Commentary

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Why Obesity Worsens Bronchial Asthma—The Bioactive Lipids Connection

Undurti N Das[1,*]

[1]UND Life Sciences, Battle Ground, WA 98604, USA
*Correspondence: undurti@lipidworld.com (Undurti N Das)
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Bronchial asthma or commonly called "asthma", is a chronic inflammatory disease of the airways that causes periodic attacks of coughing, wheezing, shortness of breath, and tightness. It is estimated that more than 25 million Americans, including 6.8 million children under the age of 18, suffer from asthma. Allergies are strongly linked to asthma. Mast cells, eosinophils, and T lymphocytes play key roles in asthma's pathobiology. Mast cells release histamine that causes many of the features of asthma, including constriction of airways. Mast cells, eosinophils, and T cells, along with other inflammatory cells (such as polymorphonuclear leukocytes, see Fig. 1 for details of cells involved in asthma), play a role in the development of airway inflammation seen in asthma that contributes to the airway hyperresponsiveness, airflow limitation, and other respiratory symptoms, and its chronic nature. In some, nocturnal asthma or in the early morning hours, attacks are seen. Some patients have asthmatic attacks when they exercise, called "exercise-induced asthma". In these subjects, airway hyperresponsiveness occurs due to exercise. Asthma is generally treated with bronchodilators. Corticosteroids and β-adrenergic stimulants. Recently, specific mediators involved in the pathobiology of asthma have been identified. As a result, specific monoclonal antibodies that can block the action of these mediators have been introduced for the treatment of asthma. Some of these monoclonal antibodies include: omalizumab, which targets immunoglobulin E (IgE), mepolizumab targets interleukin-5 (IL-5), reslizumab targets IL-5, benralizumab targets IL-5 receptor, dupilumab targets IL-4 and IL-13 and Tezepelumab targets thymic stromal lymphopoietin.

Despite all these advances, some patients still suffer from repeated attacks of asthma and need hospitalization. Recurrent attacks of asthma can result in chronic obstructive pulmonary disease (COPD) and cor pulmonale. Cor pulmonale is defined as enlargement of the right ventricle of the heart due to high pressure in the pulmonary arteries, often due to lung diseases such as COPD.

Impact of Obesity on Asthma

Obesity is known to worsen asthma. It is noteworthy that both obesity and asthma are inflammatory conditions. This association between obesity and asthma has been attributed to the impact of body mass index (BMI) on the plasma levels of IL-6 and IL-18. It was reported that those who have higher BMI have increased plasma levels of these two cytokines (IL-6 and IL-18) that have pro-inflammatory actions and hence, an increase in the severity of asthma [1]. This implies that those who are obese need more rigorous treatment of asthma and attention to reduce their BMI.

It is noteworthy that obesity is an inflammatory condition in which increased plasma levels of IL-6 and tumor necrosis factor-alpha (TNF-α) have been documented [2]. This may explain why asthmatics with higher BMI are more likely to have severe asthma since they tend to have more inflammation. Furthermore, regular use of corticosteroids (which are often used in the treatment of asthma) may increase the BMI (Cushingoid features may develop/occur due to regular use of corticosteroids) in those with asthma. Corticosteroids are potent anti-inflammatory compounds and are known to suppress the production of IL-6 and TNF-α and other inflammatory cytokines [3–5].

Eicosanoids in Asthma

Several studies documented that there is a critical role for eicosanoids in asthma. An increase in the plasma and tissue concentrations of pro-inflammatory eicosanoids (such as prostaglandins E2, prostaglandin F-2α, and leukotrienes) with a concomitant decrease in those of anti-inflammatory eicosanoids (such as lipoxin A4 resolvins, protectins, and maresins) has been reported [6–14] (see Fig. 2 for metabolism of essential fatty acids: EFAs). These results suggest that an imbalance between pro- and anti-inflammatory eicosanoids may underlie the pathobiology of asthma. It is possible that, in a similar manner, an imbalance between pro- and anti-inflammatory cytokines may also occur in asthma. These results suggest that efforts need to be made to suppress the pro-inflammatory and enhance the levels of anti-inflammatory molecules in asthma.

