INFORMATION: ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

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The continually growing family of matrix metalloproteinases (MMPs) has been the subject of intense research and has been widely demonstrated to be important in various fields of medicine (1).

However, matrix degradation is neither the sole nor the main function of these proteinases. MMPs were primarily thought to solely be involved in homeostasis and turnover of the extracellular matrix (ECM), but there has been increasing evidence suggesting that MMPs act on cytokines, chemokines and protein mediators to regulate various aspects of inflammation and immunity (2).

The Matrix metalloproteinases affects cell adhesion and growth, impacts cellular fate, and controls host tissue reactions.

Matrix metalloproteinases (MMPs) are a family of ubiquitously expressed zinc-dependent endopeptidases with broad substrate specificity and strictly regulated tissue specific expression. They are expressed in physiological situations and pathological conditions involving inflammation (3).

They can regulate transmigration of inflammatory cells from vasculature to the site of inflammation in tissue. They also regulate the recruitment and influx of inflammatory cells to the site of inflammation by processing ECM components, growth factors, cytokines and chemokines (4). Cell interactions and communication allow them to manage their functions, differentiate, develop, and perform the function of tissues. The interaction between cells occurs either chemically or electrically and occurs through the ECM (5, 6).

The **extracellular matrix (ECM)** is a meshwork of proteins and carbohydrates that supports many biological structures and processes, from tissue development and elasticity to preserve the structures of entire organs.

Cells can communicate mechanically by either one of two mechanisms: First, by responding either to mechanical deformations created by their neighbors or second, by altering the mechanical properties of the ECM of adjacent cells (6).

The interaction between cells occurs either chemically or electrically and occurs through the ECM.

There are two types of ECM – the first type is the interstitial connective tissue matrix, and the second is the basement membrane (BM). The BM is a form of ECM that has many functions. These functions include isolating the epithelium from the surrounding stroma and regulating cell organization and differentiation using connections with cell surface receptors and proteins in the ECM. The matrix in between the cells is called the interstitial matrix (7).

In the past, the ECM was thought to be a stable structure that changed according to growth and repair needs. More recently, microscopic topology of the ECM has shown that it is continuously remodeled (5).

ECM remodeling is a sequence of quantitative and qualitative alterations that can occur in the ECM during diseases such as cancer metastasis (8, 9). MMPs are manufactured as either soluble proteins or as proteinases that are anchored to the cell membrane and cleave ECM components with varied substrate selectivity (10).

Remodeling in the ECM is important in the morphogenesis of the intestine, lungs, and mammary and submandibular glands. In fibrosis and invasive cancer, along with many pathological conditions, the ECM composition becomes dysregulated, and its structure is altered and becomes stiff and more abundant (9).

MMPs are the main enzymes involved in the ECM breakdown process.

The biochemical properties of the ECM allow cells to sense and interact with their extracellular environment using various signal transduction pathways. The chemical cues are provided by ECM components, especially the adhesive proteins such as fibronectin, integrin and non-integrin receptors, as well as growth factors and associated signaling molecules. Interactions with different matrices via specific sets of receptors can trigger distinct cellular responses (11).

The ECM provides a structural scaffold via a network of protein–protein and protein–proteoglycan interactions. These interactions are involved in the formation of supramolecular assemblies such as collagen fibrils and elastic fibers, in tissue architecture, and in cell-matrix interactions that regulate cell growth and behavior (12).

ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

Increased secretion and expression of MMPs have been reported in asthma and chronic obstructive pulmonary disease (COPD), which are chronic inflammatory lung diseases that lead to chronic airflow obstruction associated with significant mortality and morbidity (13,14).

Asthma is defined as an inflammatory disease of the airways that is associated with an abnormal response mechanisms of the airway smooth muscle that leads to episodes of airway narrowing, making asthma a disease where the airways are prone to narrow excessively in response to many provoking inhaled stimuli. The chronic airway inflammation of asthma is characterized by an infiltration of CD4+ T cells, eosinophils, macrophages/monocytes, and mast cells, and sometimes neutrophils, possibly a marker of severity (15).

