

Gene-expression signatures of nasal polyps associated with chronic rhinosinusitis and aspirin-sensitive asthma

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Purpose of review

The purpose of this review is to highlight recent advances in gene-expression profiling of nasal polyps in patients with chronic rhinosinusitis and aspirin-sensitive asthma.

Recent findings

Gene-expression profiling has allowed simultaneous interrogation of thousands of genes, including the entire genome, to better understand distinct biological and clinical phenotypes associated with nasal polyps. The genes with altered expression in nasal polyps are involved in many cellular processes, including growth and development, immune functions, and signal transduction. The wide-ranging and typically nonoverlapping results reported in the published studies reflect methodological and demographic differences. The identified genes present possible novel therapeutic targets for nasal polyps associated with chronic rhinosinusitis and aspirin-sensitive asthma.

Summary

Gene-expression profiling is a powerful technology that allows definition of expression signatures to characterize patient subgroups, predict response to treatment, and offer novel therapies. Although the ability to interpret the meaning of the individual gene in these signatures remains a challenge, integrated analysis of a large number of these signatures with other genome-scale data sets and more traditional targeted approaches has a potential to revolutionize understanding and treatment of chronic rhinosinusitis and aspirin-sensitive asthma.

Keywords

aspirin-sensitive asthma, chronic rhinosinusitis, expression signatures, gene-expression profiling, microarray, nasal polyps

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Introduction

Sinusitis is one of the most commonly diagnosed and economically taxing diseases in the United States [1–3]. Patients with chronic rhinosinusitis (CRS) who are most refractory to treatment develop sinonasal polyps. A subset of these patients has aspirin-sensitive asthma (ASA, i.e. triad asthma or Samter's triad) distinguished by the presence of nasal polyps, asthma, and aspirin allergy. Sinonasal polyps are histologically characterized by numerous changes in the mucosal epithelium and underlying stroma [4], suggesting altered expression of multiple genes. We review studies that have applied microarray technology to sinonasal polyps to monitor expression of thousands of genes, and thereby gain insights into putative mechanisms of and novel targets for sinonasal polyposis, CRS, and asthma.

Gene-expression profiling in nasal polyps

Gene-expression profiling is a method of monitoring expression of thousands of genes simultaneously on a

glass slide called a microarray. The microarray technology has revolutionized the field of genetic analysis, making it possible to define patterns of gene expression, that is, expression signatures, which are unique to a given biological state. The power of expression signatures is two-fold: the enormous complexity of the expression data provides the opportunity to identify patterns of expression that reflect different and novel phenotypic subgroups with distinct biology and expression signatures can be assayed in varied contexts, including human tissue and experimentally manipulated in-vitro systems, which facilitates mechanistic insights by connecting the experimental state with the in-vivo state [5•]. When applied to nasal polyps, gene-expression profiling has a potential to define expression signatures that characterize patient subgroups within the currently heterogeneous clinical groups, predict response to various treatments, and offer novel therapeutic targets.

Several reports [6–11] have applied microarray technology to sinonasal tissues to examine expression of either a limited set of genes within small patient populations or to

Table 1 Summary of published work using microarrays to study human sinonasal polyps

