World Journal of Otorhinolaryngology-Head and Neck Surgery (2018) 4, 169—174

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Review Article

P-glycoprotein and chronic rhinosinusitis

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Received 9 July 2018; accepted 18 July 2018
Available online 24 August 2018

KEYWORDS
Sinusitis;
ATP binding cassette transporter, sub-family B;
Verapamil;
Exosomes;
Nasal polyps;
Nasal mucosa

Abstract Chronic rhinosinusitis (CRS) is a heterogeneous definition that includes different disease states that usually are associated with abnormal inflammatory responses. Besides being prevalent, the mechanisms involved in its pathogenesis are not clear and there are few therapeutic options with tolerable side effects. P-glycoprotein (P-gp) is an efflux pump responsible of extruding xenobiotics and cellular metabolites from multiple cell types. It has been widely studied in the cancer field, due to its ability to confer resistance to chemotherapy. It also promotes Type 2 helper T-cell polarizing cytokine secretion in CRS and may represent a potential target to differentiate subtypes of CRS and personalize treatment. This state-of-the-art review explores current knowledge on the participation of P-gp in the pathogenesis of CRS, the P-gp inhibition as a novel targeted therapeutic strategy and the exosomal P-gp test, a non-invasive biomarker that can represent an important advance in the field of rhinology.
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Introduction

Chronic rhinosinusitis (CRS) is a common disease that impacts 12%—16% of the total population in the United States and $6.9 to $9.9 billion is spent annually on its treatment.[1—3] CRS is comprised of many forms of disease, and the pathways involved in the initiation and maintenance of its characteristic inflammation are not well understood.[4] While corticosteroids remain the gold standard treatment and are widely prescribed, they are non-targeted and associated with significant side effects.[5—8] Therefore, the discovery of a new pathogenic mechanism for CRS could herald both the development of a novel diagnostic non-invasive biomarker and a targeted therapeutic for CRS treatment.

Permeability glycoprotein (P-gp) is an active efflux membrane transporter that is found in different types of

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Peer review under responsibility of Chinese Medical Association.

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https://doi.org/10.1016/j.wjorl.2018.07.002
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cells throughout the body and has the ability to extrude a broad range of substrates including drugs, toxins, metabolites and cytokines.[9,10] P-gp is also present in the sinonasal mucosa and its immunomodulatory activity on Th-2 skewed inflammation suggests that it may be a potential therapeutic target for high P-gp expressing CRS endotypes.[11–13] This study aims to review the association between P-gp and CRS, and how it can influence the management of the disease in the future.

P-glycoprotein

P-gp is a 170 kDa membrane protein and is also known as ATP-binding cassette sub-family B member 1 (ABCB1) and multidrug resistance protein 1 (MDR1). P-gp expression was first described in the mid-1970s and proportionally correlated with drug resistance in Chinese hamsters.[14,15] P-gp is an active efflux membrane transporter that utilizes ATP hydrolysis to transport substrates across the plasma membrane and works as biological protection for the cell by extruding drugs, toxins, and metabolites as well as secreting signaling cytokines.[9,16] The distribution of P-gp in many different types of cells and its very broad substrate specificity is consistent with its role of maintaining tissue barriers and extruding xenobiotics.[9,16]

Several physiological functions throughout the body are dependent on P-gp activity. It protects the central nervous system by maintaining the blood–brain barrier (BBB) because several ABC transport proteins are expressed on the luminal, blood-facing, plasma membrane of brain capillary endothelial cells.[17] It is also responsible for the efflux of metabolites from the membrane of bile canaliculi in the liver and from the ductal cells in the kidney.[18,19] The gastrointestinal and respiratory tract, are exposed to external threats and stimuli, and therefore P-gp provides a barrier to prevent the diffusion of xenobiotics through the epithelial cells.[20] The expression of P-gp is found on the epithelial cells of both the upper and lower respiratory tract.[21,22] In addition, there are other anatomical sites where the P-gp is expressed including: the placenta, the testis, the ductal cells of the breast, the pancreas, and the adrenal cortex.[19,23]

There is growing evidence suggesting an important relationship between P-gp expression and inflammation. P-gp mediated transport has been observed in the regulation of cytokine secretion in several different types of cells implicating a potential immunomodulatory role.[24,25] It is involved in the maturation of hematopoietic stem cells, dendritic cells, and in T-cell activation.[26–29] However, conflicting results have also been reported as to which cytokines can be associated with the selective modulation profile of P-gp in different cytokines and cell types.[30–32] The link between P-gp activity in inflammation and its expression in sinonasal epithelial cells led to the hypothesis that P-gp may participate in the pathogenesis of CRS and CRS with nasal polyps (CRSwNP).

