European Journal of Medicinal Chemistry xxx (2017) 1–15

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Drug discovery approaches targeting 5-lipoxygenase-activating protein (FLAP) for inhibition of cellular leukotriene biosynthesis

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ARTICLE INFO

Article history:
Received 28 March 2017
Received in revised form
29 June 2017
Accepted 12 July 2017
Available online xxx

Keywords:
Leukotriene
5-Lipoxygenase
5-Lipoxygenase activating protein
FLAP
Asthma
Atherosclerosis
Inflammation

ABSTRACT

Leukotrienes are proinflammatory lipid mediators associated with diverse chronic inflammatory diseases such as asthma, COPD, IBD, arthritis, atherosclerosis, dermatitis and cancer. Cellular leukotrienes are produced from arachidonic acid via the 5-lipoxygenase pathway in which the 5-lipoxygenase activating protein, also named as FLAP, plays a critical role by operating as a regulatory protein for efficient transfer of arachidonic acid to 5-lipoxygenase. By blocking leukotriene production, FLAP inhibitors may behave as broad-spectrum leukotriene modulators, which might be of therapeutic use for chronic inflammatory diseases requiring anti-leukotriene therapy. The early development of FLAP inhibitors (i.e. MK-886, MK-591, BAY-X-1005) mostly concentrated on asthma cure, and resulted in promising readouts in preclinical and clinical studies with asthma patients. Following the recent elucidation of the 3D-structure of FLAP, development of new inhibitor chemotypes is highly accelerated, eventually leading to the evolution of many un-drug-like structures into more drug-like entities such as AZD6642 and BI665915 as development candidates. The most clinically advanced FLAP inhibitor to date is GSK2190918 (formerly AM803) that has successfully completed phase II clinical trials in asthmatics. Concluding, although there are no FLAP inhibitors reached to the drug approval phase yet, due to the rising number of indications for anti-LT therapy such as atherosclerosis, FLAP inhibitor development remains a significant research field. FLAP inhibitors reviewed herein are classified into four sub-classes as the first-generation FLAP inhibitors (indole and quinoline derivatives), the second-generation FLAP inhibitors (diaryl-alkanes and biaryl amino-heteroarenes), the benzimidazole-containing FLAP inhibitors and other FLAP inhibitors with polypharmacology for easiness of the reader. Hence, we meticulously summarize how FLAP inhibitors historically developed from scratch to their current advanced state, and leave the reader with a positive view that a FLAP inhibitor might soon reach to the need of patients who may require anti-LT therapy.

Contents

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http://dx.doi.org/10.1016/j.ejmech.2017.07.019
0223-5234/

1. Introduction

1.1. Leukotrienes and 5-lipoxygenase pathway

Leukotrienes (LTs) are a family of important pro-inflammatory mediators associated with formation and progression of acute and chronic inflammatory diseases such as asthma, allergic rhinitis, cardiovascular diseases (CVD), Alzheimer and cancer [1–5]. LTs are generated from endogenous arachidonic acid (AA) which is released from phospholipid membranes by the action of cytosolic phospholipase A_2 ($cPLA_2$) upon activation. 5-Lipoxygenase (5-LO), an initiator enzyme for LT biosynthesis, then converts AA to an unstable epoxy intermediate LTA_4 (Fig. 1). It is known that 5-LO catalyzes successive reactions in a single active site. In the first reaction, AA is converted to a 5-LO-specific hydroperoxide intermediate, 5(*S*)-hydroperoxy-6-*trans*-8,11,14-*cis*-eicosatetraenoic acid (5-HPETE). In the second step, 5-LO subsequently catalyzes the synthase reaction to convert this peroxidation product into LTA_4 [6]. The product ratio of 5-HPETE and LTA_4 may depend on several factors influencing the 5-LO activity such as phosphorylation, Ca^{2+} and/or Mg^{2+} ions, activation by phosphatidylcholine, cellular compartmentalization and protein-protein interactions [7–9]. The formation of LTA_4 seems to be promoted in cellular assays upon translocation of 5-LO to nuclear membrane followed by concomitant association with its anchor protein, namely 5-lipoxygenase activating protein (FLAP) [7,10], while the 5-HPETE synthesis is more favored in cell-free assays by high substrate excess and enzyme concentration [6,11]. FLAP may act as a regulatory protein by maintaining the transfer of substrate AA to 5-LO for efficient biosynthesis of LTs in cells [7,12]. The formed LTA_4 is the junction point and acts as a precursor for biosynthesis of both LTB_4 and the cysteinyl-LTs (LTC_4, LTD_4 and LTE_4), which are physiologically active final products of the pathway (Fig. 1).

