LOX or 15-LOX can lead to the generation of lipoxins. Leukotrienes have physiological roles in innate immune responses and pathological roles in inflammatory and allergic
diseases. Consequently, anti-leukotriene therapy has proven to be efficient either through the inhibition of leukotriene synthesis or the selective antagonism of leukotriene receptors [2].

Arachidonic acid also can be metabolized by cytochrom P450 (CYP) enzymes to generate among others epoxyeicosatrienoic acids (EETs). These lipids regulate the vascular tone and reactivity, renal and pulmonary functions, ion transport, and growth [3]. EETs possess potent anti-inflammatory effects and act fibrinolytic. By this mechanism, EETs may play an important role in reducing thrombotic vascular complications. Cellular EETs are also regulated by degrading enzymes, the epoxide hydrolases (EH). Especially the soluble EH (sEH) may represent a useful target to reduce inflammatory reactions.

**Targeting Peroxisome Proliferator-Activated Receptors (PPAR)**

PPAR are members of the nuclear receptor superfamily and play important roles in lipid metabolism and homeostasis. They bind as heterodimers together with the 9-cis retinoic acid receptor (RXR), to PPAR-responsive elements (PPRE) in the promoter sequences of target genes, and regulate their transcription. PPAR-α regulates the expression of genes involved in fatty acid uptake and oxidation, inflammation, and vascular function. The most important activators of PPAR-α are fibrates. PPAR-γ is mainly involved in adipocyte proliferation and differentiation and its activation improves insulin sensitivity. Glitazones are "insulin-sensitizers" and were developed as anti-diabetics that act as selective PPAR-γ agonists. PPAR-β (or -δ) is ubiquitously expressed and involved in fatty acid metabolism and suppresses macrophage-derived inflammation. Many *in vitro* and *in vivo* studies delineate that PPAR agonists also regulate inflammatory responses.

**Lipoxins, Resolvins and Protectins**
An acute inflammatory reaction may either progress to a chronic state or enter a resolution phase for complete healing. It has become clear that this resolution phase is actively triggered by lipid mediators. These mediators derive either from arachidonic acid or from n-3 polyunsaturated fatty acids (PUFA). The major compounds were characterized as lipoxin A4 and lipoxin B4. Acetylated COX-2 may also use PUFAs as substrates to generate lipids denoted as Resolvin E and Resolvin D series. These novel lipid species have attracted a lot of interest in the last years due to their direct anti-inflammatory and resolution capacity in vivo [4].

**Targeting Cannabinoids**

The main psychoactive constituent of Cannabis was characterized as Δ⁹-tetrahydrocannabinol (Δ⁹-THC). Two high-affinity cannabinoid receptors have been described, denoted as CB₁ and CB₂. Whereas CB₁ is predominantly expressed in the central nervous system, CB₂ is mainly expressed in the periphery and on immune cells. Due to these differential expression patterns, it was suggested that CB₁ mediates most of the psychoactive effects of cannabinoids, whereas CB₂ is mainly involved in anti-inflammatory and immunosuppressive effects. Recently, a series of highly selective synthetic agonists of CB₁ and CB₂ have been developed.

**Targeting Sphingolipids**

Especially the two sphingolipids ceramide and sphingosine 1-phosphate (S1P) have been attributed a key regulatory function in the cell by building a cellular rheostat that determines cell survival or death, but also a pro- or anti-inflammatory outcome [5]. Ceramide was shown to enhance COX-2 expression and to stimulate arachidonic acid release by activating cytosolic PLA₂. However, controversial data exist on the anti-inflammatory action of S1P. It downregulates the synthesis of inflammatory enzymes like PLA₂ and inducible NO synthase. Moreover, it was shown that S1P induces an anti-inflammatory phenotype. Interestingly, it turned out that S1P activated the TGFβ/Smad signaling pathway and thereby mimics the anti-inflammatory capacity of TGFβ. A similar anti-inflammatory mechanism of action is also described for the immunomodulatory drug FTY720. All these data strongly propose that S1P mimetics and S1P receptor agonists/antagonist may have a relevant impact on inflammatory reactions.

**Perspectives**

The observations summarized above and extensively reviewed elsewhere [2] have opened a fresh chapter in our investigations how to understand molecular processes underlying inflammation and to unravel new treatment opportunities.
The discovery that lipids can act as activators of cell membrane receptors and of transcription factors has shifted back the scientific spotlight to membrane lipids. The vital elegance and the elaborate mechanisms that have evolved to regulate fundamental cell responses attract basic scientists as well as clinicians and promise to provide novel pharmacological approaches for the treatment of human diseases.

References


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