P-gp in chronic rhinosinusitis

Despite extensive studies on CRS, the inflammatory pathways involved in the disease pathogenesis are not well understood.[33,34] CRSwNP and some component of CRS without nasal polyps (CRSsNP) are predominantly characterized by the presence of eosinophilic inflammation and type 2 T-helper cell (Th2) skewing cytokines.[35] Recent evidence has focused on sinonasal epithelial cells as a primary driver of the local dysregulated immune response but the mechanisms responsible for regulating cytokine secretion are not clear.[36–43] P-gp may influence these non-classical pathways, providing greater selectivity over microenvironmental cytokine release.[44–46]

Within the nasal cavity, P-gp is localized in the epithelium of different structures such as the septum, inferior turbinate and sinonasal mucosa.[11,12,47] Patients with CRSwNP and CRSsNP present with an upregulation of P-gp in the sinus mucosa compared to healthy subjects and to non-diseased intranasal subsites, indicating that P-gp may play a role in the initiationor maintenance of chronic sinonasal inflammation.[47] Furthermore, CRSsNP patients with high P-gp expression have been shown to have greater tissue eosinophilia and worse computed tomography (CT) inflammatory scores than their low P-gp expressing CRSsNP counterparts.[48] These findings suggest that P-gp is over expressed in CRSwNP and eosinophilic CRSsNP, both of which are associated with Th2 polarized inflammation. Similarly, high levels of P-gp are linked with increased osteitis burden.[49]

From an immunomodulatory perspective, P-gp levels are associated with selective Th2-associated cytokine secretion in sinonasal cells. In healthy primary nasal epithelial cell cultures, lipopolysaccharide stimulation promoted both cytokine secretion and P-gp activity. After P-gp inhibition, the secretion of IL-6, granulocyte macrophage colony-stimulating factor (GM-CSF) and thymic stromal lymphopoietin (TSLP) decreased, while IL-8 secretion was not affected.[13] Similarly, mucosal explants of patients with CRSwNP and CRSsNP were stimulated with Staphylococcus aureus enterotoxin B and promoted IL-5 and TSLP but not IL-8 secretion relative to control in the CRSwNP explants only. Subsequent P-gp inhibition significantly reduced the secretion of these important Th2 polarizing cytokines to control levels. IL-5 and TSLP variance strongly correlated with P-gp concentration within the same explant.[50] A previous *in vitro* study in polyp derived epithelial cell cultures provided similar results.[51] Taken together, these findings demonstrate that P-gp participates in modulating secretion at the nasal mucosa surface and plays a critical role in the pathogenesis of Th2 polarized forms of CRS including CRSwNP.

P-gp inhibition therapy

The indication that P-gp participates in multiple biological processes led to the hypothesis that its inhibition could interfere in the pathophysiology of several diseases. There are currently three generations of P-gp inhibitors with increasing potency and selectivity.[52] Cancer research was the first and most studied field for a therapeutic indication of P-gp inhibition. Resistance to chemotherapy is associated with cancers that have high P-gp activity and these cancers also overexpress this membrane protein.[53–57] Despite extensive research, no P-gp modulator was

capable of reducing chemotherapy resistance with acceptable side effects.[58–60] Poor responses were also found in the treatment of autoimmune and inflammatory bowel disease.[61–64]

The discovery of the contribution of P-gp to the pathogenic mechanism of CRS led the possibility of P-gp inhibition as a novel druggable target. Verapamil Hydrochloride (HCl) was one of the first inhibitors of P-gp to be identified in 1982 and also functions as a calcium channel blocker (CCB).[65,66] Verapamil is capable of modulating inflammatory responses in human astrocytes and T-cells, and animal models of asthma and hepatocyte inflammation.[24,25,66,67] In a sinonasal polyp explant model, Verapamil demonstrated similar effects to dexamethasone in its ability to abrogate IL-5, IL-6, and TSLP.[42] While Verapamil is cardioactive and is commonly used to treat hypertension, angina and cardiac arrhythmias, it is considered the first-line prophylactic drug for cluster headache and is usually well tolerated by otherwise healthy patients.[68]

