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PI3K-AKT-mTOR signaling pathway: the intersection of allergic asthma and cataract

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Allergic asthma is a chronic inflammatory disease and involves many cells and cellular components. Cataract is a condition that affects the transparency of the lens, which the opacity of the lens caused by any innate or acquired factor degrades its transparency or changes in color. During the establishment of asthma model of rats with chicken ovalbumin nebulization, it was found that asthmatic rats were more likely to have monocular or binocular cataract symptoms than normal rats. Considering that they are all induced by immune imbalance, inflammation, etc., there may be some correlation in the mechanism, and many clues showed that both diseases are associated with activation of the PI3K-AKT-mTOR signaling pathway. Therefore, we hypothesized that the PI3K-AKT-mTOR signaling pathway produces inflammatory or immune imbalance based on allergy leading to cataract.

1. Introduction

Allergic asthma is a chronic inflammatory disease, which involves many cells and cellular components (Lambrecht and Hammad 2015). Chronic inflammation of the airway and imbalance of Th1/Th2 cells makes Th2 cells dominant can lead to asthma. Cataract is a condition that affects the transparency of the lens (Brian and Taylor 2001). There is a single layer of lens epithelial cells (LECs) under the anterior capsule of the lens, which plays an important role in maintaining the transparency of the lens and the stability of the internal environment. Any factor that damages the LECs can lead to lens opacity and cataract. Both belong to the disease induced by inflammation or immune imbalance. Studies have found that the pathogenesis of both conditions involves activation of the PI3K-AKT signaling pathway, Rho/Rock signaling pathway (Aihara et al. 2004; Giles et al. 2003), Noeth signaling pathway (Hori et al. 2013; Saravanamuthu et al. 2009), Wnt/β-catenin signaling pathway (Sharma et al. 2009; West-Mays et al. 2010), JAK/ STAT signaling pathway (Yang and Yang 2010; Jakkula et al. 2010), MAPK signaling pathway (Xiao et al. 2011; Gerits et al. 2009), TGF-β1/Smad signaling pathway (Royce et al. 2012; Xiong et al. 2012), and NF-κB signaling pathway (Park et al. 2010). Therefore, these two diseases may have certain correlation in pathogenesis. However, there is no specific experimental study about that.

By consulting the literature, it was found that the PI3K-AKT-mTOR signaling pathway is the most likely pathway to link these two diseases, so it is hypothesized that asthma and cataract are linked by the PI3K-AKT-mTOR signaling pathway.

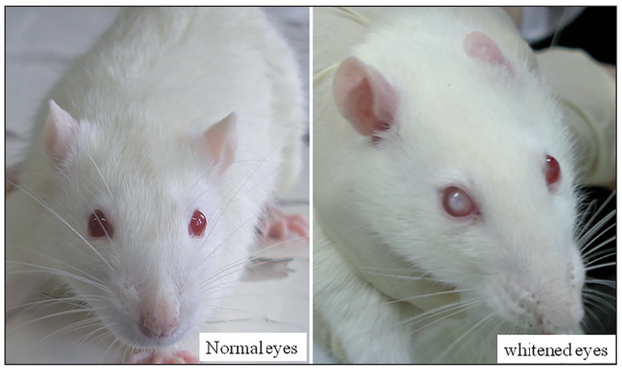

Fig. 1: The change of rat eyes color. The left picture shows rat with normal eyes in the control group, and the right picture shows rat with eyes whitening in the model group.