Reference	Expression microarray	Tissue (<i>n</i> = number of patients)	Highlighted genes	Method of validation
Fritz <i>et al.</i> [10]	HuGeneFL (Affymetrix, Santa Clara, California, USA); 5600 full-length human genes	Allergic rhinitis without polyps (<i>n</i> = 4) vs. allergic rhinitis with polyps (<i>n</i> = 3)	Mammaglobin increased in polyps	qRT-PCR
Liu <i>et al.</i> [11]	GeneChip HG-U95Av2 (Affymetrix); 10 000 full-length genes	Polyps from CRS treated with intranasal steroids for more than a month (<i>n</i> = 10) vs. controls mucosa (<i>n</i> = 4); of the CRS patients, three were allergic, five had asthma, and two had aspirin sensitivity	Statherin, <i>PIP</i> , lactoferrin, <i>DMBT1</i> increased in polyps; <i>CC10</i> (uteroglobin) decreased in polyps	qRT-PCR, IHC
Benson <i>et al.</i> [12]	HuGe-133A (Affymetrix); 22 283 genes	Polyps from CRS (<i>n</i> = 4) before vs. after topical fluticasone treatment; excluded patients with asthma, cystic fibrosis, ciliary dyskinesia, and smoke exposure	Uteroglobin increased in treated vs. untreated polyps; decreased in untreated polyps vs. healthy mucosa; mammaglobulin B increased in treated vs. untreated polyps	qRT-PCR, IHC
Wang <i>et al.</i> [6]	BionstarH-IC (United Gene Holdings, Shanghai, China); 491 genes	Polyps from CRS (<i>n</i> = 4) vs. controls from inferior turbinates mucosa (<i>n</i> = 4); one patient was allergic, none had asthma or aspirin sensitivity	<i>17</i> increased in polyps; <i>IL-17R</i> increased in polyps	WB, IHC
Figueiredo <i>et al.</i> [7]	Human Q-series cytokines (SuperArray Corp., Maryland, USA); 96 genes	Nonallergic polyps and inflamed mucosa from patients with CRS (<i>n</i> = 21) vs. healthy controls; all samples for each group were pooled and two microarrays hybridized; excluded allergic asthma, allergic rhinitis, cystic fibrosis, primary ciliary dyskinesia, and steroid use	<i>TGFβ1</i> increased in inflamed mucosa; <i>IL-5</i> increased in polyps	qRT-PCR
Orlandi <i>et al.</i> [9]	Spotted cDNA array (Amersham Biosciences, Piscataway, New Jersey, USA) 6912 unique cDNA clones	Polyps from patients with AFS (<i>n</i> = 4) and EMRS (<i>n</i> = 3)	Sialyltransferase 1 increased in EMRS; GM2 ganglioside activator protein and <i>S100</i> calcium-binding protein increased in EMRS	qRT-PCR
Bolger <i>et al.</i> [8]	Human asthma gene array (SuperArray, Inc.) 89 genes	Nasal polyps before (<i>n</i> = 10) and after (<i>n</i> = 7) oral corticosteroid treatment in the same patients; excluded patients with cystic fibrosis or systemic granulomatous disease	Chemokine and leukotriene receptor genes expressed at high levels in pretreated polyps and changed after corticosteroids	None
Liu <i>et al.</i> [13]	HG-U133A GeneChip (Affymetrix) 14 500 genes	Polyps from patients with CRS (<i>n</i> = 6) vs. healthy controls (<i>n</i> = 6)	Differential expression of <i>IL-8</i> and <i>RGS1</i>	qRT-PCR
Stankovic <i>et al.</i> [14*]	HG-U133-plus2.0 GeneChip (Affymetrix) 47 000 transcripts	Polyps from patients with ASA (<i>n</i> = 10) vs. polyps from patients with CRS (<i>n</i> = 10) vs. healthy controls (<i>n</i> = 10)	Periostin increased in CRS and ASA; <i>PIP</i> decreased in CRS and ASA; <i>MET</i> increased in CRS, not ASA; <i>AZGP1</i> decreased in CRS and ASA; <i>PP1R9B</i> increased in CRS, not ASA	qRT-PCR, IHC

AFS, allergic fungal sinusitis; ASA, aspirin-sensitive asthma; CRS, chronic rhinosinusitis; *DMBT1*, deleted in malignant brain tumor protein 1; EMRS, eosinophilic mucin rhinosinusitis; IHC, immunohistochemistry; *PIP*, prolactin-induced protein; *PP1R9B*, protein phosphatase 1 regulatory subunit 9B; qRT-PCR, real time quantitative reverse transcription-PCR; *TGFβ1*, transforming growth factor beta 1; WB, western blot.

assay the entire human genome in small [12,13] or moderately sized [14[•]] populations. These studies are summarized in Table 1, which outlines distinct patient populations that have been analyzed, and genes that have been highlighted as potentially pathogenic. The wide-ranging and typically nonoverlapping results seen in these studies reflect heterogeneity of the studied populations, effects of therapeutic medications, differences in the number of analyzed genes, diversity in the statistical and bioinformatic rigor with which data were analyzed, and disparity in the methods and extent of data validation. The challenge has been to obtain meaningful results from a large volume of data generated by relatively small patient populations. We classify the genes that have been identified as potentially pathogenic into four groups on the basis of their distinct biological roles: genes that play a role in growth and development, genes encoding cytokines, genes with immune functions, and genes with other or unknown functions.

