REVIEW

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JAK-STAT and intestinal mucosal immunology

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Abbreviations: sIgA, secretory IgA; Ig, immunoglobulin; PP, Peyer patches; MAdCAM-1, mucosal addressin adhesion molecule-1; HEV, High endothelial venule; pIgR, polymeric immunoglobulin receptor; M, microfold; TLR, toll like receptor; AS, ankylosing spondylitis; CD, Crohn disease; IBD, inflammatory bowel disease

The intestinal mucosal immune system is challenged with bacteria, viruses, and parasites, in addition to food and environmental antigens, that require dynamic immune responsiveness for homeostasis. One central signaling pathway is JAK-STAT, which regulates the adaptive and innate immune arms of mucosal immunity as well as epithelial repair and regeneration. Adaptive immunity includes lymphocyte mediated secretion of specific antibodies, while innate immune respones include secretion of non-antigen specific compounds. This review examines effects of specialized nutrition support on JAK-STAT in innate immune function and in lymphocyte modulation and epithelial antibody transport in gut-associated lymphoid tissue.

Introduction

The human intestine contains large numbers of bacteria that exist in symbiosis with the host in times of health. Although the bacteria are in close proximity to the mucosa, robust mucosal immune functions mediate this symbiosis to prevent invasion of the intestinal tissue and the systemic circulation by bacteria. Barrier integrity is multifactorial and includes contributions from both the adaptive and the innate mucosal immune system.[1] Innate defenses include the mucus covering of the epithelium produced by goblet cells,[2,3] antimicrobial peptides and proteins produced and released by Paneth cells,[4-7] tight junction proteins that bind the enterocytes to prevent passage of luminal components, and the commensal bacterial population themselves, which form an ecological barrier to pathogens. The adaptive immune system produces, transports and releases secretory IgA (sIgA) which work in concert with innate immunity as a complimentary but more specific arm of mucosal immunity.[8-10]

Our laboratory focuses on the effect of route and type of nutrition on mucosal immune function. Clinical studies demonstrate patients fed intravenously are at an increased risk of respiratory and intraabdominal infections compared with enteral fed patients. To investigate why this occurs, we established clinically relevant animals feeding models where nutrition is provided via the central vein or the gastrointestinal tract directly. More recently, these animal studies have included investigations of the role of Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathways on intestinal immune function. This review discusses the recognized roles of JAK-STAT signaling in intestinal mucosal immune system in the regulation of both adaptive and innate mucosal immune function.

JAK-STAT Mechanisms of Action

The JAK-STAT signaling pathway was originally discovered in the early 1990s by Darnell and Stark. These investigators studied IFN activation of genes involved in immunity and identified STAT1 and STAT2. We now recognize JAK-STAT as one of the most important pleiotropic cascades employed by cells to transduce signals for hormones, growth factors, and cytokines.[11-17] This pathway contains the Janus kinase (JAK) proteins JAK1, JAK2, JAK3, and TYK2 and the signal transducer and activator of transcription (STAT) proteins STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. JAK-STAT provides the principle intracellular signaling mechanism required for a wide array of cytokines, including IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-13, IL-15 IFN-γ, and others.[16-18] In addition to cytokines, JAK-STAT signals the effects of chemokines, hormones and growth factors. In general, ligand binding induces JAK phosphorylation that become competent to subsequently phosphorylate residues on assorted STAT proteins, which otherwise remain latent in the cytoplasm. Among other functions, JAK-STAT signaling is implicated in cell development, cell growth and survival, and therefore has important implications in immune function. For example, STAT proteins play vital roles in the differentiation of T helper lymphocyte cells.

Adaptive Mucosal Immunity and the Mucosal Associated Lymphoid Tissue (MALT)

The mucosal immune system comprises ~60% of the body's total immunity and produces ~80% of total immunoglobulin (Ig) per day.[19] This system is tasked with defending the large mucosal surfaces of the body, including the respiratory tract, gastrointestinal

