



The role of inflammatory cytokines in the development of idiopathic subglottic stenosis

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Idiopathic subglottic stenosis (iSGS) is a debilitating extrathoracic obstruction involving the lower laryngeal and upper tracheal airway. It arises without a known antecedent injury or associated disease process. iSGS is a fibrotic disease marked histologically by excessive accumulation of fibrous connective tissue components of the extracellular matrix (ECM, i.e., collagen and fibronectin) in inflamed tissue, which leads to airway obstruction and clinical dyspnea. Diverse diseases in divergent organ systems are associated with fibrosis, suggesting common pathogenic pathways. One of the most common is sustained host inflammation. Recent investigations focusing on the inflammatory response associated with iSGS have sought to characterize the immunophenotype and cytokine profile of the airway scar in iSGS. While the role of the immune response as inciting event in iSGS remains unresolved, the centrality of an active immune response to the observed subglottic tissue remodeling is becoming more defined.

Keywords: Idiopathic subglottic stenosis (iSGS); immunity; interleukin-17A (IL-17A); transforming growth factor beta (TGF- β)

Submitted Jul 08, 2019. Accepted for publication Dec 05, 2019.

doi: 10.21037/tcr.2019.12.37

View this article at: <http://dx.doi.org/10.21037/tcr.2019.12.37>

Introduction

Idiopathic subglottic stenosis (iSGS) is a debilitating extrathoracic obstruction involving the lower laryngeal and upper tracheal airway. It arises without known antecedent injury or associated disease process. iSGS is clinically rare, almost exclusively affects Caucasian females between the ages of 40–60 years (1). Persistent mucosal inflammation and a localized fibrotic response are hallmarks of the disease. Despite the initial clinical description of iSGS more than 40 years ago (2), the pathogenesis of this disease remains an enigma. Due to the progressive nature of this disease, surgical interventions aimed at increasing airway diameter are the primary treatment modality (3).

Surgical strategies for iSGS range from endoscopic interventions (focused in increasing airway diameter

through dilation) (1) to open cricotracheal resection (CTR) (4,5). Endoscopic dilation is safe and effective but often only temporizing (1,6). Alternatively, durable success with CTR is higher but is associated with greater postoperative phonatory disability (5,7,8). Likely as a consequence of the surgical approach to treatment, our understanding of iSGS has historically been based on histopathology.

Pathogenesis of iSGS

Investigations have repeatedly demonstrated pathologic extracellular matrix (ECM) deposition in the subglottic lamina propria (8–10). The pathology of fibrosis is defined by excessive accumulation of fibrous connective tissue components of the ECM (i.e., collagen and fibronectin)

in inflamed tissue (11), which in iSGS leads to airway obstruction. Common to all fibrotic diseases is the presence of activated ECM-producing fibroblasts, which are the key mediators of tissue remodeling and the end effector cell in fibrosis (12). During equilibrium, tissue-resident fibroblasts are in a quiescent state, although they are metabolically active and provide biomechanical support. To repair, regenerate and restore homeostasis after injury, these tissue-resident fibroblasts are activated and increase their rate of ECM synthesis as well as their resistance to apoptosis (12). In iSGS, fibroblasts isolated airway scar has been shown to be hyperproliferative and hyperfunctional (9,10,13).

Fibroblast activation, proliferation and survival are mediated by a variety of secreted, soluble and physical factors. Transforming growth factor beta (TGF- β) has been implicated as a “master switch” in induction of fibrosis in multiple tissues including the lung. TGF- β is upregulated in lungs of patients with idiopathic pulmonary fibrosis (IPF), and in animal models expression of TGF- β induces a dramatic fibrotic response, whereas the inability to respond to TGF- β affords protection from bleomycin-induced fibrosis (14). Strong data supports a role for interleukin-17A (IL-17A) in the induction of fibroblast TGF- β , and subsequent autocrine activation of ECM genes *COL1A2*, *COL3A1*, *FN1*, and *MMP9* (15). Recent work has provided a mechanistic link between the observed IL-17A upregulation, TGF- β pathway activation, and increased ECM gene expression in iSGS (13). Fibroblasts are known to manifest unique gene expression patterns in fibrotic disease, and consequently, display unique form and function. Yet, surprisingly little is known about the molecular mechanisms that orchestrate their pathologic phenotype or the epigenetic determinants responsible for clinical fibrosis.