A specific class of T cells referred to as T-helper type (Th2) cells orchestrate and perpetuate inflammation and remodelling through the secretion of many cytokines including IL-4, IL-5, IL-9 and IL-13. Each of these play distinct roles with IL-4 regulating IgE production by B cells, while IL-13 is involved in bronchial hyperresponsiveness, subepithelial fibrosis and eosinophilic inflammation (16).

COPD is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients and its pulmonary component is characterised by airflow limitation that is not fully reversible (16), usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases (17).

Different MMPs play a specific role with variations in different lung diseases. In COPD, MMP 1, MMP 9 and MMP 12 from lung macrophages play an important role in degradation of matrix leading to emphysema. MMPs may represent relevant therapeutic targets for many diseases.

MMP-9 was the first MMP to be implicated in the pathology of asthma and about which there is most data. Increased levels of active MMP-9 have been detected in bronchoalveolar lavage fluid, and in sputum and in serum.

The chronic inflammation is characterised by an accumulation of neutrophils, macrophages, B cells, lymphoid aggregates and CD8+ T cells and the degree of inflammation increases with the severity of dis-ease (18, 16).

IL-13 effects on airway wall remodelling and induction of emphysema may be related to overproduction of MMPs. In a murine model of cigarette smoking exposure, IL-13 overexpression induces MMP-2, MMP-9, MMP-12, MMP-13 and MMP-14 expression (19,20).

MMPs may participate in the pathophysiology of asthma and COPD in many ways. Apart from the obvious degradation of extracellular matrix proteins and destruction of lung tissue (16), the potential actions include many aspects involved with the regulation of airway inflammation such as the extravasation of inflammatory cells from the blood compartment to the extracellular space, the movement of inflammatory cells through the epithelium, and the chemotaxis of inflammatory cells into the inflamed tissue by modulating the activities of chemoattractants (14, 16).

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Asthma is thought to arise from the complex interplay of genetic susceptibility and environmental influences, such as timing and dose of allergen and co-exposure to infection (20). While asthma is an inflammatory disorder of the airways usually associated with atopy, an important additional component is involvement of the epithelium and underlying mesenchyme acting as a trophic unit (EMTU) (21).

Thus, while Th2-mediated inflammation is undoubtedly important in asthma pathogenesis, alone it is insufficient for the disease to be expressed. Morphometry has revealed that thickened asthmatic airways account for a large proportion of bronchial hyperresponsiveness (BHR) and excessive airway narrowing characteristic of chronic disease (21).

In the remodelled airway, mediators, cytokines and matrix molecules provide an optimal microenvironment for sustaining the chronic inflammatory response (22).

A key role of epithelial–mesenchymal communication in asthma is further endorsed by the observation that six of the seven asthma susceptibility genes discovered by positional cloning are localised to the EMTU, stating this in the form of the following hypothesis. The asthmatic state results from a combination of gene–gene and gene–environmental interactions localised to the conducting airways that involves susceptibility to injury and altered cell–cell communication between the epithelium and underlying fibroblast (mesenchymal stem cell) sheath in the airway wall. This causes activation of the EMTU, thereby initiating and propagating tissue remodelling and sustaining chronic inflammation (23).

As shown by the European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) study a key feature of more severe asthma is BHR combined with a lack of reversibility of airflow obstruction and hyperinflation that can be explained by a combination of airway wall remodelling and mucus hypersecretion involving all conducting airways, but stopping short of the respiratory bronchioles and alveoli. Recent work indicates that airway wall remodelling may be a natural protective response against repeated bronchospasm (24).

A radical new approach is needed to properly understand the combination of factors necessary for the cause(s) of chronic asthma and its progression beyond the simple concept of sequential allergen sensitisation and exposure. Chronic airway inflammation involving T-cells, mast cells and eosinophils will only translate into BHR and variable airway flow obstruction if the underlying target tissue, which "hosts" the inflammatory response, provides the appropriate microenvironment that attracts and sustains the relevant inflammatory cells and remains susceptible to the mediators that they release (25,26).

CONCLUSIONS:

Many different therapeutic approaches to the treatment of atopic diseases may be possible, yet there have been few new drugs that have reached the clinic. Topical glucocorticoids are very effective as chronic treatment in atopic diseases and suppress the underlying inflammatory process.

Conflicts of interests

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