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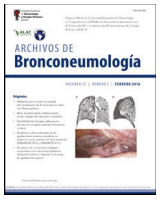

Editorial

Involvement of IGF Proteins in Severe Allergic Asthma: New Roles for Old Players

Participación de las proteínas IGF en el asma alérgica grave: nuevas funciones para viejos jugadores

Asthma is a chronic inflammatory disease characterised by reversible airflow obstruction, bronchial hyperresponsiveness (AHR), inflammation and airways remodelling (i.e., mucosal hypersecretion and goblet cell metaplasia, thickening of subepithelial basement membrane, airway smooth muscle hypertrophy/hyperplasia, angiogenesis).[1] Various clinical phenotypes have been described based on the innate inflammatory profile (e.g., eosinophilic, neutrophilic, paucigranulocytic, mixed granulocytic), remodelling and obstruction of the airways (from mild to severe), the reversibility of bronchoconstriction, the type of trigger (allergic/non-allergic), or the age of asthma onset (early or late asthma).[1] In view of this, search for the underlying pathophysiological mechanisms and the different asthma endotypes will facilitate future precision medicine for this heterogeneous disease by identifying new and more specific biomarkers and molecular targets.

Among the different molecules and pathways that can help to better understand moderate–severe allergic asthma, proteins of the IGF (Insulin-like Growth Factors) system play a relevant role. These components include the IGF1 and IGF2 ligands, the IGF receptors (IGF1R and IGF2R) and the IGF binding proteins (IGFBPs 1–6); in addition, IGFBPs interplay with other proteins (e.g., Insulin Like Growth Factor Binding Protein Acid Labile Subunit/IGFALS), specific proteases (e.g., pappalysins) and their inhibitors (e.g., stanniocalcins).[2] IGF signalling develops important roles in respiratory pathological scenarios, such as allergic asthma. Results in both murine models and patients show that IGF signalling impacts the asthmatic pathology at several levels: $T2^{high}$ inflammation (e.g., IL-4, IL-5, IL-13), eosinophilia, mucus production, AHR, subepithelial fibrosis, smooth muscle hyperplasia, bronchial remodelling.[3] The ubiquitously expressed IGF1R tyrosine kinase receptor has been recently involved in all these disease signs and proposed as an interesting target in the treatment of allergic asthma.[4,5] On the other hand, IGF2 receptor (IGF-2R/cation-independent mannose-6-phosphate receptor), an alternative receptor for IGF2 that modulates IGF1R activity by targeting IGF2 to lysosomal degradation, also interacts at the cell surface with mannose-6-phosphate-containing ligands, such as latent TGF-β and CD26/dipeptidyl peptidase 4 (DPP4).[6,7] CD26 is a serine protease involved in asthma whose membrane levels are upregulated on bronchial epithelial cells in response to IL-13.[8] In addition, shedding of CD26 generates a soluble version (sCD26) that promotes the TGF-β-induced epithelial-mesenchymal transition (EMT) in bronchial epithelial cells and contributes to airway remodelling.[9] Thus, several lines of evidence interconnect IGF signalling components, TGF-β, CD26 and asthma severity.

In an additional layer of complexity to control of IGF activity are IGFBPs, IGFALS, IGFBP-targeted pappalysin proteases and their inhibitors, stanniocalcins; most of them have been involved in asthma pathobiology.[2,10–13] IGFBP3 is a plasma protein that has been associated with the severity of asthma and bronchial remodelling as well as forms a high affinity ternary complex with IGFALS and IGFs.[2,3,10] These complexes retain IGFs in blood circulation, which inhibits their pro-inflammatory function by preventing the binding to IGF1R.[2,10] Post-translational modifications of IGFBPs (e.g., phosphorylation, proteolysis) favour the release of "free" bioactive IGF from these complexes, especially cleavage of IGFBPs mediated by members of the pappalysin (PAPP) family: IGFBP-4 by PAPP-A and IGFBP-3/5 by PAPP-A2).[2,3] Indeed, levels of PAPP-A and IGFBP-4 (but not IGF-1) are significantly higher in severe allergic asthma and reduced upon treatment with Omalizumab.[11] On the other hand, anti-inflammatory effects of IGFBP3 could be independent of IGFs and be mediated by its own receptor TMEM219/IGFBP-3R,[10] which explains why inhaled formulations of IGFBP3 peptides tested in murine models of severe neutrophilic asthma (OVALPS OVA mice) lead to reduced inflammation, AHR, and pathological changes.[12]

The importance of IGFBPs in allergic asthma has been reinforced in a recent paper, where a nontargeted strategy (iTRAQ-LC-MS/MS) was used to compare the serum proteome of healthy donors and patients with either rhinitis or allergic/non-allergic asthma with different severities.[13] Significant differences were obtained in a good number of proteins, with IGFALS standing out for its association with a particular phenotype: moderate–severe allergic asthma.[13] IGFALS is an 66–85 kDa leucine rich repeat (LRR) glycoprotein present in various biofluids, vesicles (exosomes), and cell types (hepatocytes, epithelial cells, monocytes). The IGFALS gene encodes a protein with 20 LRRs, domains also present in numerous paralogue genes (e.g., LRRC32, Toll-like receptors; https://www.genecards.org/cgi-bin/carddisp.pl?gene=IGFALS#paralogs), some of them associated with asthma.[14,15] Elevation of IGFALS in

moderate–severe allergic asthma was further validated by ELISA in a small group of patients.[13] However, a potential translation to the clinical setting will require a much more extensive validation in different asthma phenotypes/endotypes and an exhaustive search for the biological functions of IGFALS, both ongoing processes. In conclusion, several lines of evidence and recent experimental data collected by multidisciplinary research groups seem to strengthen the role of the IGF proteins and related proteins as potential therapeutic targets in severe allergic asthma.

Conflicts of Interest

The authors have no conflicts of interest.

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