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Role of the TGF- β cytokine and its gene polymorphisms in asthma etiopathogenesis

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Transforming growth factor beta (TGF- β) is a pluripotent cytokine expressed by all cells of the human body which plays important roles in maintaining homeostasis and allowing for proper individual development. Disturbances in TGF- β signaling contribute to the development of many diseases and disorders, including cancer and organ fibrosis. One of the diseases with the best-characterized correlation between TGF- β action and etiopathogenesis is asthma. Asthma is the most common chronic inflammatory disease of the lower and upper respiratory tract, characterized by bronchial hyperresponsiveness to a number of environmental factors, leading to bronchospasm and reversible limitation of expiratory flow. TGF- β , in particular TGF- β 1, is a key factor in the etiopathogenesis of asthma. TGF- β 1 concentration in bronchoalveolar lavage fluid samples is elevated in atopic asthma, and TGF- β expression is increased in asthmatic bronchial samples. The expression of all TGF- β isoforms is affected by a number of single nucleotide polymorphisms found in the genes encoding these cytokines. Some of the SNPs that alter the level of TGF- β expression may be associated with the occurrence and severity of symptoms of asthma and other diseases. The TGF- β gene polymorphisms, which are the subject of this paper, are potential diagnostic factors. If properly used, these polymorphisms can facilitate the early and precise diagnosis of asthma, allowing for the introduction of appropriate therapy and reduction of asthma exacerbation frequency.

KEYWORDS

TGF- β , asthma, single nucleotide polymorphism, genomics, gene polymorphism, pathogenesis

Introduction—TGF- β

Transforming growth factor β (TGF- β) is a pluripotent cytokine expressed by all somatic human cell types (1), which plays several important roles in maintaining homeostasis (2). TGF- β occurs in three isoforms (TGF- β 1, 2 and 3). All forms of TGF- β are receptor ligands of three receptor types (T β RI, II and III), have similar biological activity and participate in processes such as regulation of proliferation, migration, differentiation and apoptosis (3).

TGF- β regulates cell proliferation, contributes to epithelial-to-mesenchymal transition (EMT), regulates immune cell function by modulating immune responses, contributes to the conversion of fibroblasts to myofibroblasts, and causes overproduction of the extracellular matrix (ECM) in tissues undergoing fibrosis (4). TGF- β stimulates expression of proteins such as collagens, basal lamina proteins, and ECM proteins (5). Additionally, in the early stages of tissue fibrosis, TGF- β stimulates myofibroblasts and other stromal cells to increase the synthesis of collagen-crosslinking enzymes (6). Furthermore, TGF- β decreases the synthesis of matrix-depleting proteins, such as matrix metalloproteinases. Ultimately, the increased synthesis of matrix proteins and

decreased activity of matrix metalloproteinases due to TGF-β activity contribute to the remodelling of epithelial tissue and may result in fibrosis (7–9).

The canonical TGF-β signalling pathway is activated by the binding of TGF-β ligands to their receptors. TGF-β is secreted in a latent, inactive form (L-TGF-β) and activated in an integrin-dependent manner (10). Active TGF-β binds to TGF-β type II receptors (TβRII), which are transmembrane receptors with serine/threonine kinase activity. TGF-β-TβRII interactions lead to the recruitment and phosphorylation of TGF-β type I receptors (TβRI) (11). Upon activation, TβRIs phosphorylate SMAD2 and SMAD3, which then assemble into heterodimers and trimers with SMAD4. Complete SMAD protein complexes translocate to the nucleus and influence the expression of TGF-β target genes. SMAD3 and SMAD4 bind DNA directly, with low affinity, and require the presence of other transcription factors to fully

regulate target gene expression. SMAD2 does not bind DNA directly (12). Target genes regulated by TGF-β include plasminogen activator inhibitor-1 (PAI-1) and *Smad7*, which acts as an inhibitor of TGF-β/SMAD signalling by labelling activated TβRI for proteasomal degradation (13). Figure 1 is a simplified visual representation of the TGF-β signalling scheme.

Dysfunction of TGF-β signalling influences the development of many diseases and disorders, including cancer and organ fibrosis (14, 15). Excessive TGF-β activity promotes organ fibrosis by increasing connective tissue growth factor (CTGF) expression, inhibiting extracellular matrix (ECM) degradation, and increasing collagen synthesis. TGF-β also induces fibroblast proliferation and differentiation (16). The induction of organ fibrosis by TGF-β is mediated by Smad-dependent pathways, which directly increase the transcription of genes involved in ECM production, and Smad-independent pathways, including MAP kinase pathways (17).

