Immune checkpoint skewing might be the cause of continuous immune activation in nasal polyps: New opportunities for therapies

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Chronic rhinosinusitis (CRS) with or without nasal polyps is a localized major upper respiratory tract disease with an unknown cause. Initially, it resembles an infection that has gotten out of control and progressed into severe inflammation, eventually resulting in chronic sinusitis and nasal polyps. Patients with nasal polyps and sinusitis showed persistent symptoms, including nasal obstruction, loss of smell, nasal discharge, and facial pain or pressure, which are clinically the reasons for treating these patients.1 These issues require basic scientific research, therefore necessitating detailed characterization. There is no adequate translational model available. In nasal polyps, various processes take place; they range from epithelial mesenchymal transition, fibrosis, and local lymphocytic immune responses involving local production of antibodies IgA, IgM, IgE, and IgG to activation of neutrophils, eosinophils, and mast cells.1 In addition, focal dense infiltrates resembling ectopic lymphoid tissues are frequently seen, and localized fibrosis with stromal cell–immune cell cross talk occurs. Because the nasal mucosa is continuously exposed to the outside world, there is continuous exposure to antigens and pathogens. Wang et al performed a detailed characterization of T-cell responses by using the combination of tissue homogenates, cell suspensions, single-cell RNA sequencing, and histology of nasal mucosa tissue and polyp tissue to investigate the following immune checkpoints: programmed death 1 (PD-1), the soluble programmed death receptor ligands (sPD-L1 and sPD-L2), and membrane-associated programmed death ligands (PD-L1 and PD-L2).2 The balanced constitutive expression of PD-L1 and PD-L2 in the nasal mucosa, which ensures effective immune suppression in “healthy nasal mucosa tissue,” seems skewed and the cause of immune activation in nasal polyps (Fig 1).2

Wang et al have studied what happens immunologically with T cells when expression of the ligands of the immune checkpoints in the nasal mucosa is nonexistent or too low.2 They observed increased production of T-cell cytokines (including IL-21) and B-cell activating capacity, illustrating that they went beyond immune checkpoint control.2 These lymphocytes are not located in ectopic lymphoid tissues because they lack expression of CXCR5, a homing marker for lymphoid tissue.7 With correct and balanced expression of immune checkpoints and ligands, there will be no aberrant immune response (normal nasal mucosa [Fig 1]). Circulating PD-1+CXCR5+CD4+ T cells are associated with autoimmune disease.3 Constitutive expression of PD-L1 and PD-L2 has a presumptive role in controlling inflammation by inhibiting activated T cells in the heart, skeletal muscle, placenta, lungs, and eye.4 Nasal inferior turbinates also express significant levels of PD-L1 and PD-L2,5 acting as an immune suppressive milieu (Fig 1). Lower expression levels of PD-L1 and PD-L2 already suggest an immune activation milieu in nasal polyps.2

Are nasal polyps the result of skewing immunity toward an injurious hyperactive response? Are they a localized autoimmune disease mixed with a Th2 phenotype?6 A broader look at what is known about immune checkpoints and ligands in the field of oncology, in the field of autoimmunity, and in basic scientific research may help in understanding the available data and might result in new opportunities for therapeutic targeting.7 The major progress from the last decades in cancer therapy has been immune checkpoint blockade to prevent tumors from immune escape. This breakthrough in the knowledge regarding immune checkpoints in health and disease was acknowledged by awarding Tasuku Honjo and James Allison the 2018 Nobel Prize in Medicine. In addition, accumulating human data on immune checkpoint blockade treatment of oncology patients are being published.1 The main conclusions are that when the immune checkpoints have been blocked, the immune system becomes activated, with the result that certain tumors can no longer hide from the immune system, are recognized by the immune system, and might be resolved. When immune checkpoint blockade is used, side effects due to immune activation also occur in a group of patients. This induces an exacerbation of psoriasis or can lead to sarcoidosis or dry eye symptoms. And in allergy, asthma, and chronic obstructive pulmonary disease (COPD), it can also lead to increased inflammation. The latter is also important for the study by Wang et al because there is a relatively high comorbidity between having allergy and/or asthma and having nasal polyps. Wang et al observed that local reduced PD-L1 expression leads to T-cell activation and inflammatory effects.7

