What do we know and what can we do about asthma?

Asthma affects more than 300 million people of all ages and both genders worldwide and causes a huge financial burden on health systems and governments. Asthmatics have sensitive airways which over react to triggers such as allergens, pollutants and chemicals, making it harder for them to breathe. Typically, asthma is characterised by recurrent attacks of breathlessness and wheezing that can be reversed spontaneously with the help of specific medications.

A major focus in asthma research has been to understand how allergies influence the development of asthma. However, not everyone who suffers from an allergy develops asthma. Since the air we breathe is common between people who suffer from asthma and non-asthmatics, this suggests that there are specific mechanisms at tissue and cellular level associated with asthma development. We should not neglect these underlying mechanisms and emphasises the need to continue research into this fundamental area, which is crucial if we are to produce effective treatment and management solutions for a wider range of asthma sufferers.

The epithelium is the thin tissue lining the outer layer of the airway surface and is the first protective barrier between inhaled particles; e.g. allergens and viruses, and the internal environment of the lung. As such, how the airway epithelium reacts to these stimuli is likely to be crucial to the development of asthma. The epithelium consists of different population of cells; some are basal cells which are also the progenitor/stem cells that are capable of dividing to produce more basal cells or differentiate to other cells that produce mucus or cilia. The balance between these cell populations is essential for normal function of epithelium, suggesting that differentiation of the epithelium is key to optimal defensive function. There are also different proteins that connect these neighbouring cells with each other or to the structure underneath the epithelium. In asthma, the epithelium fails to defend the lung against normally innocuous inhaled particles and we think this is due to abnormalities in the normal development of the epithelium. Indeed, we and others have shown that there are greater numbers of undifferentiated cells in the epithelium of asthmatics. There is also greater plasticity in these cells. These abnormalities in asthmatic epithelium prevent normal regeneration after epithelial wounding resulting in a vicious cycle of inflammatory and detrimental effects.

There are different cellular mechanisms that determine the fate of cells and whether they remain undifferentiated or differentiate to more mature cells. One of the key components of these pathways is a protein called ?-catenin. Many studies have shown that depending on which proteins it binds, ?-catenin determines the cell’s destiny. For example, coupling of ?-catenin with CBP encourages cells to remain at immature basal level, whereas the coupling of ?-catenin with p300 facilitates basal cells to form other types of cells. We have used the specific inhibitor of the ?-catenin/CBP binding ICG-001 to demonstrate a reduction in immature basal cell numbers and plasticity. This improved epithelial defence barrier and wound healing. Thus, targeting specific cellular machinery involved in differentiation provides us with key insights into epithelial development and abnormalities and how they may play a role in the pathogenesis and progression

of asthma.

Publication

Disruption of ?-catenin/CBP signaling inhibits human airway epithelial-mesenchymal transition and repair.
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