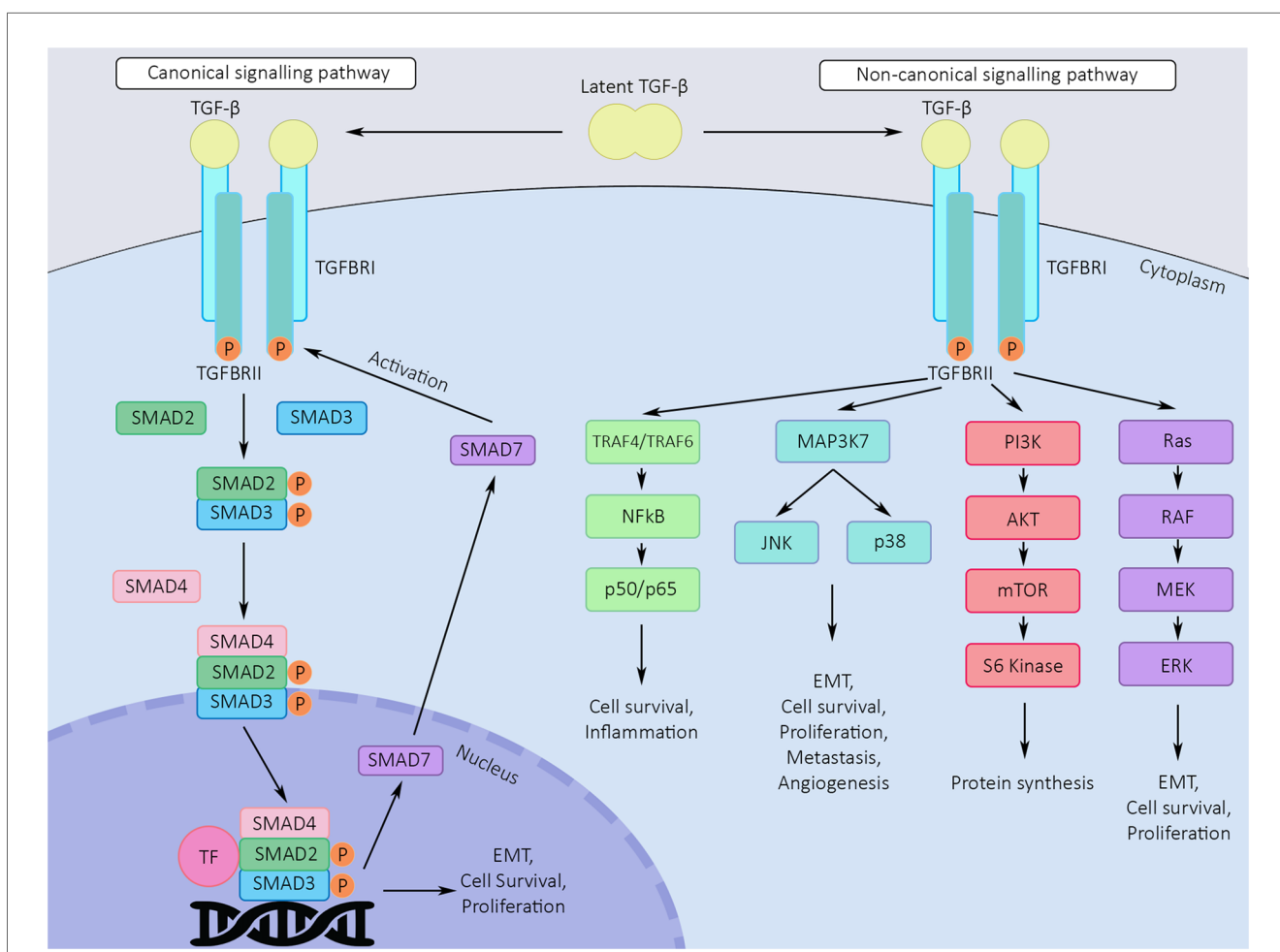


FIGURE 1 Canonical and non-canonical TGF-β signalling pathways. TGF-β is secreted in a latent, inactive form and activated in an integrin-dependent manner. Active TGF-β binds to TGF-β type II receptors (TGFβRII), which are transmembrane receptors with serine/threonine kinase activity. TGF-β-TβRII interactions lead to the recruitment and phosphorylation of TGF-β type I receptors (TGFβRI). In the canonical signalling pathway, upon activation, TβRIs phosphorylate SMAD2 and SMAD3, which then assemble into heterodimers and trimers with SMAD4. Complete SMAD protein complexes translocate to the nucleus, interact with transcription factors and influence the expression of TGF-β target genes. SMAD7 inhibits TGFβRII, acting as a regulatory factor in the signalling pathway. In the non-canonical signalling pathway, phosphorylated TGFβRII instead activates one of several alternative pathways, including the ERK, JNK, p38 and PI3K-Akt pathways. P, phosphorylation; TF, transcription factor; EMT, epithelial to mesenchymal transition.

Introduction—asthma

Asthma is the most common chronic inflammatory disease of the respiratory tract (18), characterized by bronchial hyperresponsiveness to a number of factors, which leads to bronchoconstriction and reversible airflow limitation. Asthma is a heterogeneous disease with a significant degree of variability in phenotypes (clinical symptoms in conjunction with patient characteristics, such as age of asthma onset, clinical response to pharmacological therapies and presence of comorbidities) and endotypes (pathophysiological mechanisms leading to the development of the disease) (19). Characteristic symptoms of asthma include wheezing, shortness of breath, cough, and chest tightness. Symptoms vary in severity and frequency and occur mainly during disease exacerbations (20). Bronchial asthma can be divided into two main endotypes based on the presence of inflammatory responses mediated by T helper type 2 (Th2) lymphocytes. The two classically recognized endotypes are type 2 (eosinophilic) asthma and non-type 2 (non-eosinophilic) asthma (21). The discovery that innate lymphoid cells type 2 (ILC2) are capable of releasing Th2 cytokines has led to a more precise classification of asthma endotypes into T2-high, T2-low, and non-T2 (22).

The clinical picture of asthma depends on complex gene-gene and gene-environment interactions. These components make asthma a dynamic disease, and its classifications can change both due to treatment and independently of it. At the outset of asthma development, airway hyperresponsiveness to normally harmless antigens, such as pollen or mites, causes epithelial cells to release inflammatory mediators, including many interleukins (23). Inflammatory mediators trigger an immune activation cascade that leads to activation and recruitment of ILC2s, mast cells, Th2 cells, eosinophils, and dendritic cells to the site of inflammation (24). Repeated exposure to allergens can lead to chronic airway inflammation and airway remodelling, which ultimately leads to partial loss of respiratory function (25). Airway remodelling in asthma includes subepithelial fibrosis, abnormal extracellular matrix deposition, goblet cell proliferation, smooth muscle and mucous gland hypertrophy, and epithelial damage (26).

The disease develops under the influence of variables that, according to the Global Strategy for Asthma Management and Prevention (GINA) report (27), can be divided into exacerbation-inducing (inducing disease exacerbations in patients with pre-existing asthma) and asthma-causing (causing the development of asthma in patients without pre-existing asthma). According to the current GINA guidelines, the Asthma Control Questionnaire (ACQ) (28) or the Asthma Control Test (ACT) (28) can be used to assess symptoms. The severity of the disease is assessed not based on the severity of symptoms before treatment, but only after several months of treatment, when the level of severity and the intensity of treatment required to achieve and maintain asthma control are established (29).