2. Investigations and results

Physiological status of the rats: (1) Control group: the rats had a slight shortness of breath during each atomized inhalation, and relief occurred about 5 min after inhalation. After continuous stimulation for the same number of days, symptoms did not aggravate, and the weight of rats, hair color, mental condition

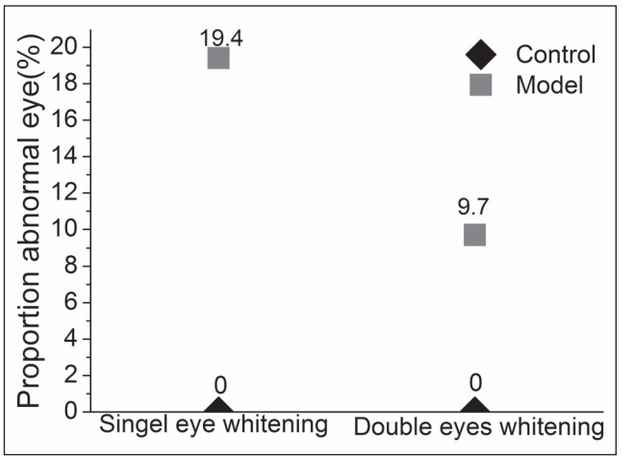

Fig. 2: Data of single eye or double eyes whitening in asthma rats. In the control group, the proportion of single eye whitening and double eyes whitening is 0%, 0%, respectively. In the model group, the proportion of single eye whitening and double eyes whitening is 19.4% and 9.7%, respectively. The whitening rate of single eye or double eyes was significantly different in the control group and the model group.

and eye color were not significantly abnormal. (2) Model group: The weight of the model rats slowly increased after inhalation of ovalbumin (OVA), and the weight of some rats began to decrease. In the process of inhaling atomized OVA, the rats exhibited typical asthma symptoms. These symptoms were relieved about 10 min after the inhalation, and the symptoms were aggravated after several days of continuous stimulation.

Some rats had a single eye or both eyes that turned white. The change of rat eyes color is shown in Fig. 1. This experiment was repeated three times. The number of rats of single eye whitening and double eyes whitening in the control group was 0 and 0, respectively, and the average number of rats of single eye whitening and double eyes whitening in the model group was 12 and 6, respectively. The experimental data of eye changes in Fig. 2.

3. Discussion

In the established asthma model, we found a large proportion of rats with cataract symptoms in one or even both eyes, indicating that allergy may contribute to cataract development. Therefore, we hypothesized that asthma and cataract are linked through the the PI3K-AKT-mTOR signaling pathway, which produces inflammation or immune imbalance based on allergy leading to cataract (Fig. 3).

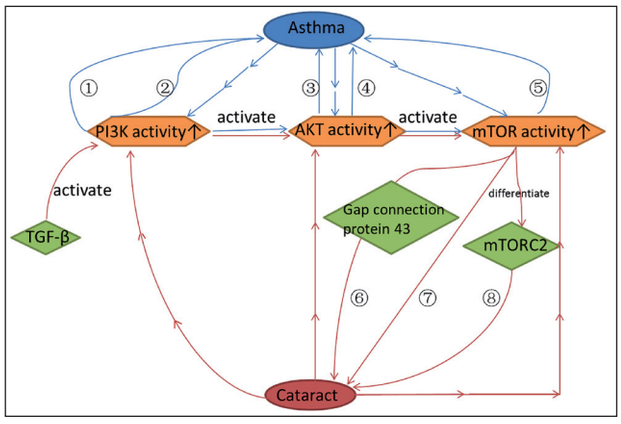

Fig. 3: Hypothetical mechanism of the link between asthma and cataract. ①Participate in airway remodeling by promoting the proliferation of ASMC and AEC. ②Regulation of proliferation, activation and apoptosis of Th2 cells and eosinophilic granulocytes, etc. ③Participate in airway remodeling and airway inflammation. ④Regulates Th cells differentiation and cytokine production. ⑤Participate in airway remodeling and airway inflammation. ⑥The EMT of LECs is induced by gap connection protein 43. ⑦Promoting the proliferation and migration of LECs. ⑧The EMT of LECs is induced by mTORC2.

The PI3K-AKT signaling pathway is widely present in many cells and is composed of PI3K and AKT and its downstream related proteins (mTOR, etc.) (Franke 2008). AKT is a threonine/serine protein kinase whose activity is expressed by phosphorylation (Hemmings and Restuccia 2012; Xue and Hemmings 2013). Phosphorylation-activated AKT regulates various biological processes like cell proliferation, apoptosis, differentiation, and migration by activating or inhibiting related downstream proteins (Laplante and Sabatini 2009; Jewell et al. 2013; Mahesh et al. 2013). The current study suggested that mTOR has two complexes in mammalian cells, namely mTORC1 and mTORC2 (Chen et al. 2016).