The therapeutic challenge is to restore the expression of PD-L1 and PD-L2 or the immune suppression of PD-1+CXCR5+CD4+ T cells. Both can be used as potential therapeutic targets. PD-L1 expression in cancer cells is upregulated in response to a DNA double-strand break. Upregulation of immune checkpoints (PD-L1 and PD-L2) can also take place during acute or persistent viral infections, which means that a pathogen can escape from the host immune system. This might be one of the problems due to respiratory viruses. Immune checkpoint expression could be induced by cytokines, including IFN-γ, TNF-α, and IL-6, resulting in...
upregulation of PD-L1 in a Janus kinase/signal transducer and activator of transcription (JAK/STAT)-dependent manner and attenuation of the activation of immune cells.1 Recently published papers have described the underlying mechanism of immune checkpoints via the activation of adenylyl cyclase as a result of immunosuppressive mediators such as prostaglandin E2 (PGE2). Adenylyl cyclases are found on all cells and are linked to G-protein–coupled receptors; they cause the formation of cyclic AMP (cAMP). cAMP, cyclic guanosine monophosphate (cGMP), and Ca$^{2+}$ are second messengers. In general, increasing Ca$^{2+}$ concentration is immune activating, whereas increasing cAMP and cGMP concentration is generally immunosuppressive. Phosphodiesterases (PDEs) catalyze cAMP and cGMP; consequently, PDE inhibition results in immune suppression. In vitro, influence on the expression of immune checkpoints occurs via PDE4A; overexpression of PDE4A causes PDE4A to behave as an immune checkpoint inhibitor.2 PDE4A is responsible for the catabolization of cAMP; it results in immune activation and restores T-cell activation and cytotoxic function, both of which are very important in curing cancer.2 PDE4A is constitutively expressed at high levels in CD4 T cells (T$_{H1}$, T$_{H1}$/T$_{H17}$, T$_{H2}$, and regulatory T cells) (PDE4A [proteinatlas.org identifier ENSG00000065989]-PDE4A/tissue/T cells). Inhibition of mechanistic target of rapamycin (mTOR) reduces PDE4A expression and sensitizes natural killer cells to PGE$_2$-mediated suppression. Inhibition of PDE4 generally increases cAMP level and is immune suppressive.3 This is achieved by cAMP-driven JAK/STAT-mediated cytokines, in particular IL-10. Studies on inhibition of PDE4, including PDE4A, have shown that these drugs are effective immune suppressors in psoriasis, psoriatic arthritis, COPD, and experimental autoimmune uveitis. The latter example is remarkable because the structural cells in the eye express very high levels of immune checkpoint ligands (PD-L1 and PD-L2) and already creates already an immune suppressive environment.4 CRS with nasal polyps has hallmarks that point in the direction of an autoimmune disease. Autoimmunity is treated with systemic anti-inflammatory drugs such as prednisolone or methotrexate. The use of PDE4 inhibitors merits investigation because there is a comparable elevated T-cell phenotype of PD1$^{+}$CXCR5$^{+}$T$_{H}$ cells in psoriasis, rheumatoid arthritis psoriatica, and lupus. In addition, PDE4 inhibition reduces the expression of CD11b on granulocytes and prevents extravasation of

FIG 1. Anatomic and functional characteristics of normal nasal mucosa, nasal poly, and nasal polytreatment opportunities. The nasal mucosa surface comprises ciliated epithelial cells and goblet cells. The epithelium constitutively expresses a range of immunomodulatory factors, including cell surface molecules (soluble and membrane-bound PD-L1 and PD-L2). Secretory IgA (s IgA) is the predominant immunoglobulin in nasal epithelial lining fluid and acts in concert with a wide variety of antimicrobial molecules to facilitate catabolization and/or limit the growth of pathogenic organisms. During the early stages of nasal mucosa infection, ciliated epithelial cells might lead to the release of preformed IL-33. The initial inflammatory response triggered by a Toll-like receptor (TLR), leads to cytokine production through activation of downstream signaling effectors, which lead to increase of gene transcription of a range of proinflammatory cytokines and chemokines, including IL-1$\alpha$, IL-6, IL-8, IL-33, TNF-α, and GM-CSF. IL-33 activates T$_{H2}$ cells, macrophages (M$^{\phi}$s), and mast cells (MCs) to produce profibrotic pathogenic factor, resulting in localized fibrosis with stromal cell–immune cell cross talk and production of TNF-α as well as other MC proteases and mediators, such as platelet-activating factor (PAF) and N-formyl-L-methionyl-L-leucyl-L-phenylalanine (fMLP). PAF and fMLP are responsible for a local microenvironment that activates granulocytes and recruits granulocytes in a CD11b-dependent manner. Immunosuppressive intranasal corticosteroids are the mainstay of treatment for patients with CRS, targeting the majority of inflammatory processes in the nasal mucosa. Anti-IgE and anti–IL-5 treatment has been shown to be effective in the treatment of CRS. PDE4 inhibitor therapy has merits worth investigating. ECM, Extracellular matrix.
granulocytes. Accumulating data regarding the use of anti-IgE and anti–IL-5 therapy in CRS are being published. Checkpoint inhibitor treatment of patients with an oncologic problem and comorbidity of psoriasis and/or COPD demonstrate that the oncologic problem is addressed but psoriasis or COPD worsens during checkpoint blockade treatment. Immunosuppressive intranasal corticosteroids are the mainstay of treatment for patients with CRS, and it is interesting to see whether intranasal corticosteroids restore the skewed immune checkpoints, resulting in curing CRS. Wang et al show that when PD-L1 or PD-L2 are pathophysiologically reduced, nasal mucosa T cells are uncontrolled and produce pathogenic cytokines, resulting in B-cell activation and production of excessive amounts of IgM, IgA, and IgE, as well as in granulocyte inflammation. This observation is an important addition to the current knowledge regarding dysregulated stromal immune communication and invites us to look further in the direction of immune checkpoints and the related therapeutic opportunities provided by them.

REFERENCES