Asthma has also been studied in the context of pharmacogenomics. In a systematic review of pharmacogenomic studies, García-Menaya et al. focused on four genes with the potential to be implemented in pharmacogenomics for asthma

therapy. *FCER2* was shown to be related to inhaled corticosteroid (ICS) response, *ABCC1* and *LTC4S* were related to anti-leukotriene agents, and *ADRB2* was related to beta-agonist response (30). In another systematic review which examined 30 studies involving over 6,000 subjects, variant rs1042713 of the *ADRB2* gene was consistently associated with response to long-acting beta-agonists (LABA) (31). Another systematic review focused on the main findings of pharmacogenetic studies of pediatric asthma published in 2018–2019. The findings of the studies discussed in this review led to the validation of previously established gene-treatment response associations in asthma, and more importantly—allowed the identification of novel associations (*PRKG1*, *DNAH5*, *IL1RL1*, *CRISPLD2*, *MMP9*, *APOBEC3B-APOBEC3C*, *EDDM3B*, and *BBS9*). Critically, many of the results were not consistent between studies, underlining the need for large studies in diverse populations and a harmonization of treatment response definitions (32). It is important to note, that despite over 35 guidelines being published for pharmacogenomics-based optimization of therapy by the Clinical Pharmacogenetics Implementation Consortium (CPIC), there are no guidelines for asthma (33). In spite of much effort put towards researching pharmacogenomic biomarkers for asthma therapy, more compelling, robust clinical evidence is required for diagnostic implementation.

TGF- β and its signaling pathways in asthma etiopathogenesis

TGF- β , in particular TGF- β 1, is a key factor in the etiopathogenesis of asthma. TGF- β 1 levels in bronchoalveolar lavage fluid (BALF) are elevated in atopic asthma (34, 35), and TGF- β expression is increased in bronchial tissue (36), sputum (37) and serum (38) samples from asthmatics. TGF- β 2 levels have been found to be significantly increased in airway tissues extracted from patients with severe asthma (39). Peripheral blood neutrophils from asthmatic patients were found to express higher levels of TGF- β than those of non-asthmatic subjects (40). Human bronchial fibroblasts (HBF) from asthmatic patients also exhibit increased secretion of TGF- β 1, both when unstimulated (41, 42) and when stimulated with interleukin-13 (IL-13), a cytokine and central mediator of asthmatic inflammation (43). Lastly, a relationship between airway TGF- β levels and asthma severity has been suggested by several researchers (44–46).

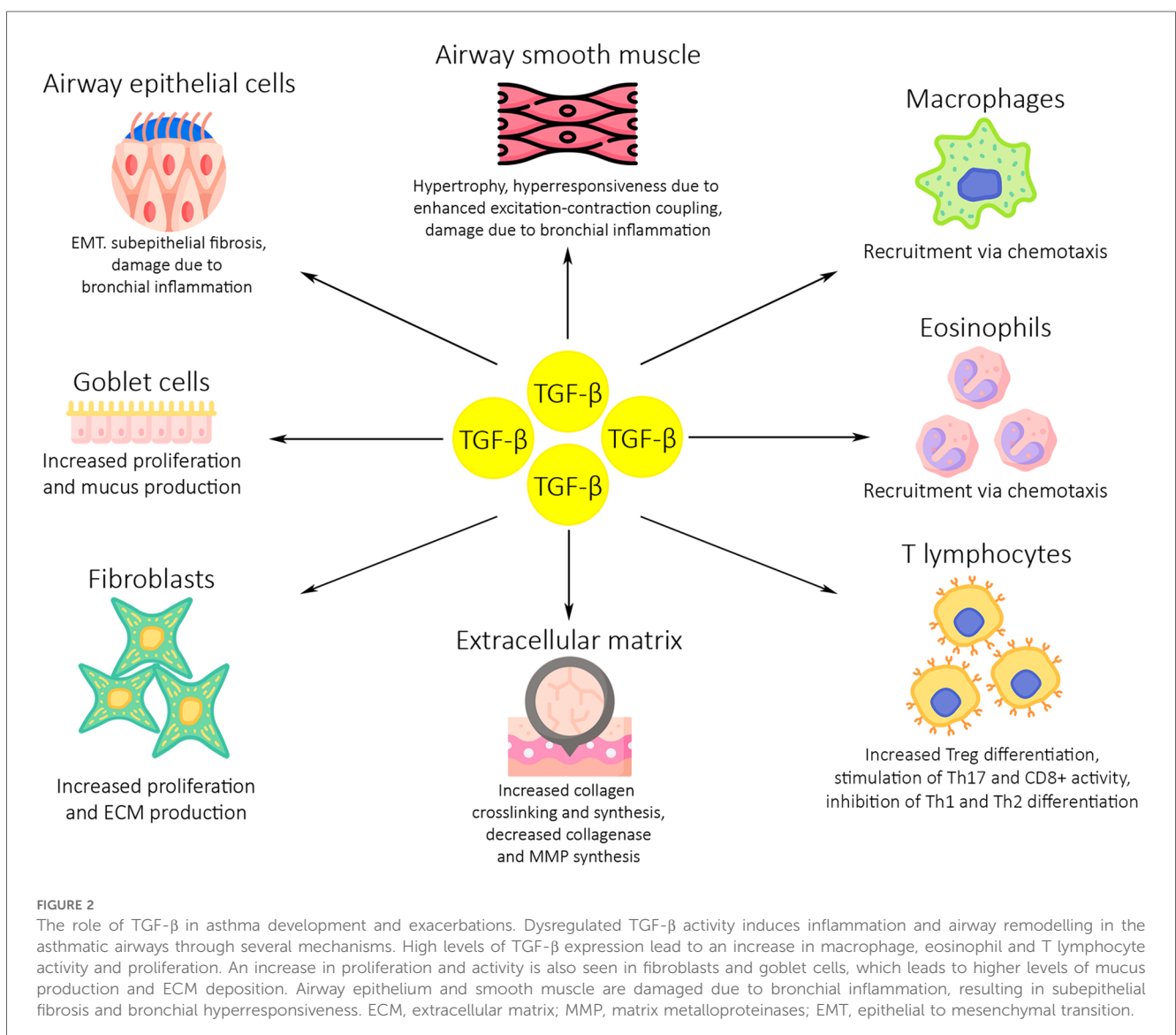
Bronchial epithelial cells and eosinophils are the main source of TGF- β in the airways of asthmatics (47). TGF- β stimulates airway smooth muscle proliferation and extracellular matrix (ECM) deposition by activated fibroblasts, ultimately leading to structural changes in the airways. Furthermore, TGF- β 1 promotes airway smooth muscle shortening and hyperresponsiveness by enhancing excitation-contraction coupling (48). Multiple studies using animal models of asthma have pointed towards the role of TGF- β in the remodelling of asthmatic airways. McMillan et al. have shown that anti-TGF- β antibody treatment prevents the progression of airway remodeling using a murine model of prolonged allergen challenge. Furthermore, anti-TGF- β antibody treatment was shown to limit activation and expression of Smad 2, while upregulating the