PI3K/AKT/mTOR Pathway in Asthma

In this context, it is noteworthy that MIF (macrophage migration inhibitory factor, a pro-inflammatory molecule) is released from macrophages and T lymphocytes stimu-

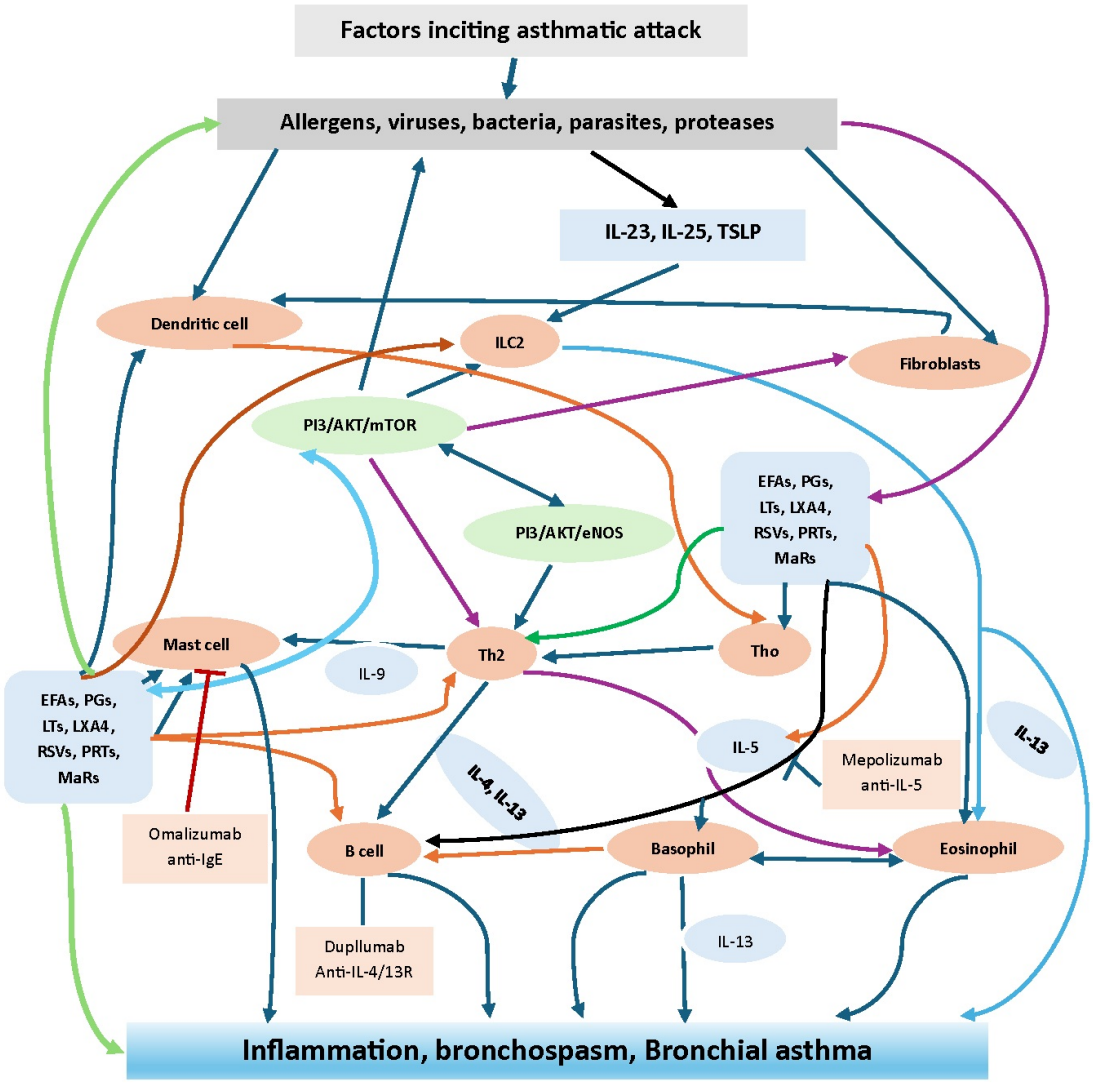

Fig. 1. The Scheme shows triggers of asthma and various cells and their soluble mediators involved in its pathobiology. Specific monoclonal antibodies that block selectively the soluble mediators involved in asthma are also shown. The potential interaction(s) between essential fatty acids (EFAs), prostaglandins (PGs), leukotrienes (LTs), lipoxin A4 (LXA4), resolvins (RSVs), protectins (PRTs), and maresins (MaRs) with various cells and the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) and PI3K/AKT/endothelial nitric oxide synthase (eNOS) pathways are also shown. It may be noted here that EFAS and their metabolites can influence all types of cells and their soluble mediators including cytokines. IL-25, interleukin-25; TSLP, thymic stromal lymphopoietin; ILC2, group 2 innate lymphoid cells; IgE, immunoglobulin E. Fig. 1 was created by Microsoft Word.