3.1. Relationship between PI3K-AKT-mTOR signaling pathway and asthma

There have been many studies on the relationship between PI3K/AKT signaling pathway and asthma, confirming that the PI3K/AKT signaling pathway is involved in the pathogenesis of asthma, which plays an important role in airway inflammation, airway hyper-reactivity and the proliferation of airway smooth muscle cells (ASMC) and airway epithelial cells (AEC) (Duan et al. 2005; Burgess et al. 2008).

The mechanism how PI3K regulates asthma is mainly manifested in two aspects: (1): The activation of PI3K can promote the proliferation of ASMC and AEC, thicken airway smooth muscle, narrow airway lumen, and thus participating in the process of airway remodeling. (2): PI3K can regulate the proliferation, activation, apoptosis and other processes of Th2 cells and eosinophils, thus affecting the development and progression of asthmatic inflammatory reaction; AKT can be activated by PI3K stimulation, and thus participating in the regulation of many pathways such as airway inflammation, airway hyper reactivity, and airway remodeling. Studies have found that AKT activity is associated with neutrophil apoptosis and can inhibit inflammatory reaction by modulating AKT activity (Day et al. 2006). Moreover, AKT can also affect the differentiation of Th cells and the production of cytokines, thereby directly or indirectly breaking the balance of Th1/Th2 and thus participating in the pathogenesis of asthma.

The PI3K/AKT signaling pathway stimulates the proliferation of ASMC and regulates the growth cycle of ASMC. In animal experiments, it was found that the activity of PI3K and AKT in the asthma model of rats was significantly enhanced, and after the application of PI3K inhibitors, some pathological manifestations of asthma (such as the expression level of activating chemokines in eosinophilic, the expression level of IL-5 and IL-13 in alveolar lavage fluid, the increase of eosinophilic in lung tissue, increased mucous secretion of airway, airway hyper reactivity, etc.) were significantly inhibited (Ammit and Panettieri 2001; Lee 2006).

Studies have also found that there is a high expression of mTOR in asthma, which may be involved in the process of asthmatic airway inflammation and airway remodeling. 4EBP1 is a direct target downstream of mTOR, through the integration of internal and external environment signal activated mTOR can be further phosphorylation. 4EBP1 makes mTOR activation to play its series of pathophysiological effects. Immunohistochemistry and immunoblotting were used to find that p-mTOR and p-4EBP1 in lung tissue of asthma group were significantly higher than those in control group, indicating the activation of mTOR/4EBP1 in asthma, and it was found that the expression of p-mTOR and p-4EBP1 after the intervention of antagonist was significantly lower than that in asthma group. All this indicates that the PI3K/AKT/mTOR signaling pathway plays an important role in asthma.

3.2. Relationship between PI3K-AKT-mTOR signaling pathway and cataract

TGF-β2 is a cytokine known to be most closely related to the production of epithelial-mesenchymal transition (EMT) in lens epithelial cells (LECs). It can induce the expression of EMT-related genes such as α-smooth muscle actin and gap junction protein, and induce EMT in LECs (Wang et al. 2013; Yao et al. 2012). In the EMT process of LECs, TGF-β2 activates AKT through the PI3K signaling pathway, which then activates mTORC1 and mTORC2. Activation of mTORC1 helps to increase cell size, and promotes cell migration and invasion. Activation of mTORC2 is required for phenotypic transformation of epithelial cells into mesenchymal cells. Moreover, the PI3K/AKT signaling pathway is involved in TGF-β2-induced EMT in human LECs via gap junction protein 43 (Gao et al. 2016; Guo et al. 2015; Yao et al. 2008).

