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Title: New way forward in polyp research; changes in TLR9-expression of apparently healthy nasal mucosa behind polyp growth

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Body: Background: The origin of nasal polyps in chronic rhinosinusitis is unknown, but it is a well-known clinical fact that viral infections tend to stimulate their growth. Toll like receptors (TLRs) have recently emerged as key players in our local airway microbial defense. Among these, TLR9 has gained a special interest in viral disease. Nearly all studies of chronic rhinosinusitis with polyps (CRSwNP) have been focus on comparing polyp tissue with nasal mucosa from polyp free individuals. The information about changes in the apparently healthy mucosa bordering the polyp is limited. Objective: To find new ways forward in CRSwNP research by focusing on the role of TLR9 in polyp adjacent nasal mucosa. Methods: Biopsies from polyp and adjacent mucosa from CRSwNP-patients (n=11) and healthy controls (n=11) were collected and stimulated in vitro with CpG. Receptor expression and cytokine release were analyzed using flow cytometry and Luminex. Another 8 patients were intranasally challenged with either CpG -OND, a TLR9 agonist or placebo 24 hours before surgery. Results: A reduced expression of TLR9 was found in epithelial cells from adjacent mucosal in CRSwNP-patients compared to healthy control. CpG stimulation reconstituted this expression, both in vivo and in vitro. It also decreased the expression of VEGFR2 on adjacent mucosal epithelial cells suggesting inhibition of polyp growth. Conclusion: Defects in the TLR9 mediated microbial defense in the mucosa close to the anatomic origin of the polyp might explain virus induced polyp growth. The focus on polyp adjacent mucosa opens new perspective in CRSwNP research.