lated by glucocorticoids. MIF is released from the anterior pituitary and counteracts the inhibitory effects of glucocorticoids. MIF is released from macrophages and T lymphocytes stimulated by glucocorticoids. MIF overcomes the inhibitory action of glucocorticoids on the production of inflammatory TNF-α, IL-1β, IL-6 and IL-8. Another important action of MIF is to suppress the protective action of corticosteroids against lethal endotoxaemia. In addition, MIF antagonizes glucocorticoid inhibition of T cell proliferation by restoring the production of IL-2 and interferon-gamma (IFN-γ). Thus, despite the use of corticosteroids in asthma, T cell proliferation continues, and hence, T cells continue to produce IL-2 and IFN-γ. This may explain the failure of glucocorticoids to suppress asthmatic attacks in some since their T cells continue to produce IL-2 and IFN-γ, and hence, the inflammatory process persists. This may also explain why corticosteroids fail to suppress sepsis [5]. In this context, the role of phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) and toll-like receptor 4 (TLR4)/myeloid differentiation primary response 88 (MyD88)/nuclear factor-kappa B (NF-κB) Signaling pathway in asthma needs close attention since inhibition of this pathway was found to be of benefit in asthma

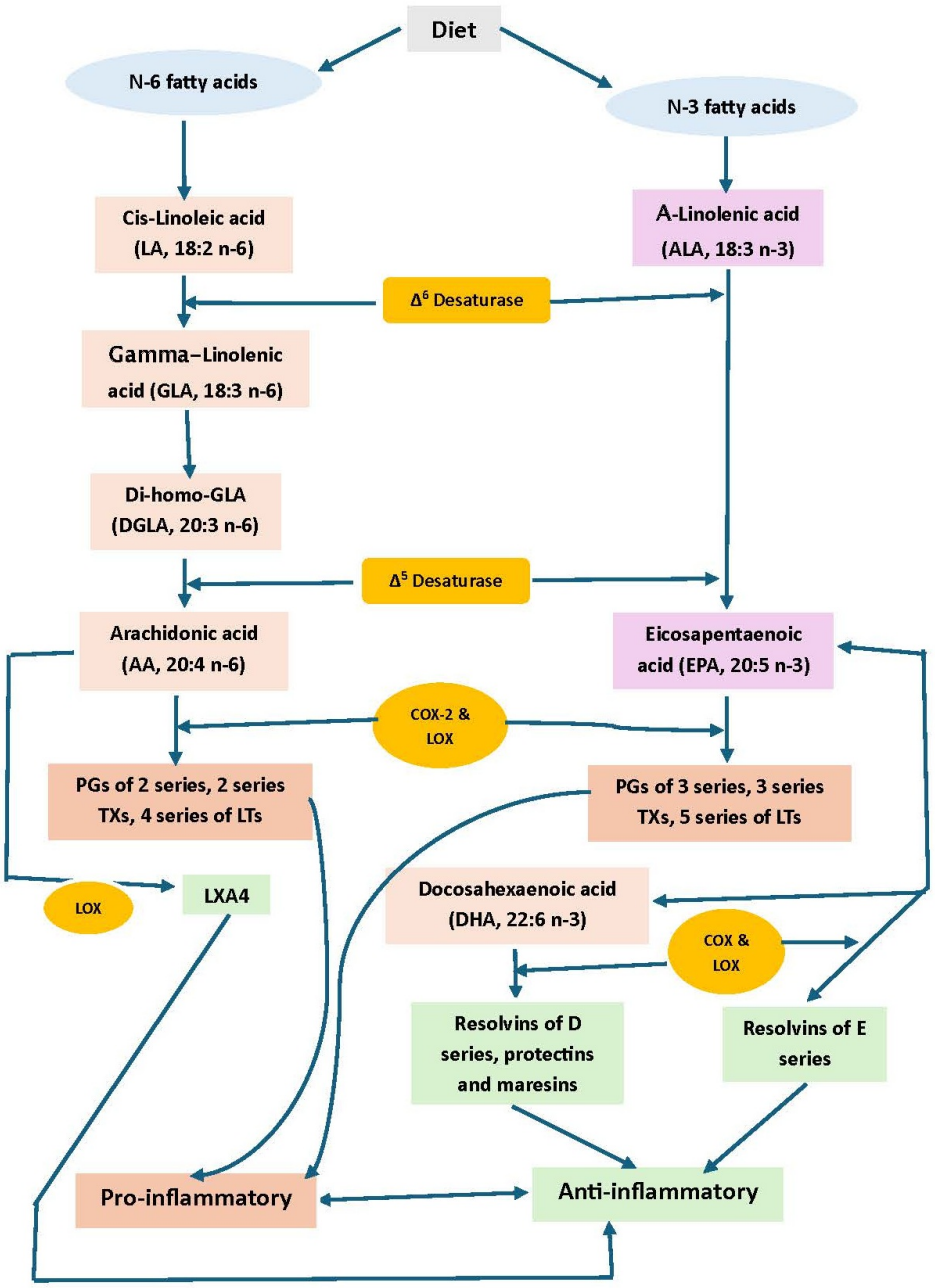

Fig. 2. Diagram of essential fatty acids metabolism and their resulting metabolites. LA and ALA are EFAs. COXs (cyclooxygenases) and LOXs (lipoxygenases) are enzymes involved in the metabolism of various long-chain metabolites of LA and ALA that convert them to their respective products. Desaturases are enzymes involved in converting EFAs: LA and ALA to their respective long-chain metabolites. Varius PGs (prostaglandins), TXs (thromboxanes) and LTs (leukotrienes) formed from AA and EPA are pro-inflammatory in nature. AA is also the precursor of lipoxin A4 (LXA4) that ia a potent anti-inflammatory molecule. Resolvins are formed from EPA and DHA are anti-inflammatory in nature. Protectins and maresins are formed from DHA and are also anti-inflammatory in nature. Thus, AA and EPA are the precursors of both pro- and anti-inflammatory molecules, whereas DHA is the precursor of only anti-inflammatory molecules: resolvins, protectins and maresins. Various PGs, TXs and LTs have bronchoconstrictor properties whereas LXA4, resolvins, protectins and maresins possess bronchodilator actions. This implies that enhanced production of PGs, TXs and LTs causes asthma whereas methods designed to induce increased generation of LXA4, resolvins, protectins and maresins will resolve asthma. All cells and tissues involved in the pathobiology of asthma can generate PGs, TXs, LTs, LXA4, resolvins, protectins and maresins. Maintaining the delicate balance between pro- and anti-inflammatory and bronchoconstrictor and bronchodilator bioactive lipids is crucial to prevent bronchial asthma. EFAs and their various metabolites have a variety of biological actions in the regulation of inflammation, immune response and PI3/AKT/mTOR/eNOS pathway. Fig. 2 was created by Microsoft Word.