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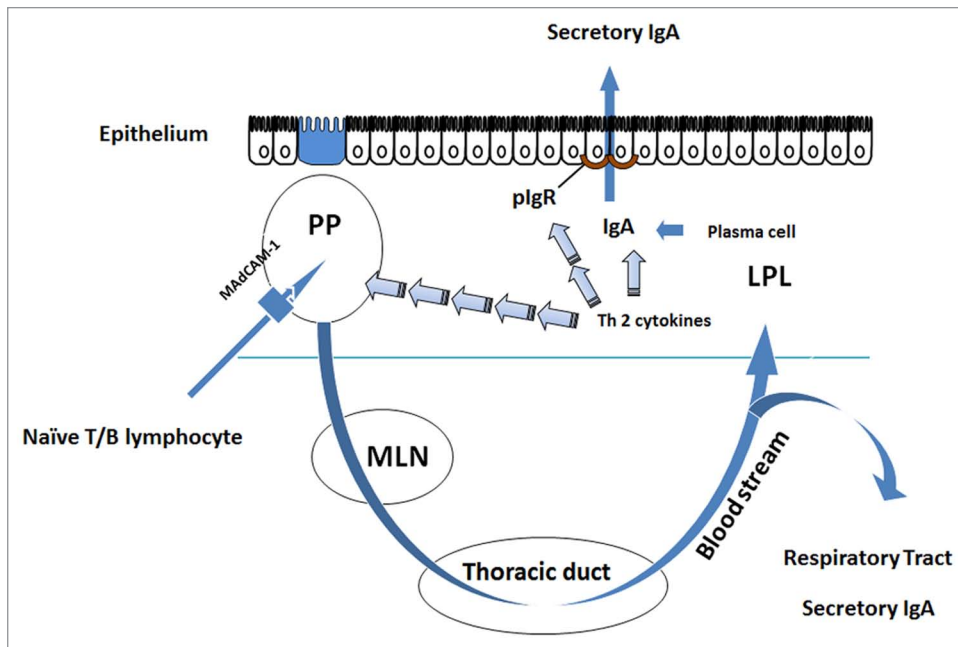
Figure 1. Adaptive mucosal immune function in the small intestine. Naïve T and B lymphocytes enter the Peyer patches (PP) via interaction with their integrins L-selectin or α4β7 and MAdCAM-1 which is present on the high endothelial venules (HEV) of the PP. The cells are sampled and sensitized to antigen in Microfold (M) cells inside the PP. Sensitized cells return to the peripheral circulation via the thoracic duct and are distributed to other mucosal effector sites. Within these effector sites, Th2 cytokines (IL-4, IL-5, IL-6, and IL-10) produced by T lymphocytes stimulate maturation of B cells into competent IgA producing cells, i.e., plasma cells. These cells produce the principal molecule of adaptive immunity, dimeric IgA, in the lamina propria where it undergoes transepithelial transport via polymeric immunoglobulin receptor (pIgR) which is expressed on the basal surface of mucosal enterocytes.

tract, uro-genital tract, nasal passages, and mammary glands.[20,21] To defend these surfaces, the hallmark molecule of acquired immunity is specific and non-specific secretory IgA (sIgA) at mucosal surfaces.[22] sIgA neutralizes bacteria through opsonization providing immune exclusion. Bacteria are also bound and neutralized in the mucus layer, limiting their ability to directly attach and invade tissues. The adaptive mucosal immune system is organized into inductive sites, for antigen sensitization, and effector sites, where IgA is produced and released. Circulating naïve B and T cells enter the Peyer patches (PP) through interactions between L-selectin and α4β7 expressed on the circulating lymphocytes and mucosal addresin adhesion molecule-1 (MAdCAM-1) expressed on the high endothelial venules (HEV) of the PP.[23-25] After stimulation and sensitization in PP, T and B lymphocytes migrate via lymphatics to the thoracic duct for distribution into the vascular system and homing to effector sites, such as the lamina propria of the intestine.[26] Within these effector sites Th2 cytokines (IL-4, IL-5, IL-6, and IL-10) produced by the T lymphocytes stimulate maturation of B cells into competent IgA producing cells, i.e., plasma cells. These cells produce dimeric IgA, comprised of 2 IgA monomers linked by a small peptide called J-chain.[27] The dimeric IgA produced in the lamina propria then undergoes transepithelial transport via polymeric immunoglobulin receptor (pIgR) expressed on the basal surface of mucosal enterocytes (**Fig. 1**). Within the lumen, sIgA provides protection at mucosal surfaces by attaching to bacteria

and preventing bacterial attachment to the mucosa[28] and by reducing expression of virulence factors by enteric pathogens.[29] JAK-STAT signaling regulates several aspects of adaptive immunity, including Th differentiation, B cell maturation, and production of the transport protein pIgR.