expression of inhibitory Smad7 (49). Another study used a murine model of ovalbumin sensitization and challenge to assess the effects of isoform-specific anti-TGF- β antibodies on asthma-associated airway remodelling. Antibodies against TGF- β 1 and TGF- β 2 were shown to inhibit ovalbumin-induced subepithelial collagen deposition, while anti-TGF- β 1 antibodies additionally limited TGF- β 1-mediated fibroblast decorin (a protein which influences collagen fiber development) deposition (50).

Several studies carried out on human bronchial tissues have also suggested that TGF- β signalling has a significant role in asthmatic airway remodelling. In one such study, acute allergen challenge led to an increase in expression of TGF- β 2, Smad 2/3 and Smad 4 in airway epithelial cells and leukocytes. Furthermore, the same study indicated that increased TGF- β 2 expression may be responsible for an increase in the deposition of tenascin, an ECM glycoprotein, in bronchial tissues (51). Another, similar study has shown a correlation between higher connective tissue growth factor (CTGF) levels and increased basement membrane thickness. CTGF

expression is induced by TGF- β 1 (52). Human bronchial epithelial cells exposed to TGF- β 1 have exhibited an upregulated expression of disulfide-isomerase, a profibrotic enzyme, compared to non-stimulated cells (53). Wnuk et al. examined the effects of TGF- β on the balance between the profibrotic Smad2/3 and antifibrotic Smad1/5/9 pathways and myofibroblast formation in human bronchial fibroblast populations from asthmatic and non-asthmatic patients. They showed that TGF- β strongly enhanced the Smad2/3 pathway activity, while diminishing activity of the Smad1/5/9 pathway in fibroblasts from asthmatic patients. Additionally, these changes in signalling pathway activity were correlated with enhanced fibroblast-to-myofibroblast transition (FMT). Interestingly, activation of the Smad1/5/9 through administration of BMP7 was shown to prevent FMT and downregulate profibrotic gene activity in fibroblasts from asthmatic patients (8). Figure 2 depicts the effects of TGF- β on asthma development and exacerbations.

The role of TGF- β in asthma is not limited to airway remodelling. In CD4⁺ CD25⁻ T cells, TGF- β induces expression



of the *Foxp3* gene upon stimulation of T cell receptors. Expression of the *Foxp3* gene leads to the differentiation of regulatory lymphocytes (Treg) with immunosuppressive activity (54). Importantly, TGF- β is also produced by Treg lymphocytes. TGF- β in combination with IL-6 also stimulates the proliferation of Th17 lymphocytes, which contribute to the recruitment of neutrophils to the airways, which ultimately leads to the development of an eosinophilic Th2-type inflammatory reaction (55, 56). TGF- β inhibits the differentiation of Th1 and Th2 lymphocytes by silencing the transcription factors T-beta and GATA3 (57). This indicates a dual role of TGF- β in the Th2-type inflammatory reaction. In summary, TGF- β stimulates the activity of NK, Treg, Th17, and CD8+ T cells while inhibiting the differentiation of Th1 and Th2 cells. TGF- β influences the immune system in the asthmatic airways by playing multifunctional roles in T cell differentiation and homeostasis (58).

SMAD proteins responsible for TGF- β signal transduction also influence the course of chronic airway inflammation. Mice with inactivated *Smad3* gene developed significantly less peribronchial fibrosis, smooth muscle proliferation and mucus production in the airways after allergen challenge compared to wild-type mice (59). Overexpression of SMAD2 in the epithelium may, on the other hand, increase subepithelial collagen deposition and smooth muscle hyperplasia without causing airway inflammation (60). Studies conducted on asthmatics treated with mepolizumab, a monoclonal antibody against IL-5, clearly indicate a link between the level of eosinophil proliferation in the airways and the expression of TGF- β and asthmatic airway remodelling. Patients who received mepolizumab for 3 months showed significantly lower levels of eosinophils in bronchoalveolar lavage (BAL). Importantly, the reduction in BAL eosinophils led to a significant reduction in BAL TGF- β 1 levels in this group of patients. The reduction in eosinophil and TGF- β 1 levels was accompanied by a reduction in ECM protein levels in the airways (61). This suggests that anti-IL5 therapy had an inhibitory effect on airway remodelling.

Allergic airway inflammation and airway hyperresponsiveness (AHR) are hallmarks of asthma crucial for the pathogenesis of this disease. With respect to the immunology of asthma pathogenesis, Th2 cytokines such as IL-4, IL-5, IL-9, and IL-13 are considered key mediators in the development of airway inflammation and AHR (62, 63). IL-13 is currently considered to be a central mediator in the development of allergic asthma (64). TGF- β 1 is a key mediator in the development of IL-13-mediated asthma phenotypes. TGF- β 1 is thought to be involved in the phenotypic changes of myofibroblasts, resulting in airway remodelling due to overexpression of IL-13 in TG(+) mice (65). These findings suggest that TGF- β 1 signalling pathways are involved in the development of AHR.