Diverse diseases in divergent organ systems are often hallmarked by fibrosis, suggesting common pathogenic pathways (16). One of the most common findings is sustained host inflammation. Recent investigations focusing on the inflammatory response associated with iSGS have sought to characterize the immunophenotype and cytokine profile of the airway scar in iSGS. While the role of the immune response as inciting event in iSGS remains unresolved, the centrality of an active immune response to the observed subglottic tissue remodeling is becoming clearer.

The immune response and cytokine signaling in iSGS

Recent attempts to characterize the inflammatory

infiltrate on iSGS have utilized immunohistochemical and flow cytometric analysis to identify specific immune cell types present in iSGS tissue. The results of this have demonstrated an inflammatory infiltrate primarily comprised of T-cells as indicated by the cell surface marker cluster of differentiation 3 (CD3) (9,13). Interestingly, T-cells have been implicated in the pathogenesis of multiple disease states that are characterized by fibrosis. IPF, a more well-defined fibrotic disease similar to iSGS which results in the accumulation of ECM around the alveoli, has been related to a chronic maladaptive T-cell immune response (17,18). Continued investigation into the underlying immune response in iSGS as well as other fibro-inflammatory conditions will hopefully result in identification of shared disease mechanisms and lead to global treatment strategies for disease processes characterized by fibrosis.

IL-23/17A signaling axis

Expansion of research investigating T-cell phenotypes over the past 15 years has led to the identification of unique roles for multiple T-cell subtypes including Th1, Th2, Th17 cells, and T-regulatory cells. Recognition of these phenotypes has thus inspired investigation into the immunophenotype and associated T-cell signaling pathways in fibrotic disease, including iSGS.

Mucosal biopsies of obstructive airway scar in iSGS demonstrate increased protein and mRNA expression of IL-17A. IL-17A is secreted from local inflammatory cells secondary to stimulation from upstream IL-23, which was also demonstrated to be increased in iSGS tissue (9). IL-17A is an inflammatory cytokine with a demonstrated role in tissue injury at epithelial and mucosal barriers. Although crucial in protecting the host from invasion by many types of pathogens, dysregulated IL-17A production can drive chronic inflammation (19-21) with subsequent tissue damage and fibrinogenesis (22,23). IL-17A is also specifically implicated in many inflammatory lung diseases, including asthma (20,24), cystic fibrosis (21) and chronic obstructive pulmonary disease (19). Additionally, several studies in the last 5 years have linked IL-17A and the development of fibrotic lung disease. Human studies offer strong support for a critical role of IL-17A in the pathogenesis of obliterative bronchiolitis seen after pulmonary transplant (22). The expression of IL-17A is derived from immune cells located in non-lymphoid tissues where they are poised to respond immediately to tissue

injury or pathogenic insults. Stimulation of these cells by IL-23 induces local tissue inflammation, which is mainly mediated by IL-17A (25). However, the mechanisms governing IL-17A-mediated fibrosis in pulmonary fibro-inflammatory disease remain poorly understood.

In an attempt to delineate the role of IL-17A in iSGS Morrison *et al.* showed that IL-17A promotes proliferation of fibroblasts isolated from iSGS scar. Additionally, IL-17A synergizes with TGF- β to drive increased collagen production in fibroblasts associated with iSGS scar (13). The cooperative effects of TGF- β and IL-17A may be mediated by increased expression of TGF- β receptor on fibroblasts. Additionally, IL-17A directly stimulated scar fibroblasts to produce chemokines (chemokine ligand 2) and cytokines (IL-6 and granulocyte-macrophage colony-stimulating factor) critical to the recruitment and differentiation of myeloid cells (13).