Th1 and Th2 Differentiation Requires IL-4, IL-12, STAT4, and STAT6

Naïve CD4+ lymphocytes are classically understood to differentiate into one of two subsets: Th1 or Th2 cells.[30,31] Each subset generates unique cytokine profiles with distinct functions.[32] IL-12 and IL-4 are the key cytokines that are involved in the differentiation of Th1 and Th2 responses, respectively.[33,34] Differentiated Th1 cells produce and release IL-2, TNF-α, and IFN-γ that promote cell-mediated immune function. Differentiated Th2 lymphocytes release IL-4, IL-5, IL-10, and IL-13, which promote B cell function and humoral mediated immunity. A balance between the Th2-type secreted cytokines (IL-4, IL-5, IL-6, and IL-10), which stimulate IgA production, and the Th1-type secreted cytokines (IFN and TNF), which inhibit IgA production, is required for appropriate humoral responsiveness (**Fig. 2** and **Table 1**).

Complete development of the Th1 response requires IL-12 signaling of STAT4 while Th2 response requires IL-4 signaling of STAT6. Mouse studies using knockout mice demonstrate the importance of these two responses and the requirement for JAK-STAT signaling. Mice with insufficient expression of IL-12 or IL-12Rβ1 chain fail to generate Th1 cells, while mice with insufficient expression of IL-4 or IL-4Rα chain fail to generate a Th2 response.[35-40] Furthermore, elevated activation of one response appears to suppress the other. For example, Th2 responses generate SOCS3 activation that inhibits Th1 signaling while Th1 responses prevent full activation of the transcription factor GATA3 that is necessary for Th2 differentiation.

STAT4, originally thought to be expressed only in lymphoid cells, is also expressed in monocytes, macrophages, and dendritic cells.[41] Under the direction of microbial signals from the gut, dendritic cells and macrophages are activated and secrete IL-12. When antigen is sensed by these cells, IL-12 induces STAT4 phosphorylation that promotes maturation of naïve CD4+ cells into Th1 cells that produce and secrete IFN-γ, a pro-inflammatory cytokine[42,43] (**Fig. 2** and **Table 1**).

The cytokines IL-4 and IL-13 induce STAT6 phosphorylation and activation through several receptors depending on cell type. Type-II IL-4 receptors, expressed on non-hematopoietically derived cells, consist of IL-4Rα1 and IL-13Rα1 chains and are activated by both IL-4 or IL-13. Type-I receptors, expressed on hematopoietically derived cells such as lymphocytes, consist of IL-2Rγ and an IL-4Rα1 chain and are activated only by the cytokine IL-4.[13] Following binding of IL-4 and IL-13 binding to the IL-4 receptor (IL-4R), activated JAK proteins then phosphorylate a tyrosine residue on STAT-6, which is otherwise latent in the cytoplasm.[44] Uniquely, IL-4 and IL-13 induce tyrosine or serine phosphorylation and activation of STAT-6. Studies demonstrate STAT6 dependence for the maturation of CD4+ naïve cells into Th2 effector cells.[45] Additionally, in the Peyer's patches, IL-4 signaling via STAT 6 is essential for B cell development and class switching to IgA+ cells.

Th17 Differentiation Requires IL-6, TGFβ, and STAT3

Recent studies demonstrate additional T helper cell lineages, including the Th17 cells that selectively induce expression of the pro-inflammatory cytokines IL-17, IL-21, and IL-17F. Emerging data demonstrate the direct role of Th17 responses in protecting the host mucosal surfaces from extracellular pathogens, including bacteria and fungi.[46-50] Complete development and differentiation of the Th17 response requires the cytokines IL-6, IL-21, and IL-23 and signaling through STAT3. Specifically, IL-6 binds the IL-6R inducing IL-21, which drives subsequent expression of IL-23R. Once expressed, IL-23R binds IL-23 produced and released by activated antigen presenting cells. IL-6 synergizes with TGF-β to promote expression of IL-17 and other Th17 lineage cytokines, including IL-22 and IL-17F. In the absence of IL-6, TGF-β promotes Foxp3 expression and expansion of the Treg lymphocytes, a T cell subset that provides intestinal immune homeostasis. The role of STAT3 in Th17 differentiation is demonstrated in mice where altered Th17 production is either impaired in mice that were abalted for T cell STAT3 expression or augmented in mice with overexpressed STAT3. CD4+ T cells are imperative in promoting the adaptive immune response by producing and secreting specific cytokine profiles that activate an appropriate immune response. Th1 cells provide protection from intracellular organisms, such as viruses, while Th2 responses are necessary to defend the mucosa from extracellular pathogens. Finally, Th17 cells provide defense against extracellular bacteria and fungi (**Fig. 2** and **Table 1**).