Genes that play a role in growth and development

Mesenchymal–epithelial transition (*MET*) factor, periostin and protein phosphatase 1 regulatory subunit 9B (*PP1R9B*) emerged as key genes whose increased expression characterized patients with severe CRS [14[•]]. Transforming growth factor beta 1 (*TGFβ1*) was highlighted in a study of nonallergic polyps [7].

Periostin is a potent regulator of fibrosis and collagen deposition [15], and overexpression of periostin has been associated with accelerated cell growth, reentry into the cell cycle [16], and angiogenesis [17]. Upregulation of periostin has also been identified in polyps of patients with ASA [14[•]] and in airway epithelial cells of patients with asthma [18[•]]. Downregulation of periostin after treatment of asthmatic patients with corticosteroids [18[•]] suggests that normalization of periostin expression is a part of the therapeutic effects of corticosteroids. This opens a possibility of specifically targeting periostin in future therapies for nasal polyps and asthma. The relevance of the same drug for diseases of both the upper and lower respiratory tract is consistent with the unified airway theory [19[•]], which proposes that common genetic and environmental factors similarly affects the entire respiratory tract.

MET encodes a tyrosine kinase membrane receptor with a high affinity for hepatocyte growth factor (*HGF*) [20]. *MET* plays an important role in cell growth processes, including wound healing, regeneration, and angiogenesis, as well as morphogenic differentiation processes such as embryonic development, cell migration, and metastasis [21–25]. *MET* and *HGF* have been shown to be deregulated in a number of major cancers [22,26,27]. Nicotine and cigarette smoke affect expression of the *HGF/MET* pathway in the lung [28]. By evoking the unified airway

theory, altered *MET* signaling may underlie negative effects of cigarette smoking on sinusitis. Increased expression of *MET* in polyps associated with CRS but not ASA [14[•]] suggests that putative therapeutic strategies aimed at interfering with the *HGF/MET* pathway [29] may be effective against a subset of nasal polyps.

PP1R9B is a ubiquitously expressed gene that plays a role in cell growth and molecular scaffolding [30]. The existing protein phosphatase 1 inhibitors [31] offer potential novel treatments for CRS.

TGFβ1 is a potent regulator of extracellular matrix, and it is expressed in eosinophils and nasal polyp tissue [32]. Peptide inhibitors of *TGFβ1* have been shown to alter immune function in regulatory T-cell activity [33], and may be useful in decreasing the immune dysregulation in CRS.

Gene-encoding cytokines

Cytokines are soluble signaling proteins, which include interleukins and chemokines. Gene-expression profiling of nasal polyps associated with CRS has identified three interleukins with increased expression in polyps: *IL-5* [7], *IL-17* [6], and *IL-18* [13]. *IL-5* is a potent chemoattractant and inhibitor of apoptosis in eosinophils. There is a strong correlation between the degree of tissue eosinophilia and the severity of CRS [34] so that eosinophils are thought to be involved in polyp formation [35]. *IL-5* release from nasal polyps has been shown to be induced by *Staphylococcus aureus* enterotoxin B [36[•]], suggesting a mechanism by which infection contributes to CRS. *IL-17* is a proinflammatory cytokine that is secreted by T cells and upregulated in asthma [37]. *IL-8* is a chemotactic agent for leukocytes.

Therapies directed against these specific interleukins are not available. However, a variety of treatments that target the inflammatory cascade, including topical corticosteroids [38] and immunotherapies [39] have resulted in immunomodulation of cytokines. Oral corticosteroid treatment effected chemokine and leukotriene receptor gene expression in sinonasal polyps, including alteration of chemokine (C-C motif) receptor 2 (*CCR2*), *CCR5*, chemokine (C-X3-C motif) ligand 1 (*CX3CL1*), and leukotriene B4 receptor (*LTB4R*) [8].

