Nasal polyposis and epithelial wound healing: a pathophysiological hypothesis

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Key points

Nasal polyposis (NP), asthma, and chronic bronchitis are chronic inflammatory diseases of the upper airways. They may be caused by an injury of the respiratory epithelium occurring in a chronic inflammatory context. Several studies show that in NP, nasal epithelial cells are involved in the overexpression of cytokines and growth factors. Among these, the transforming growth factor β1 (TGF-β1) appears to play a major role in the genesis of NP. Models of differentiated respiratory epithelium, obtained from in vivo or in vitro models, are used in an attempt to analyze wound healing in inflammatory contexts, to elucidate the pathophysiology of NP, and to improve understanding and management of upper airway inflammatory diseases.

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Nasal polyposis (NP) is one of the inflammatory diseases that affect the upper airways, similarly to asthma and chronic obstructive pulmonary disease (COPD) [1]. Conducting airways are covered by a pseudostratified prismatic and ciliated respiratory epithelium of which one of the roles is to constitute a barrier against the aggressions of outside environment. Such aggression of the epithelium occurring in a chronic inflammatory context appears to be a major factor in the pathophysiology of these diseases [2, 3].

Clinical aspects

NP affects the nasal respiratory mucosa in the upper airways. NP concerns 4% of the population in western countries [4]. It is generally a primitive affection, sometimes associated with asthma and aspirin intolerance (Widal’s disease). Secondary forms are infrequent and related to cystic fibrosis or a ciliary congenital affection. NP is characterized by a bilateral and bifocal development of polyps which are oedematous fibro-epithelial tumours. Polyps spread into nasal fossae and sinuses. They are characterized by an eosinophil inflammatory cell infiltrate [5] and by disorders of the epithelial differentiation: squamous metaplasia, goblet-cell and basal hyperplasia [6]. Symptoms are a combination of nasal obstruction, anosmia, cephalalgia and rhinorrhoea that cause some disability due to a significant impact on patient’s daily living. Nasal obstruction is usually permanent. Associate anosmia is very frequent. Headaches are inconstant and sometimes replaced by a sensation of facial pressure. Rhinorrhoea generally consists of serous nasal secretions but it may also be purulent. Despite significant progress, the therapeutic management of NP remains difficult. The aim of the treatment is to control the inflammatory process and to stop polyps growth by long-term corticoid therapy [4]. In case of disabling and drug-resistant symptoms, surgery is considered: simple polypectomy or, preferentially, ethmoidectomy. Beneficial outcomes are reported but continuation of medical treatment is necessary [4] (figure 1).

The conducting airways epithelium

In the conducting upper airways, the epithelium is a pseudostratified prismatic and ciliated respiratory epithelium, separated from the underlying chorion by a basal membrane. It consists of three principal cell types: the basal cells, the mucous cells, and the ciliated cells. Basal cells are small round cells fastened to the basal membrane that permit other cells fixing [7]. They may proliferate and, in this case, they undergo a transformation, becoming either mucous cells or ciliated cells [8]. Mucous cells are exclusively involved in secretion. The mucus capture the inhaled particles (pollutants, micro-organisms) and exert an anti-bacterial action [9]. Aggressions and inflammation increase mucus secretion [9]. Ciliated cells are highly differentiated cells that hold, at their apical part, specific cytoplasmatic extensions: the cilia. Together with the mucous cells, they participate in mucociliary clearing by ciliary beats [8]. These characteristic features make the epithelium the first line of defence of the respiratory system.

In NP, the distribution of the different cell types may be modified. The number of ciliated cells is usually diminished, favouring goblet-cell hyperplasia [10]. Zones of squamous metaplasia or basal hyperplasia may also be encountered [6].

Involvement of the epithelium in the pathophysiology of nasal polyposis

The epithelium appears to be a major actor in NP pathophysiology. The role of the epithelial cells has been evidenced ex vivo in polyp mucosa. In comparison with non-polyp nasal mucosa, an increased proliferation index of the epithelial cells [11], and an overexpression of cytokines and growth factors [12] have been observed. Strongly expressed cytokines are the interleukin 5–IL-5) [13] and the granulocyte-macrophage Colony-Stimulation Factor (GM-CSF) [14] that both are likely to promote eosiinophil infiltration. Overexpressed growth factors are the Platelet Derived Growth Factor (PDGF), the Transforming Growth Factor (TGF-ß1) [15], and the Vascular Endothelial Growth Factor (VEGF) [16] which are involved in tissue remodelling. Last, by expressing the intercellular Adhesion Molecule-1 (ICAM-1) and molecules of the major histo-compatibility complex Human Leucocyte Antigen-DR (HLA-DR) [17], epithelial cells promote inflammatory cells adhesion.