B Cell Maturation Requires STAT5 Activation by IL-7R

IL-7 is a cytokine that is integral to normal T and B cell development during lymphopoiesis and normal T and B cell function are essential to a proper antibody response by the mucosal immune system. IL-7 mediates its actions by binding to the IL-7R, consisting of the IL-7Rα chain and the γ chain (γc). Early stages of lymphocyte development require IL-7Rα, which is commonly expressed by lymphoid progenitor cells.[51,52] After IL-7 binding to
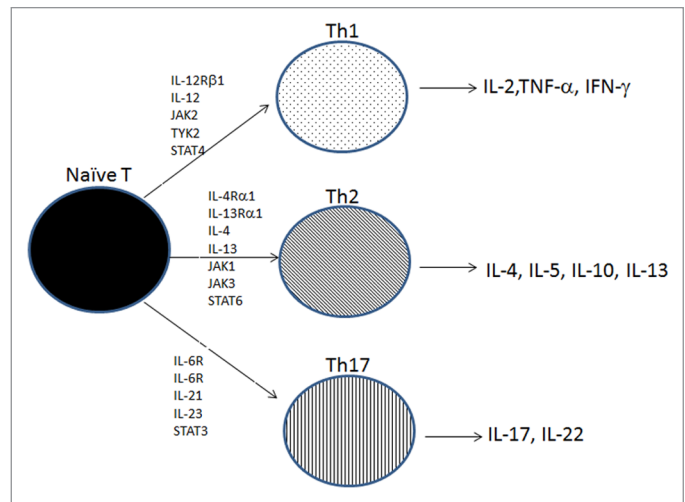
Figure 2. JAK-STAT and T helper cell differentiation of naïve T cells. Naïve T cells differentiate into several T helper cell subsets, Th1, Th2, of Th17. IL-12 is required for the differentiation into Th1 cells that secrete IFN-γ, TNF-α, and IL-2 to generate a response to intracellular pathogens. IL-4 is required for the differentiation into Th2 cells that secrete IL-4, IL-5, and IL-10 to generate defenses against Helminth infections. IL6, IL-21, and IL-23 are required for the differentiation into Th17 cells that secrete IL-17 and IL-22 to promote defense against extracellular pathogens.

the IL-7Rα, JAK1 and JAK3 are activated[53] and phosphorylate STAT5. After phosphorylation, STAT5 dimerizes and translocates to the cell nucleus. Ablation of the cytokine IL-7,[51] the receptors IL-7Rα[52] and γc,[54,55] or the proteins JAK1 or JAK3[56] impairs normal B cell development in mice. STAT5 consists of two isoforms: STAT5A and STAT5B.[57] Interestingly, B cell development is normal in mice lacking either isoform, but not both.[58,59] However, complete STAT5 ablation results in mice with perinatal lethality associated with reduced T and B cell numbers and impaired maturation of B lymphocytes, αβ T lymphocytes, and γδ T lymphocytes.[58,60] Studies using IL-7R−/− mice are characterized by reduced T-cell lymphopoiesis in the thymus and reduced B-cell lymphopoiesis in bone marrow. These studies demonstrate a direct role for IL-7R signaling through STAT5 in the process of T cell survival and B cell development that are essential to mounting a focused, adaptive response to antigen. Although the role of these pathways in sIgA synthesis have not been specifically investigated, JAK-STAT signaling is required for B cell maturation and plasma cell development.

sIgA Transport Protein pIgR Requires JAK1 and STAT6

The secretion of sIgA across the intestinal epithelium, via the polymeric immunoglobulin receptor (pIgR), is regulated by JAK-STAT. sIgA is the principle molecule of adaptive immunity secreted across the mucosa into the small intestinal lumen. sIgA provides antigen-specific and non-specific protection at the mucosal surfaces against ingested pathogens, microbes, and environmental antigen through several mechanisms, including immune exclusion and downregulation of bacterial virulence.

