ETIOPATHOGENESIS OF CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS

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Introduction Chronic rhinosinusitis (CRS) is presently classified into two subgroups: CRS without and with nasal polyps. CRS may occur in macroscopically different morphological variants such as: i) a simple hyperplasia of the sinus mucosa; ii) polypoid degeneration; iii) polyposis.

A variety of inflammatory mediators, including cytokines and chemokines, as well as adhesion molecules and matrix metalloproteinases, are upregulated in both subgroups of CRS; remodeling is also observed in both. These conditions are extremely clinically variable; differences are, in part due to the existence of different clinical subgroups, in part to factors not yet defined.

The pathogenesis of these processes is currently not completely understood and in particular is not clear which are the initial stimuli and how they are related to the progression of tissue remodeling process that determines the morphological expression of the disease. Recent research advanced knowledge about the different profiles of cytokines related to nasal chronic inflammation and polyps and assessed the degree of involvement of different elements (cell immunity, infectious agents, etc.) in the pathogenesis of these processes. In this regard it is particularly attractive the hypothesis that the formation of biofilms of microbic agents (bacterial, fungi, etc) could promote the chronic inflammation and tissue remodeling.

Some authors have also suggested the involvement of innate immunity receptors (Toll-like receptors, TLR2 in particular) in the development of chronic inflammation and in the increased expression of cytokines and growth factors (TGF-β, IL-4, and VEGF-A). In particular Lane and co. demonstrated increased levels of expression of TLR2 and a variety of inflammatory genes in sinonasal mucosa of CRS patients compared with controls. However, despite numerous studies on the morphology and the

molecular mechanisms, it is still poorly defined the upstream mechanisms of the tissue alterations associated with chronic nasal inflammation.

In order to clarify some of the mechanism underlying the process of tissue remodeling responsible for such clinical conditions, we have investigated:

- the expression and functions of a class of receptors of innate immunity (N-formyl peptide receptors)
- The level of MMP-2 MMP-7 MMP-9 and their tissue inhibitors (TIMP-1 and TIMP-2) as well as the correlation between their levels and different forms of polyposis

Therefore, this study was designed:

1) to assess whether nasal epithelial cell lines express FPRs;

2) to investigate whether FPRs ligands stimulates cell migration;

3) to evaluate whether FPRs agonists could induce the expression in nasal epithelial cell lines of TGF-β and VEGF-A, two key mediators of tissue remodeling.

4) to determine tissue levels of MMPs and TIMPs in different forms of polyposis

Methods We examined FPRs expression in a nasal epithelial cell line (RPMI-2650) at mRNA and protein levels. To determine whether FPRs were functional we performed chemotaxis experiments. In addition we evaluated the effects of FPRs agonists on the expression (PCR and ELISA) of VEGF-A and TGF-β, two key mediators of tissue remodeling.

We also evaluated, by immunohistochemical analysis, the expression of metalloproteinases MMP-9, MMP-7, MMP-2 and their tissue inhibitors TIMP-1 and TIMP-2, on tissue samples collected from patients with different forms of polyposis (associated with allergy, to a genetically determined syndromes or to alterations morphostructural) compared to a control group not affected by rhinosinusitis

Results RPMI-2650 express FPR and FPRL2, but not FPRL1. fMLP, a bacterial products active on FPR, and $uPAR_{84-95}$, an inflammatory mediators agonist for FPRL2, stimulated migration of nasal epithelial cells. fMLP and $uPAR_{84-95}$ induce expression and secretion of VEGF-A and TGF-β.

As regards the expression of MMPs and TIMP we observed:

- an increase in the levels of MMP-9, MMP-7 and MMP-2 and a concomitant reduction of TIMP-1 and TIMP-2 in patients with nasal polyposis compared to controls.
- the values of MMP-9, MMP-7 and MMP-2 appeared higher in patients with syndromic disorders compared to subjects with allergic diathesis and those with morphostructural nasal alterations;
- the values of TIMP-1 and TIMP-2 were lower in the same group of patients.

Therefore, the ratio MMP / TIMP appears increased in the polypoid nasal tissue compared to controls, especially in the group of syndromic patients. In the latter, the ratio MMP / TIMP appears higher than the other groups: this data is associated with a greater rate of recurrence of the disease.

Conclusions Our results suggest a possible mechanisms initiating tissue remodeling observed during chronic rhinosinusitis. This study provides further evidence that FPRs play a more complex role in human pathophysiology than bacterial recognition.

Once triggered the mechanism of activation of receptor-based tissue remodeling, in our opinion the ratio of MMP / TIMP plays an important role in the formation of polyps and in the trend towards recovery of the disease after its surgical removal.