Genes with immune functions

Consistent with the view that altered immune function contributes to development of nasal polyps [40[•]], gene-expression studies of nasal polyps associated with CRS [11,12,14[•]], ASA [14[•]], or eosinophilic mucin rhinosinusitis [9], a variant of CRS similar to allergic fungal sinusitis, have identified several genes with immune functions. These genes include prolactin-induced protein (*PIP*) [11,14[•]], lactoferrin [11], deleted in malignant brain tumor protein

1 (*DMBPT1*) [11], sialyltransferase 1 [9], uteroglobin (*CC10*) [11,12], and zinc-alpha-2-glycoprotein (*AZGP1*) [14[•]].

PIP encodes a protein that is secreted by various apocrine glands, and has been implicated in host defense against infections and tumor immunity [41,42]. Lactoferrin is an iron-binding protein involved in innate immunity and found in exocrine secretions [43]. *DMBT1* is a bacterial-binding protein involved in innate immunity. Sialyltransferase is thought to be involved in B-cell activation and humoral immunity [44]. Uteroglobin is thought to be an anti-inflammatory and immunomodulatory molecule [45]. Uteroglobin was found to be expressed at low levels in CRS polyps [11], and the expression levels were increased after prolonged intranasal steroid treatment [12]. *AZGP1* is a member of major histocompatibility complex class I genes, and its expression is regulated by glucocorticoids [46]. Decreased expression of *AZGP1* in nasal polyps associated with CRS and ASA [14[•]], along with the demonstration that corticosteroids stimulate *AZGP1* protein production in other tissues [47], suggests that *AZGP1* deficiency may contribute to nasal polyps. Therefore, novel therapies targeted to specifically increase *AZGP1* expression may help treat nasal polyps.

Liu *et al.* [11] found increased expression of *PIP*, lactoferrin, and *DMBT1* in polyps of patients with CRS and ASA, whereas Stankovic *et al.* [14[•]] found decreased expression of the same genes in a different and larger cohort of patients with CRS and ASA. Differences in the reported results may reflect methodological and demographic differences, including the inflammatory status of the control tissue and use of intranasal steroids.

Genes with other or unknown functions

Genes involved in signal transduction have been identified in nasal polyps associated with CRS [13] or eosinophilic mucin rhinosinusitis [9], including *RGS1* [13] and *S100* [9]. Ganglioside activator protein, *GM2*, which binds and transports lipids, was increased in eosinophilic mucin rhinosinusitis [9]. Statherin, a gene involved in maintenance of mineral homeostasis and described in nasal secretions [48], was expressed at high levels in CRS and ASA [11].

Increased expression of mammaglobin was found in polyps of patients with allergic rhinitis compared with allergic rhinitis patients without polyps [10], and expression levels of mammaglobin in CRS polyps were increased after a prolonged course of intranasal steroids [12]. Mammaglobin encodes a protein of unknown function; the gene is mapped to chromosome 11q12.3-q13.1.3 [49], which is in close proximity to the beta subunit of the IgE receptor. Mammaglobin is related to epithelia secretory proteins (including uteroglobin) that modulate

inflammation [50] and bind steroids [51], suggesting a possible role in the mechanisms by which corticosteroids decrease polyp load.

Complementary methodologies for study of nasal polyps

This review focuses on insights gained about nasal polyps in patients with CRS and ASA while using a specific technology, high throughput gene-expression profiling. This technology complements other studies that use different techniques to explore nasal polyps. These complementary techniques include targeted explorations of specific genes such as those encoding cytokines [40[•]] and markers of epithelial inflammation [52], genes involved in innate immunity [53], cultures of sinonasal epithelium [53], characterization of polymorphisms in specific genes [54], or eventually the entire genome to uncover genetic determinants that confer susceptibility to CRS and ASA.

Conclusion

Gene-expression profiling has revolutionized the field of genetic analysis by defining expression signatures that enable identification of new disease subtypes, prediction of clinical outcomes, and discovery of novel therapeutic targets. The ability to interpret the large amount of data generated, and to determine the meaning of the individual genes within these signatures remains a challenge. Nonetheless, several genes with altered expression in nasal polyps have been proposed as putative targets for novel therapies for CRS and ASA. Integrated analysis of gene expression signatures and other genome-scale data sets, combined with more traditional single gene/protein approaches, has a potential to substantially advance the current understanding and treatment of CRS and ASA.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 81–82).

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