The PI3K/AKT/mTOR signaling pathway plays an important role in the proliferation, migration and apoptosis of LECs (Kumar et al. 2008; Liegl et al. 2014). The junction of platelet-derived growth factor and β-receptor in the aqueous humor activates PI3K kinase, and activates the PI3K-AKT signaling pathway to enhance the migration capability of LECs. Furthermore, it was observed in LECs that epidermal growth factor binding to its receptor phosphorylates AKT and initiates PI3K/AKT/mTOR signaling pathway to promote the migration of LECs (Xiong et al. 2010; Jiang et al. 2006).

PI3K inhibitors can effectively inhibit the TGF-β2-activated PI3K signaling pathway, inhibit the proliferation and migration of LECs, promote their apoptosis, and also inhibit the EMT process of LECs. AKT kinase inhibitor AR-12 inhibits LECs synthesis AKT in rats, blocks the AKT signaling pathway, and promotes the apoptosis of

LECs. The mTOR inhibitor rapamycin inhibits the proliferation of LECs in rabbit and promotes apoptosis of LECs in human. mTOR inhibitors can attenuate the differentiation of LECs and inhibit their migration. This indicates that the PI3K/AKT/mTOR signaling pathway plays an important role in cataract development (Liu et al. 2010; Meng et al. 2013).

3.3. Conclusion

Many studies have confirmed that PI3K-AKT-mTOR signaling pathway is active during the onset of asthma and cataract. Activation of PI3K can activate AKT, which further activates mTOR. PI3K triggers asthma by promoting the proliferation of ASMC and AEC to participate in airway remodeling, as well as regulating the proliferation, activation and apoptosis of cells such as Th2 and eosinophilic cells. Akt triggers asthma by participating in airway inflammation and airway remodeling, as well as regulating the differentiation of Th2 cells and the production of cytokines. mTOR triggers asthma by participating in airway remodeling and airway inflammation. On the other hand, TGF-β2 is an important cytokine that causes asthma and cataract. It activates the PI3K-AKT-mTOR signaling pathway to promote the occurrence of EMT in LECs (acting on gap junction 43 and mTORC2), and promotes the proliferation and migration of LECs to cause cataract. From the complex cross-pathogenesis mechanism, in the case of asthma caused by allergy, the body may increase the incidence of cataract through the PI3K-AKT-mTOR signaling pathway. Therefore, our study argued that asthma may be associated with cataract through the PI3K-AKT-mTOR signaling pathway, causing inflammation or immune imbalance based on allergy that can lead to cataract. But so far, there is not a lot of reliable experimental and epidemiological data to verify the relationship between the two diseases and the above content. And it is hoped that more research will be done in the future to focus on the common pathogenesis of asthma and cataract in order to find a cure for suffering from these two diseases at the same time.

4. Experimental

Healthy female Wistar rats (about 150±15 g) were randomly divided into control group and model group, with 10 control groups and 70 model groups. The experimental protocols of this study were reviewed and approved by Animal Ethical and Welfare Committee of Hebei University. These rats were free to eat special food and water of removing ovalbumin. The normal rats were placed in a self-made sealed glass box, and the rats were stimulated with a medical ultrasonic atomizer YC-Y800 (Beijing Yadu Company) to ultrasonically atomize 0.5% phosphoric acid histamine salt physiological saline solution to observe the changes in respiratory function of rats. Rats with asthma symptoms such as shortness of breath, forelimb contraction, nodding or abdominal breathing within 20 s after inhalation of histamine were selected as experimental rats. Model group in 1 d, 14 d with fresh preparation of OVA (OVA, Grade V, sigma Company) 1 mg + 10% aluminum hydroxide gel of saline suspension total 1 mL in the medial limbs of rats subcutaneous injection, 0.2 mL per point, peritoneal injection of 0.2 mL, while intraperitoneal injection of inactivated pertussis Bacillus $5x10^9$; normal control group received saline instead. At day 21d atomized inhalation by 1.0% OVA was applied, which stimulated asthma in rats, and each animal was atomized 25~30 min over 7 d, and the normal control group was stimulated by saline instead of OVA.

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Conflict of interest statement: None declared

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