[15]. It is interesting that lipoxin A4 (LXA4), resolvins, and protectins can modulate PI3K/AKT/mTOR pathway [16–20]. This may explain why LXA4, resolvins, protectins, and maresins (the potent anti-inflammatory eicosanoids) could be of significant benefit in asthma.

The PI3K/AKT/mTOR pathway has a crucial role in cellular metabolism, growth and survival. Various growth factors activate this pathway. Its dysregulation is seen in many cancers. I contrast to this, the PI3K/AKT/endothelial nitric oxide synthase (eNOS) pathway has not been studied in detail. It is known that the PI3K/AKT pathway interacts with several other pathways, including eNOS and enhances NO generation. NO is a bronchodilator and has anti-inflammatory action [21–25]. In contrast to this, iNOS (inducible nitric oxide synthase) is involved in inflammation. Further research is needed to gain insights into the interactions between PI3K/AKT/NOS and its potential interaction with PI3K/AKT/mTOR pathways.

Conclusions

Based on the preceding discussion, it is evident that more studies are called for to understand the involvement of various factors in the pathobiology of asthma, so that it will enable us to develop more appropriate therapeutic strategies that will give long-lasting benefits. It is particularly necessary to study the interactions between corticosteroids and EFAs metabolism, cytokines and EFAs pathway, and the role of PI3K/AKT/mTOR and PI3K/AKT/NOS pathways and their ability to alter not only EFAs metabolism but also their ability to modulate the formation and action of LXA4, resolvins, protectins, and maresins.

Availability of Data and Materials

Not applicable.

Author Contributions

UND contributed to the conception and design of the manuscript, drafted the work, and performed critical revisions for important intellectual content. He approved the final version to be published and agrees to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

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Conflict of Interest

The author declares no conflict of interest. Undurti N Das is the founder of UND Life Sciences and used to serve as one of the Guest editors of this journal. We declare that he had no involvement in the review of this article and has no access to information regarding its review.

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