Table 1. JAK-STAT interactions regulating mucosal immunity in the intestine

Receptor	Stimulus	JAK	STAT	Produces	Process
IL-12Rβ1	IL-12	JAK2, TYK2	STAT3, STAT4	IL-2, TNF-α, IFN-γ	Th1 differentiation, defense against intracellular pathogens
IL-4Rα1, IL-13Rα1	IL-4, IL-13	JAK1, JAK3	STAT6	IL-4, IL-5, IL-10, IL-13	Th2 differentiation, mucus production, pIgR
IL-6R	IL-6, IL-21 IL-23		STAT3	IL-17, IL-17F, IL-22	Th17 differentiation, defense from extracellular pathogens, tissue inflammation
IL-7Rα	IL-7	JAK1, JAK3	STAT5a, STAT5b		B cell maturation, T cell development
IFNαR1, IFNαR2	IFNα	JAK1, TYK2	STAT1, STAT2		Anti-viral defenses
IFNγR1, IFNγR1	IFNγ	JAK1, JAK2	STAT1		Inflammatory and anti-bacterial defenses

In vitro work demonstrates that the activated STAT6 forms dimmers, translocates to the nucleus where it binds specific DNA elements and activates transcription of several products, including pIgR.[27,61-65] In addition to STAT6 mediation of pIgR by Th2 cytokines, proinflammatory cytokines also directly modulate the pIgR expression in mucosal epithelial cells.[66,67] IL-4, IL-1, TNF-α, and IFN-γ all upregulate the expression of pIgR, demonstrating the necessity of this conserved immune protein during contrasting inflammatory profiles. Signaling with the cytokine IFN-γ receptor causes activation of STAT1 dimers, while signaling from IL-4 causes activation of STAT6.

Since dietary and environmental antigens constantly stimulate the intestinal mucosa, our novel animal models study intestinal JAK-STAT signaling in the absence of enteral feeding, with the use of intravenously administered nutrition to prevent malnutrition. Initially this model was established to investigate changes in mucosal immunity that occur in clinical populations fed by intravenous nutrition. In these patients, the incidence of nosocomial pneumonia and intra-abdominal abscess is significantly greater with intravenously nutrition compared with enteral feeding, especially in the most critically ill. Animal studies demonstrate that the lack of enteral contents during intravenous feeding downregulates many aspects of intestinal immune function, including altered cytokines with reduced Th2 profiles, decreased T and B lymphocyte counts in both inductive and effector sites, reduced expression of the transport protein pIgR, and decreased levels of sIgA secretion at effector mucosal sites. Functionally, these changes result in reduced anti-viral and anti-bacterial defenses when mice are challenged with H1N1 virus and *Pseudomonas aeruginosa*, respectively.

Specific to JAK-STAT, these studies showed that parenteral nutrition—infusion of simple amino acids, sugars, minerals, and vitamins delivered directly into the central vein without enteral feeding—lowers tissue levels of IL-4, IL-13, pIgR, and luminal sIgA. Direct decreases in tissue levels of both phosphorylated JAK1 and STAT6 accompanied these changes. These data suggested the role of JAK-STAT signaling in adaptive immunity and the importance of phosphorylated JAK1 and STAT6 as mediators of pIgR transcription. A causative relationship was confirmed by administering exogenous IL-25 to the mice receiving intravenous nutrition. IL-25 stimulates production of the cytokines IL-4 and IL-13 by Th2 lymphocytes. Mice given intravenous nutrition with exogenous IL-25 had elevated tissue IL-4, IL-13, pIgR, and luminal sIgA that were associated with increases in phosphorylated JAK1 and STAT6.[68]

In another model examining the route and type of nutrition on mucosal defenses, animals were given the parenteral nutrition solution—comprised of simple amino acids, sugars, minerals, and vitamins—but delivered directly to the stomach using a gastrostomy tube. This route of feeding also lowers many parameters of intestinal immune function—since the diet contains only simple amino acids, sugars, minerals, and vitamins—but not to the degree associated with delivering the same solution into the vein without any enteral stimulation. Complex polyphenolic compounds, proanthocyanidins isolated from cranberry,[69] were added to the elemental diet to stimulate the intestinal mucosa. That study observed the administration of elemental enteral diet alone decreased levels of IL-4, IL-13, pIgR, and sIgA with associated decreases in JAK1 and STAT6. The addition of proanthocyanidins to the elemental enteral diet increased IL-4, IL-13, pIgR, and sIgA, associated with increased JAK1 and STAT6 phosphorylation, suggesting the relationship between these cytokines, JAK-STAT proteins, and pIgR expression in the animal models.