In summary, in asthmatic airways, TGF- β 1 causes immunosuppression of Th1 and Th2 lymphocytes, stimulates the proliferation of Th17 lymphocytes, is a chemotactic factor for macrophages, fibroblasts and eosinophils (after the introduction of allergens to the airways), stimulates the synthesis of ECM proteins while inhibiting the expression of collagenase and

matrix metalloproteinases, and stimulates the proliferation of bronchial myocytes (66).

Review methodology

For the following section (“TGF- β gene polymorphisms and asthma etiopathogenesis”), literature research has been performed in the PubMed and Google Scholar databases using the following keywords: “snp” or “polymorphism” and “tgf” or “tgfb” or “tgf beta” and “asthma”. The inclusion criteria were as follows: (1) studies focused on the effects of transforming growth factor- β gene polymorphisms on asthma risk and severity, and (2) articles written in English. The exclusion criteria were as follows: (1) reviews, editorials, opinion articles or case studies; (2) animal or *in vitro* model studies; (3) papers that mentioned but did not directly study TGFB gene polymorphisms. A stepwise evaluation of each position in the search results according to the inclusion and exclusion criteria has been conducted based on the title, the abstract, and lastly the full text. Each paper has been independently evaluated by both authors.

TGF- β gene polymorphisms and asthma etiopathogenesis

The *TGFBI* (Transforming Growth Factor Beta 1) gene is located on 19q13.2 and encodes a secreted protein (44 kDa) of 390 amino acids. The protein, also named Transforming growth factor beta 1, is secreted in a latent form and must be activated in an integrin-dependent manner (67). The *TGFB3* (Transforming growth factor beta receptor 3) gene is located on 1p33-p32 and encodes a protein (300 kDa) of 849 amino acids, of the same name, with a single transmembrane domain and a short section of the intracellular domain (68).

The expression and activity of all TGF- β isoforms is influenced by a number of single nucleotide polymorphisms (SNPs) occurring in the genes encoding these cytokines. SNPs are substitutions of single nucleotides at a specific genomic position. SNPs do not necessarily change the encoded protein due to the genetic code being degenerated. If a SNP is defined by a C being replaced with a T in some individuals, those two variations (C/T) are defined as alleles of that SNP. Some SNPs change the level of TGF- β expression and may be associated with the occurrence and intensity of asthma and other diseases (69, 70). Polymorphic forms of the *TGF β* genes may significantly contribute to the development of asthma, induce disease progression and its complications, and have a clinically significant impact on symptom control (71).

Currently, the exact role of SNPs in the pathogenesis of asthma is the subject of widespread discussion, and numerous studies are being conducted in this area. It should be noted that the studies are being conducted on populations of disparate characteristics and sizes, thus not all results are reproduced. It should be noted that many studies have demonstrated and confirmed the functional role of *TGF β* SNPs in asthma (72–74). From the point

of view of both basic science and clinical applications, gaining an understanding of the influence of these SNPs on TGF- β signalling pathways in asthma is highly important.

–509C/T (rs1800469)

A growing body of evidence suggests that alterations in TGF- β signalling pathways may lead to the development of allergic disease, in which IgE specific for normally harmless substances is produced. IgE binds to the surface of mast cells, and cross-linking of IgE through allergen binding results in mast cell degranulation and allergic symptoms (75). One of the early findings suggesting a role for TGF- β in atopy came from a study of 20 families with an asthmatic proband and 10 families without asthma. This study identified a polymorphism in the *TGFBI* promoter (a sequence bound by proteins to initiate RNA transcription) 509C>T (rs1800469), meaning the cytosine at position 509 in the *TGFBI* promoter sequence has been replaced with a thymine. The polymorphism was present in a homozygous form in 16 individuals and significantly associated with increased total IgE in a population of 47 unrelated individuals (76). Subsequent studies with larger study populations have shown that 509C>T was strongly associated with increased plasma TGF- β 1 levels and was associated with the development of asthma (77, 78). An association of the 509C>T polymorphism with increased serum IgE levels or increased risk of asthma development was confirmed in some (78–84) but not all studies (85–88). These disparate results may stem from differences in the ethnicities, ages and sexes of populations recruited for these studies. For example, Hobbs et al. (76) recruited families of undetermined ethnicity from the National Jewish Medical and Research Center in the USA. Grainger et al. (77) recruited a population of post-menopausal (mean age 57 years) white British twins. Nagpal et al. (78) examined two cohorts of young Indian adults (mean ages 28 and 33 years for the two cohorts). Chiang et al. recruited 217 adult Taiwanese asthmatic subjects (79). Yucesoy et al. studied adult, Caucasian French Canadians exposed to diisocyanates (chemicals used in industrial processes, known to induce occupational asthma) (80). Wiśniewski et al. examined 247 adult Polish asthmatic patients (87). Lastly, Silverman et al. (86) examined DNA samples from a population of white North American adults. As asthma is a heterogeneous disease associated with a range of genetic and environmental factors, conducting studies on populations which differ ethnically and clinically (age, years from disease onset, disease severity) may lead to significant discrepancies in results. The T allele of rs1800469 in the *TGFBI* promoter region has also been found to be associated with elevated plasma TGF- β 1 levels, elevated total IgE levels, and an increased risk of bronchial remodelling (89).

Whereas Salam et al. showed that within a group of 927 Hispanic and 2,096 non-Hispanic white children, those with the previously discussed –509TT rs1800469 genotype had a 1.8-fold increased risk of persistent asthma in California (90), de Faria et al. (91) suggested that there was no association between the presence of the –509C/T polymorphism and an increased risk of developing severe asthma in Brazilian children. A meta-analysis including a total of 12 case-control studies conducted in Chinese

populations (92) suggested that the –509C/T polymorphism is associated with an increased risk of asthma. Subgroup analysis of these populations by age showed that the –509C/T polymorphism was strongly associated with the risk of asthma in Chinese children, but this polymorphism was not associated with asthma in adults. Subgroup analysis by asthma severity showed that the –509C/T polymorphism was associated with both mild to moderate asthma and severe asthma (92).