The production LTB_4 from LTA_4 requires the action of a zinc-bound epoxide hydrolase, namely LTA_4 hydrolase (LTA_4H). Conjugation of LTA_4 with glutathione mediated by LTC_4 synthase (LTC_4S) also occurs in the nuclear membrane to produce the first of the cysteinyl-LTs, so-called LTC_4. LTB_4 and LTC_4 are exported from cell

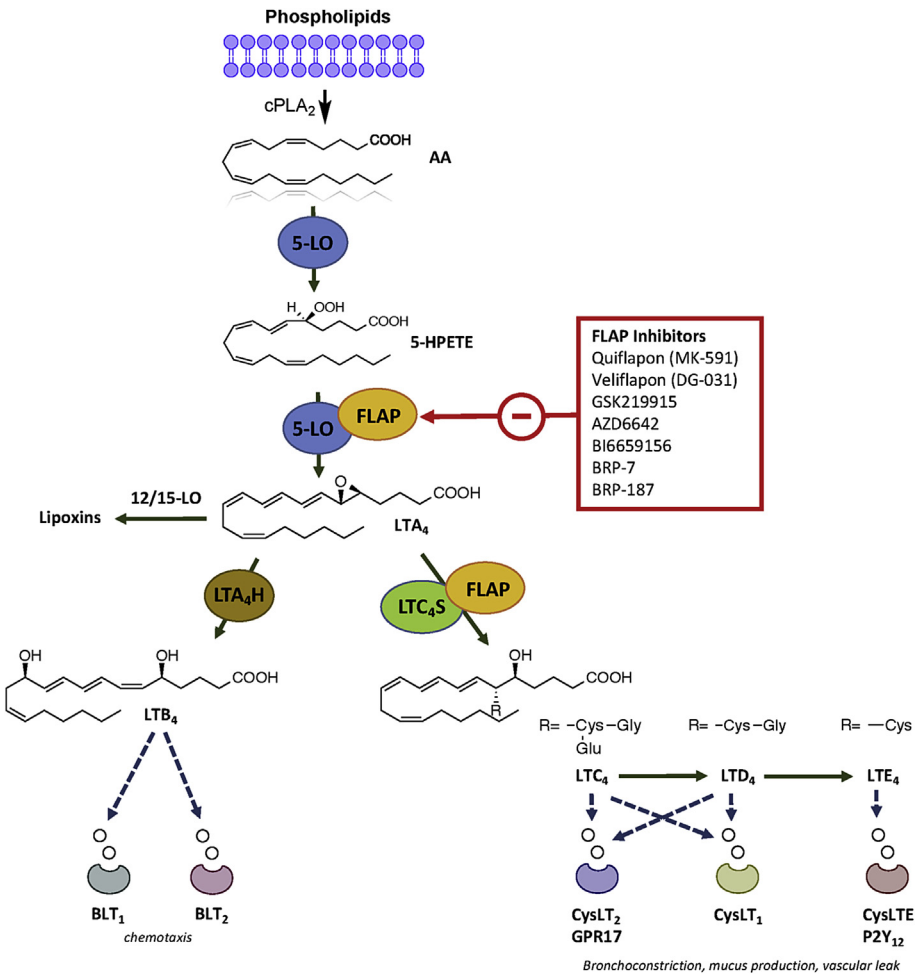

Fig. 1. Leukotriene pathway.

Please cite this article in press as: Z.T. Gür, et al., Drug discovery approaches targeting 5-lipoxygenase-activating protein (FLAP) for inhibition of cellular leukotriene biosynthesis, European Journal of Medicinal Chemistry (2017), http://dx.doi.org/10.1016/j.ejmech.2017.07.019