Therefore, a randomized, double-blind, placebo-controlled trial to test the efficacy of low dose oral Verapamil HCl for the treatment of CRSwNP was conducted.[69] This study reported a significant effect size, comparable to previously reported values using both biologic agents and corticosteroids, with no significant side effects.[70–72] However, patients with elevated BMI and high total mucus P-gp levels experienced less benefit. This suggests that a low dose of a relatively low potency inhibitor was used and that patients with greater P-gp expression may need higher concentrations to achieve adequate pump suppression. Future studies with higher doses of Verapamil or others P-gp inhibitors may demonstrate even higher efficacy.

Another way that P-gp inhibition may contribute to CRS treatment is by potentiating the effect of corticosteroids in sinonasal epithelial cells. Similar to chemotherapy resistance, P-gp expression induces steroid resistance by limiting intracellular retention.[73–75] *In vitro* studies confirmed that P-gp inhibition enhances steroid activity, including in nasal polyp explants.[76,77] Corticosteroids remain the best studied and most effective CRS treatment and P-gp is capable of transporting some of the most common steroids utilized for systemic and topical use, including dexamethasone, prednisone and budesonide.[5–8,76] This suggests that P-gp inhibition could potentiate steroid activity in the treatment of CRS thereby improving local efficacy with lower doses and less systemic exposure.

Other drugs traditionally used in the treatment of CRS are also capable of inhibiting P-gp.[78–80] Clarithromycin, a macrolide antibiotic, and itraconazole, a triazole antifungal, presented similar P-gp inhibitory dose response curves when compared to Zosuquidar, a high affinity third generation P-gp inhibitor.[81] Therefore, the anti-inflammatory effects of these agents in CRS may be derived, in part, from their unrecognized influence on P-gp.

Exosomal P-gp as a noninvasive biomarker

In order to personalize treatment for CRS, biomarkers of disease and endotype will need to be developed. Recently, a proof-of-concept study was published, where partition based cluster analysis of tissue derived cytokines and inflammatory proteins yielded discreet clusters which correlated well with phenotypic characteristics.[82] However, there were several limitations to this tissue-based biomarker technique including the requirement of invasive tissue sampling and the possibility of inter-patient heterogeneity in tissue composition. Also, pre-surgical/pre-collection medical treatments were not included in the analysis. A non-invasive novel biomarker method is needed to overcome these limitations. Ideally, the sampling would be done in an outpatient setting prior to the initiation of medical therapy. This non-invasive collection method must be a direct reflection of and participate in the underlying pathophysiology, and the biomarkers would be intrinsically resistant to degradation.

Exosomes are 30–150 nm vesicles surrounded by a lipid bilayer that are released from most biological fluids including nasal mucus secreted by sinonasal epithelial cells.[83–87] Exosomes are ideal candidate for biomarkers of CRS because of their reflection of the underlying cell and pathophysiology, their presence in nasal mucus, and their protective lipid bilayer. Our group recently reported on the presence of a secreted form of P-gp which could be detected in whole nasal mucus and exosomes isolated from nasal mucus. While the presence of P-gp in mucus is physiologic, we showed that total P-gp concentrations above 250 pcg/μg of total protein are associated with CRSwNP as well as more severe subjective and objective clinical findings of disease, including sino-nasal outcomes test (SNOT-22) and Lund–Mackay score.[88] We subsequently discovered that this secretion was mediated by the release of exosomes which are differentially enriched with P-gp, as measured by P-gp per exosome, among patients with CRSwNP. In light of the importance of P-gp overexpression to the pathogenesis of CRSwNP, the development of a non-invasive test of expression which intrinsically resists degradation and can be correlated with disease severity would be extremely valuable.

Conclusion

Th2 skewed forms of CRS are prevalent and lack an effective treatment with few side effects. Studies on P-glycoprotein have elucidated its role in promoting Th2 inflammation thereby positioning it both as a non-invasive diagnostic as well as a novel therapeutic target using currently available 1st–3rd generation P-gp inhibitors including Verapamil HCl.

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Edited by Yi Fang