The –509C/T polymorphism locus is located in the promoter region of the *TGFBI* gene and may alter the activity of the *TGFBI* promoter-reporter and affect the interaction of the promoter region with transcription factor YY1, which ultimately leads to a change in the plasma TGF- β 1 concentration (86). As the polymorphism is located in the promoter region, it does not affect the structure of the protein, but changes the amount of protein produced. The T allele is known to prevent AP1 from binding the promoter, increasing the levels of protein expression (93). Several studies have shown that the *TGFBI* –509C/T polymorphism has a statistically significant association with increased serum TGF- β 1 levels in patients with asthma (76). Moreover, the –509T variant was found to be the *TGFBI* polymorphism with the strongest association to the severity of asthma (94). These results indicate that the presence of the –509C/T polymorphism may enhance the transcription of the *TGFBI* gene and may be a useful factor in the diagnosis of asthma.

In a meta-analysis conducted in 2016, 20 studies involving over 3,500 asthmatic patients were examined to analyse the association between TGF- β SNPs and asthma development risk. For the C509T polymorphism, a significant association was found both in overall analysis, and in subgroup analysis by ethnicity, for the Asian ($P=0.004$, OR=1.43) and Caucasian ($P=0.05$, OR=1.16) population. For the T869C polymorphism, a small but significant association was found in overall analysis (OR=1.14, $P=0.03$), but not in subgroup analysis by ethnicity. The authors point out limited sample size after subgrouping as an explanation for this discrepancy, once more emphasising the need for more studies on asthmatic populations from varied ethnic backgrounds (95).

+869T/C (rs1982073)

Sharma et al. conducted the first study of the association between *TGFBI* variants and disease exacerbation in people with asthma. This study examined two populations of children and showed that the T allele of the rs1982073 (+869T/C) polymorphism in *TGFBI* was associated with a lower risk of exacerbations (96, 97).

The +869T/C *TGFBI* polymorphism locus is in a domain which likely promotes the transport of newly synthesized protein to the endoplasmic reticulum (98). This variant may affect the function of TGF- β 1, likely by affecting intracellular transport or the efficiency of cellular protein export. The SNP is located in the first exon of the gene, which allows it to impact the structure and function of the protein product (99). The +869T/C polymorphism may play an important regulatory role in *TGFBI* mRNA expression (100). The T allele has been shown to be associated with reduced *TGFBI* expression, while the C allele has been shown to exhibit 2.8-fold higher TGF- β 1 secretion than the

T allele (101). The 869T allele may result in lower efficiency of cellular protein export and lead to reduced protein production. The C allele has also been associated with elevated plasma TGF- β 1 concentrations in Japanese patients with myocardial infarctions (102). Studies have shown that the +869T/C polymorphism may also be involved in the modulation of asthma severity (91), indicating that this variant may influence asthma susceptibility and development and serve as a diagnostic factor in asthma.

Other polymorphisms

In 2022, a study was conducted on the association between SNPs in the TGF β genes and the occurrence and asthma severity in a Polish population. It was found that there are four SNPs located in introns of the TGF β 2 gene (rs2796821, rs10779329, rs4903359 and rs11083616), the occurrence of which has a statistically significant association with the risk of asthma (66). In this study, data from 237 families with atopic asthma and 268 families without asthma were analysed. Statistical analysis confirmed previously published associations between many SNPs and asthma. In this study, very strong statistically significant differences in the occurrence of asthma were observed for rs2796821. The heterozygous (C/T) form of rs2796821 increased the risk of asthma by 93%, while the homozygous C/C form increased the risk by 102%. Importantly, this analysis also allowed the discovery of new relationships between the occurrence of the C/C genotype for rs10779329 and the A/G genotype for rs4903359 in the TGF β 2 gene and a statistically significantly increased risk of asthma (66). The occurrence of the rs11083616 polymorphism was also found to be associated with bronchial obstruction, as well as increased airway wall thickness, which increases the risk of obstructive diseases (66).

Another study conducted on a Polish population showed that the T/C genotype of the rs8109627 polymorphism is significantly associated with an increased score in the ACT test, which is associated with better disease control—controlled asthma (7). Moreover, these studies indicated an association between the G allele of the rs2796822 polymorphism and a decreased score in the ACT test, which is associated with worse disease control and the possibility of uncontrolled asthma. The G allele of the rs2796822 polymorphism in the TGF β 2 gene occurs with different frequency in patients with mild and severe asthma. The risk of severe asthma in rs2796822 G allele carriers was 71% higher in comparison to patients without this version of the polymorphism (7).

In a study conducted on a population of Korean asthmatics, 19 SNPs of the TGF β 3 gene were examined using direct re-sequencing (103). A small but statistically significant positive association was found between the methacholine challenge result and the A allele of the +2753G>A polymorphism. No other allele or haplotype examined showed a similar association, indicating that genetic variation at this locus may be partially related to the development of AHR. This study also showed that the strength of the association with nonatopic asthma was significantly greater when the Ht3 (TA) haplotype [consisting of +44T>C (S15F) and +2753G>A] was present rather than when the 2753A allele was present alone (103). The number of patients or families

examined is important when drawing conclusions from genetic association studies. Greater statistical power can be achieved by increasing the sample size than by increasing the number of polymorphisms examined. Typically, for candidate gene studies sampling from 500 patients was considered sufficient to provide reproducibility and detect the presence of polymorphisms with a relatively small effect size (104). More recently, candidate gene studies have begun to be replaced by more advanced approaches, such as GWAS using genotyping microarrays or NGS techniques, which require far larger sample sizes. More than 2,000 subjects were recruited for this study (103), which was deemed sufficient for strong reproducibility by the authors.

Additionally, a Pakistani population of 52 asthma patients and 56 healthy controls was genotyped for TGF β 1 SNPs rs1800469 and rs2241715 (an intron variant) using SNaPshot minisequencing assays. No association between any rs1800469 alleles and asthma occurrence was found. However, under codominant, dominant, over dominant and recessive inheritance models, the T allele of rs2241715 was found to be strongly associated with asthma occurrence, and identified as a risk factor for the Pakistani population (105). A Thai population of 250 patients was examined for the effects of SNPs in the TGF β 1, ADAM33, VEGFA and PLAUR on asthma occurrence. Interestingly, the TGF β 1 SNPs examined (rs2241715, rs11466345) were not found to be associated with asthma, while The ADAM33 rs528557/S2 2151G>C and the VEGFA rs833069+450T>G SNPs had a strong positive association with the risk of asthma development (106).