TGF- β

TGF- β has been well-defined as a pro-fibrotic cytokine that is secreted by numerous cell types including fibroblasts. Multiple disease processes hallmarked by fibrosis have demonstrated that TGF- β , and its related signaling pathways, are up-regulated and contribute to fibrosis (26). TGF- β signaling occurs through an initial activation in which the inactive form of TGF- β catalyzed to its active isoform (27). Activated TGF- β then binds to a transmembrane receptor that leads to activation of intracellular signaling proteins known as Smad proteins. These Smad proteins have been shown to modulate the transcription of procollagen 1 and 3 (28). In preclinical models of fibrosis, inhibition of TGF- β signaling has been shown to reduce collagen deposition and attenuate fibrosis.

In tissue samples from iSGS it has been demonstrated that the TGF- β is up-regulated compared to control tissue (29). The aforementioned association of TGF- β and fibrosis coupled with upregulation of TGF- β in iSGS has justified preclinical attempts to inhibit TGF- β signaling in models of subglottic stenosis in a hope of developing novel treatment strategies. In a rat model of subglottic stenosis treatment with TGF- β neutralizing antibodies led to a significant reduction in ECM expression (30). Moreover, similar results were observed in a canine model of subglottic stenosis when treated with anti-TGF- β (31). While these studies have demonstrated some potential to attenuate disease in subglottic stenosis, this strategy has not been adopted as a contemporary treatment for iSGS patients.

IL-4

Brush biopsy samples obtained from iSGS scar have also revealed increased expression of the Th2 cytokine IL-4. This response appeared conserved across multiple disease subtypes, as both patients with iSGS and those who developed their stenosis after endotracheal intubation showed elevated IL-4 mRNA levels (10). Interestingly, other diseases hallmarked by fibrosis such as IPF, renal fibrosis, and hepatic fibrosis have been shown to have an accentuated Th2 mediated CD4⁺ T-cell response potentially indicating a shared pathogenic mechanism underlying all of these fibrotic conditions (32).

IL-4 is a dynamic cytokine with a wide array of function including immunosuppression, macrophage and T-cell differentiation, wound healing, and chronic fibrosis. Mast cells and basophiles, natural killer cells, and CD4 T-cells represent the primary source of IL-4. IL-4 signaling is mediated through Janus kinase (JAK) related phosphorylation of signal transducer and activator of transcription family protein 6 (STAT-6). IL-4 signaling in fibroblasts via the STAT-6 signal transduction pathway has been shown to increase collagen expression (33,34).

In these disease states IL-4 represent an attractive target for disease modulation; however, preclinical and clinical attempts at blockade have been met with disappointing results.

Interferon gamma (IFN- γ)

IFN- γ has been implicated in fibrosis in multiple organ systems. In animal models of pulmonary fibrosis IFN- γ production has been shown to be upregulated. In a bleomycin-induced model of IPF using C57BL/6 mice, IFN- γ mRNA peaked 3 days after injury and protein levels increased at 6 days. CD4⁺, CD8⁺, and natural killer cells each contributed significantly to IFN- γ production (35). The role of IFN- γ in fibrosis is less clear with conflicting data that suggests both a pro-fibrotic and an anti-fibrotic role. IFN when comparing the effect of bleomycin in IFN- γ knockout mice to wild type mice, lung hydroxyproline content was reduced in IFN- γ knockouts. Conversely, attempts at increasing IFN- γ through immunomodulatory strategies have demonstrated a protective role for IFN- γ in pre-clinical models of IPF (36,37).