In vitro, polyp epithelial cells maintain an expression of cytokines (GM-CSF and IL-8) higher than that of normal mucous cells [13, 14]. In vivo, polyp formation has been analysed in two experimental models: the rat otitis media [18, 19], and the rabbit maxillary sinus [20]. The authors carried out a mechanical epithelial inva...
sive procedure and then created an inflammatory reaction by bacterial inoculation. In both models, polyps with a structure close to that encountered in human pathology was obtained, with oedema and massive infiltration of inflammatory cells. Thus, the initial mechanism of polyp formation is likely to be a loss of epithelial continuity related to an aggression (mechanical, chemical, infectious, topical, etc.), followed by a dysregulation of the repair process [20]. In this mechanism, the epithelial rupture promotes the formation of a conjunctive tissue hernia (fibroblasts and inflammatory cells) through the epithelial gap. Secondarily, proliferation and migration of the epithelial cells from the lesion’s edges results in an “epithelialisation” of this conjunctive hernia.

The development of nasal polyps appears to consist therefore in a dysregulated process of tissue repair involving not only the epithelial cells but also the inflammatory cells (figure 2).

**Initiation and uncontrolled evolution of a chronic inflammatory process**

The anatomical specificities of nasal and sinus cavities (narrowness of drainage and ventilation orifices) may be a promoting factor to polyp genesis by the creation of a confinement syndrome that maintains permanent the superinfection and the inflammatory reaction [21].

In the polyps, the increase of inflammation markers such as albumin, histamine and immunoglobulin E [22], together with the presence of an important inflammatory cellular infiltrate [5] indicate the existence of a strong local inflammatory reaction. The inflammatory cellular infiltration consists of mastocytes, activated lymphocytes T, and, over all, polynuclear eosinophils [5, 22, 23]. Polynuclear eosinophils are, with the epithelial cells, the main source of cytokine secretion [23]. They express, in particular, the IL-4, IL-5 [12, 24], GM-CSF [5, 23, 24] and the TGF-β1 [15, 22]. IL-4, IL-5, and the GM-CSF have a pro-inflammatory action since they draw, activate and prolong eosinophil survival [13, 25]. Conversely, the TGF-β1 has an anti-inflammatory action since it decreases immunoglobulin E synthesis and eosinophil activation [3]. The TGF-β1 appears to have a preponderant place in NP due to its abundance as compared to other cytokines, and its absence in the control non-polyp mucosa [15]. Its localisation into the polyps corresponds to the zones of extracellular matrix accumulation and stromal-cell infiltration (myofibroblasts) [22]. Because it stimulates the accumulation of extracellular matrix, the TGF-β1 has a pro-fibrosing action [3]. Thus, both formation and growth of polyps appear to be closely related to the occurrence of an epithelial aggression in a local chronic inflammatory context of the upper airways [4].

Figure 1
Decision tree for the management of nasal polyposis

Aggressed epithelial cells may be participating to the maintenance of a vicious circle that in turn maintains chronic inflammation [26]. In these processes, cytokines, especially the TGF-β1, are key factors since they have an important role in both chronic inflammation and epithelial repair [27].

**Experimental models**

**Models of in vitro cellular culture**

Some methods are available for the sampling of epithelial cells in conducting upper airways. They permit obtaining either animal bronchial cells or human nasal respiratory cells from operative tissues of patients with NP having undergone ethmoidectomy. Culture of these cells makes available in a few days an adequately differentiated epithelium close to that observed in vivo. These purely epithelial models display the mechanisms of repair and differentiation following a chemical [28], or a mechanical [29] aggression. These models show that in the closure of an epithelial disruption, cells of the wound edges acquire a migratory phenotype, which permits the coverage of the wounded zone [30, 31]. These models permit also analyzing cytokines effect on the repair process. In particular, the TGF-β1 added to the culture environment shortly after the aggression increases the migration speed of the cells [29]. Last, TGF-β1 inhibits the expression of the CFTR (Cystic Fibrosis Transmembrane Conductance Regulator), an ion channel of which the morbid mutation is involved in cystic fibrosis pathophysiology, and modifies ion transportation into nasal epithelial cells [32]. Other models are based on co-culture of epithelial cells and fibroblasts or epithelial cells and inflammatory cells with the objective of analysing the interactions between these cell populations. For instance, in vitro, polyp epithelial cells activate and increase eosinophil survival by the expression of GM-CSF and IL-8 [13, 14, 25].

**In vivo models**

Various experimental animal models of aggression-repair of the upper airways are available, for more than 10 years [18-20]. More recent models, more complex, are under development, based on the heterografting of human cells into immunotolerant animals. A few weeks after these manipulations, a mature pseudostratified epithelium with a beginning of sub-mucous glands is obtained [33].

**Conclusion and perspectives**

Current research on cellular and molecular aspects of NP aims at elucidating the mechanisms that cause chronic inflammation. It aims also understanding the involvement of abnormal epithelial differentiation in the dysregulation of the repair and tissue remodelling process. Advances in this domain may contribute in an improved comprehension of other conducting airways diseases (asthma and COPD) and should result in more efficient and better targeted therapeutic strategies.

**Conflicts of interests :** none

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**Figure 2**

**Diagram of the respiratory epithelium aggression-repair process**

A) Epithelial wound responsible for a basal membrane rupture. Proliferation of inflammatory cells: macrophages (red elements), and polymuclear neutrophils (brown elements). B) Repair process: conjunctive tissue hernia and migration of epithelial cells. C) Restoration of an epithelial coverage on the hernia.
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References