118 children affected by childhood asthma and 120 healthy children in Guangxi, China were genotyped for TGF β 1 SNPs rs1800469, rs1800470, rs2241712, rs224171 and rs4803455. No significant correlation between any of the SNPs and asthma occurrence was found (107).

The T allele of the rs8179181 polymorphism in an intron of the TGF β 1 gene has been shown to be associated with an increased risk of childhood asthma and atopy in a population of Mexican children and adolescents. It has also been shown to be associated with a more severe course of the disease and elevated levels of TGF β 1 mRNA (108). The A allele of the rs4803455 polymorphism, also in a TGF β 1 intron, was found to be associated with an increased risk of the disease in a study conducted on 380 asthmatics in the Netherlands. In asthma, the presence of this SNP is associated with decreased lung function and a higher degree of airway remodelling (109).

A study conducted on 297 Japanese asthmatic childhood atopic asthma patients revealed an association between a TGF- β 2 SNP, and increased risk of childhood atopic asthma. The SNP described in this study was 3'UTR 94862T>A ($p = 0.00041$). The SNP was also found to be associated with a significant increase in eosinophil counts. However, the authors stated that the functional significance of the SNP remains unknown (88).

In summary, genetic variation within the TGF- β genes has been shown to have a definite association with asthma. Variants such as the T allele of the -509C/T and C allele of the +869T/C polymorphisms in TGF β 1 strongly associated with an increased risk of asthma development in several studies. Other variants such as the A allele of the +2753G>A TGF β 3 polymorphism or the G allele of the rs2796822 polymorphism in TGF β 2 have also been shown to

influence asthma development, albeit only by single studies carried out on ethnically homogeneous populations. Importantly, the results of studies on $-509C/T$ and $+869T/C$ exhibit strong discrepancies across studies carried out on differing populations, preventing current knowledge on these associations from being applied clinically.

As previously discussed, using the $-509C/T$ polymorphism an example, most studies of asthma-associated alleles show poor reproducibility across genetically diverse populations, which is likely due to variability in the distribution of genetic risk alleles in different ethnicities and differences in the prevalence of gene polymorphisms associated with increased risk of asthma development (110). This lack of reproducibility may reflect genetic heterogeneity underlying the variation in asthma phenotypes. Differences in the allele frequencies of asthma-predisposing genes have been shown between the Chinese population and Central European white, Puerto Rican and Yoruba African populations (111). Additionally, studies carried out on the same polymorphism can lead to disparate results in different age groups, even within the same ethnicity (92).

Table 1 Contains a summary of all the SNPs described here and their association with asthma occurrence.

Limitations of current studies, GWAS and future perspectives

Importantly, all of the studies described in this manuscript so far were candidate gene studies or meta-analyses of such studies. This type of studies focuses on specific genes hypothesized to be involved in a particular disease, selected based on established knowledge or biological plausibility. This approach involves examining only a limited number of polymorphisms within the chosen genes of a sample population. It is useful in cases of a known strong association between a gene and a disease, but not for discovering novel associations (112). Indeed, this approach has several limitations. It requires prior knowledge, which limits the rate of novel association discoveries, and can introduce bias. What is more, a small range of hand-picked genes may not reflect

TABLE 1 Characteristics of single nucleotide polymorphisms (SNPs) of *TGFB* genes studied for association with asthma occurrence.

NCBI SNP ID	Gene	Location	Alleles	Minor allele	MAF	Studied population (ethnicity, mean age \pm SD)	Odds ratio, <i>p</i> value	Association with asthma
rs1800469	<i>TGFB1</i>	promoter	C/T	C	0.497	Polish, 47 \pm 16 (60); Hispanic, non-Hispanic white, aged 10–16 ^a (67); Pakistani, aged 4–15 ^a (78); Chinese, children ^a (80)	(60); 0.98, < 0.05 (67)	Elevated plasma <i>TGFB1</i> levels, increased risk of bronchial remodelling and asthma development (60, 67) No association with asthma (78, 80);
rs1982073	<i>TGFB1</i>	exon	C/T	T	0.461	Costa Rican, aged 6–14 ^a (57);	–2.58 ^b , 0.009 (57)	Lower risk of asthma exacerbations (57)
rs8179181	<i>TGFB1</i>	intron	C/T	T	0.076	Mexican, aged 4–17 ^a (59)	1.48, 0.04 (59)	Increased risk of childhood asthma and atopy, increased disease severity and <i>TGFB1</i> mRNA levels (59)
rs4803455	<i>TGFB1</i>	intron	C/A	A	0.476	Dutch, no age given (41)	–11.4, 0.03 (41)	Accelerated FEV1 decrease, increased risk of asthma occurrence (41)
rs11083616	<i>TGFB1</i>	intron	G/A	A	0.446	Polish, 46 \pm 16 (42)	1.85, 0.02 (42)	Increased asthma symptom severity (42)
rs2796821	<i>TGFB2</i>	intron	C/T	C	0.291	Polish, 46 \pm 16 (42)	1.71, 0.02 (42)	93% increased risk of asthma (heterozygous form), 102% increased risk of asthma (homozygous form) (42)
rs10779329	<i>TGFB2</i>	intron	C/T	C	0.421	Polish, 46 \pm 16 (42)	1.72, 0.02 (42)	Increased risk of asthma occurrence (42)
rs4903359	<i>TGFB2</i>	intron	G/A G/C G/T	G	0.201	Polish, 46 \pm 16 (42)	0.74, 0.05 (42)	Increased risk of asthma occurrence (42)
rs8109627	<i>TGFB1</i>	intron	C/T	C	0.351	Polish, 48 \pm 15 (7)	1.45, 0.01 (7)	Increased ACT scores (7)
rs2796822	<i>TGFB2</i>	intron	A/G	A	0.401	Polish, 48 \pm 15 (7)	1.97, 0.04 (7)	Decreased ACT scores, 71% increased risk of severe asthma (7)
rs2241715	<i>TGFB1</i>	intron	A/C A/G	A	0.341	Pakistani, aged 4–15 ^a (78); Thai, 26 \pm 19 (79)	0.24, 0.02 (78)	Increased risk of asthma development (78); No association with asthma (79)
rs11466345	<i>TGFB1</i>	intron	T/C	C	0.126	Thai, 26 \pm 19 (79)		No association with asthma (79)
rs1800470	<i>TGFB1</i>	missense	G/A G/C	G	0.427	Chinese, children ^a (80).		No association with asthma (80)
rs2241712	<i>TGFB1</i>	promoter	C/T	C	0.302	Chinese, children ^a (80).		No association with asthma (80)

MAF, minor allele frequency.