In human studies of iSGS, endolaryngeal brush biopsy generated sufficient RNA quantity and quality for gene expression. iSGS patients demonstrated a significant

elevation in *IFN- γ* gene expression compared to matched normal controls. Furthermore, *IFN- γ* expression in the iSGS samples was significantly higher than patients who developed subglottic stenosis following endotracheal intubation [iatrogenic laryngotracheal stenosis (iLTS)]. There was no significant difference in *IFN- γ* expression in iLTS samples compared to matched normal controls ($P=0.82$) potentially indicating a biomarker that can be used to differentiate iSGS and iLTS (10). In an *in-vitro* model of iLTS airway scar, *IFN- γ* reduced collagen-1 gene expression and soluble collagen production as well as inhibited fibroblast proliferation (38).

While the cause of this increased *IFN- γ* expression is unclear it is possible that it is related to the increased population of $\gamma\delta$ T-cells associated with iSGS, which have been shown to be potent producers of *IFN- γ* (9). Additionally, mycobacterium species, which have been shown to be present in a significant majority of patients with iSGS, are also potent inducers of *IFN- γ* secretion (39). Further research on the source and role of *IFN- γ* in iSGS is clearly needed to define its contribution to the pathophysiology of this disease.

Preclinical models of iSGS

A barrier to our scientific understanding of iSGS is lack of a suitable animal model of disease. A number of animal models of subglottic stenosis have induced airway scar via direct mechanical tissue injury (electrocautery, traumatic brush, and chemical injury) Similar to models of IPF, bleomycin has been used to propagate scar formation. Hillel *et al.* (40) describe a mouse model of subglottic stenosis where pathologic scar tissue is invoked through chemomechanical disruption of the subglottic lamina propria with a wire brush coated with bleomycin. While all of these models effectively create subglottic scar, they likely are not representative of iSGS which lacks an antecedent history of subglottic injury. Knowing this, it is very hard to draw conclusions about iSGS pathogenesis from current animal models. The development of a more applicable animal model of iSGS is needed to improve our understanding of pathogenesis and allow for investigation of translational treatment strategies.

Translating scientific insight to clinical impact

Medical therapies aimed at reducing the host inflammatory response, or slowing the deposition of pathologic ECM have

been employed in iSGS. However strong data is lacking to demonstrate clear benefit. Application of topical mitomycin C, which is an antineoplastic agent that inhibits fibroblast proliferation and function, has been commonly used during routine endoscopic dilation procedures (41,42). While a theoretical beneficial; investigation into its utility has demonstrated conflicting data in regards to added benefit (6,43). Subepithelial steroid infusion is another strategy that has been utilized to moderate the rate of restenosis in iSGS patients. Corticosteroids exert broad transcriptional changes in both infiltrating immune cellular subsets, as well as local fibroblasts. Small retrospective cohort studies of serial office-based steroid injections suggest an ability to increase airway diameter and potentially reduced the need for repeat dilation (44,45). However more rigorous prospective blinded studies are necessary to define the degree and duration of injected corticosteroids.

Conclusions

iSGS a rare fibrotic disease of the subglottic mucosa affecting adult Caucasian females. Persistent mucosal inflammation and a localized fibrotic response are hallmarks of the disease. Recent study has begun to uncover the role of several key inflammatory cytokine-signaling pathways in the disease. Deeper mechanistic insight coupled with translational human study will be necessary to further define the role of these cytokines in disease pathogenesis and allow for new therapeutic approaches.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Benoit Jacques Bibas, Paulo Francisco Guerreiro Cardoso and Konrad Hoetzenecker) for the series “Recent Developments in Benign Tracheal Stenosis” published in *Translational Cancer Research*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2019.12.37>). The series “Recent Developments in Benign Tracheal Stenosis” was commissioned by the editorial office without any funding or

sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Motz KM, Gelbard A. The role of inflammatory cytokines in the development of idiopathic subglottic stenosis. *Transl Cancer Res* 2020;9(3):2102-2107. doi: 10.21037/tcr.2019.12.37