^aNo mean participant age specified.

^bZ-score.

the complexity of the pathophysiology and etiology of a disease by not examining the wider genomic context (112).

On the other hand, genome-wide association studies (GWAS) utilise a hypothesis-free approach, and scan the entire genome via modern techniques such as next-generation sequencing (NGS), which has revolutionised the field of genetics. This approach examines millions of SNPs across the whole genome, and usually requires a large study population, which can be difficult to recruit. The major advantage of GWAS is its ability to discover numerous novel associations and create a comprehensive view of the entire genomic complex of a studied disease. Additionally, GWAS can detect variants with small effect sizes or rare variants with larger effects far more efficiently than candidate gene studies (113, 114).

Numerous GWAS have been published on asthma, however most of them do not describe any associations between the disease and TGF- β genes (115–117). Nevertheless, a number of genome-wide studies have found associations of asthma and genes related to TGF- β , or TGF- β genes themselves and other conditions affecting the airways. A GWAS conducted on a UK Biobank, including over 50,000 asthmatic subjects and over 350,000 controls led to the discovery of a causal association between TGFBR1 and asthma development, however no particular gene variants were described (118). Another GWAS described an association between asthma and two SNPs in the GSDMB gene (rs2305480 and rs11078927), which is implicated in TGF- β signalling (119). Several SNPs of SMAD3 (rs16950687, rs1729363, rs744910) the protein product of which is a downstream signalling component of TGF- β and important for regulatory T-cell and TH17 cell pathways, have been associated with asthma in several GWAS (120–122). Importantly, in a GWAS conducted on Mexican subjects with childhood asthma, rs2241715 in TGFBI has been associated with an increased risk of asthma development. However, the study included only 492 subjects, which is not sufficient for a comprehensive GWAS analysis (123). In a 2011 GWAS conducted on 48,201 European subjects, TGFBI2 was found to be a locus strongly associated with pulmonary function (124).

Lastly, two GWAS analyses have found associations between chronic obstructive pulmonary disease (COPD) and loci within TGFBI2 (125, 126).

However, despite the numerous candidate gene studies and several GWAS linking TGF- β and related genes to asthma, so far this data has not been applied clinically. In general despite many novel asthma target genes being identified recently, not many of these discoveries have been used in the clinical environment. A major hurdle in applying GWAS findings is the unclear relationship between the novel gene-disease associations and biological mechanisms underlying them (117). Identification of drug targets, such as classical surface receptors and genomics-based drug repositioning, for drugs such as soproxil, olamkicept or inarigivir have been proposed as potential application of GWAS data in asthma (117). However, much GWAS data is still missing for asthma. Many asthma-related genes are missing functional annotations in GWAS, and many cell types relevant to asthma have not had expression quantitative trait locus (eQTL)

mapping carried out. Mechanistic links between SNPs identified through GWAS and gene expression in asthma have to be established and validated in cell types involved in asthma pathogenesis (117).

Epigenetic studies are another recent approach used to study relationships between asthma, pharmacological interventions and the human epigenome. These studies have improved our understanding of the molecular basis of treatment response to corticosteroids, bronchodilators and immunotherapy, and how those pharmaceuticals interact with immune and inhibitory pathways, such as IL-2, TNF- α , NF- κ B, and C/EBPs (127). Histone modifications are another layer of the epigenome, for which associations with allergic phenotypes, including those related to asthma, were discovered (128).

Importantly, several of these studies have discovered associations with TGF- β signalling pathways. In an epigenetic study of nasal epithelia taken from asthmatic Puerto Rican children, epigenomic responses to albuterol treatment in 22 genome-wide significant CpGs were characterised. TGFBI was found to be one of the genes, the methylation patterns of which were influenced by albuterol treatment (129). RUNX3, a gene involved in TGF- β signalling, was found to have disparate methylation patterns in peripheral blood leukocytes from children with atopic asthma and non-asthmatic children (130). A genome-wide DNA methylation study examining leukocytes from asthmatic Latino children identified associations between epigenetic regulation of leukocytes and inflammatory signalling pathways. The strongest associations in this study were found for the TGF- β signalling pathway (131). A comprehensive evaluation of these epigenetic associations has the potential to contribute significantly to precision medicine development and new therapeutic target discovery. What is more, epigenetic patterns (including those of the TGF- β pathways) may provide novel tools in the diagnosis of allergic disorders and asthma.

Conclusions

Asthma exacerbations remain a significant burden for patients, especially young children (132–135). The TGF- β gene polymorphisms discussed in this review show potential as diagnostic factors. In particular, T allele of the -509C/T and C allele of the +869T/C polymorphisms in TGFBI were shown to strongly associate with the risk of asthma development. Diagnostic use of these polymorphisms may facilitate earlier and more accurate diagnosis of asthma, allowing appropriate therapy to be initiated and the frequency of exacerbations to be reduced. However, nearly all of the studies published on the associations between TGF- β gene polymorphisms are based on candidate gene studies, and the representation of different ethnic groups should be improved. More studies based on robust and modern methods such as GWAS or NGS techniques, and focused on both genomic and epigenomic associations, need to be carried out on genetically diverse populations to provide stronger evidence and apply TGF- β gene polymorphisms in clinical practice as asthma development risk biomarkers.

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