The Innate Intestinal Barrer

In addition to the transcytosis of sIgA across the enterocytes, the more basic aspect of intestinal mucosal defense is the epithelial barrier itself, which is collectively comprised of absorptive columnar enterocytes, mucin secreting goblet cells, antimicrobial secreting Paneth cells, hormone secreting enteroendocrine cells, and microfold (M) cells covering Peyer patches.[70] These cells differentiate from pluripotent stem cells located at the base of intestinal crypts of Leiberkuhn and extend to form a continuous layer of columnar epithelial cells held together by tight-junction proteins. The total mucosal surface can reach 300 m² in humans and is faced with maintaining a barrier between the host and over 100 trillion individual bacterial cells, parasites, environmental antigens, and toxins[71] (**Fig. 2**).

The epithelium responds with specific cytokine profiles when exposed to potentially infectious organisms or harmful substances. For instance, viruses, pathogenic bacteria, and bacterial components stimulate various Toll-like receptors (TLRs) at the basolateral or apical surface of epithelial cells that leads to the release of classical pro-inflammatory Th1 cytokines, such as

IFNs, inducing STAT1 activation.[72] Since persistent inflammatory responses can be harmful and sometimes fatal, maintaining the necessary interactions for proper immune and inflammatory signaling is imperative (i.e., proper release of cytokine profiles in response to bacteria, virus, fungi, etc.). Many studies have investigated these interactions, and TLR signaling emerges as one factor that directly mediates this response.[73,74] Classically, past studies focused on the role of the host in eliminating pathogenic bacteria, that required TLR signaling. Interestingly, recent studies demonstrate commensal bacteria also signal through TLR receptors. For example, the work from Medzhitov and colleagues demonstrate the necessity of TLR stimulation from commensal bacteria for the control of intestinal homeostasis and protection from injury.[75] Specifically, they examined signaling from antibiotic-treated mice and demonstrated a necessary role for commensal bacteria in facilitating a proper response to stimuli since antibiotic treatment ablated certain cytokine signaling in the colon.

Viruses stimulate IFNα while bacterial components stimulate IFNγ.[72,76] The IFNα receptor is comprised of IFNαR1 and IFNαR2 chains containing JAK1 and TYK2, where activation leads to STAT1:STAT2 dimerization and transcription of antiviral immune molecules. The IFNγ receptor is comprised of IFNγR1 and IFNγR2 chains containing JAK1 and JAK2, where activation induces STAT1:STAT1 dimerization and inflammatory and antibacterial immune responses. Other microbiome compositions, such as murine segmented filamentous bacteria, stimulate Th17 responses through TLR5 that are mediated through IL-17, IL-22, and IL-23, inducing STAT3 activation.[77] Activation of STAT3 in the epithelium stimulates antimicrobial production, such as β-defensins and RegIIIγ, and inhibits NFκB activation that can induce proinflammatory tissue injury.[78] Enteric parasites such as nematodes stimulate Th2 cytokine profiles, including IL-4, IL-9, IL-13, and IL-25, and are classically anti-inflammatory.[79] Type-II IL-4 receptors, expressed on epithelial cells, consist of IL-4Rα1 and IL-13Rα1 chains and are activated by both IL-4 or IL-13.[13] Epithelial responses to STAT6 activation during nematode infection includes downregulation of enterocyte ion absorption, increased mucous secretion by goblet cells, and release of antimicrobial compounds by Paneth cells, which aid in clearing parasites from the intestinal tract.

Goblet cells migrate to the intestinal villi tip every 3–5 d following differentiation before sloughing into the intestinal lumen. Goblet cell differentiation is stimulated by the Th2 cytokines, IL-4 and IL-13, which bind the Type-II IL-4 receptor and activate STAT6. Goblet cells produce and secrete mucin glycoproteins that are vital in maintaining barrier integrity and localize antimicrobial compounds at the epithelial surface. The primary secreted mucin in the small intestine is MUC2. Additionally, goblet cells also produce Trefoil factor 3 (TFF3) and Relmβ, compounds that are thought to stabilize the mucin layer and repair damaged epithelial cells. Cell culture lines demonstrate IL-4 and IL-13 upregulate TFF3 and MUC2 expression through STAT6 dependent mechanisms.[80] In the colon, STAT3 activation stimulates MUC1, MUC3, and MUC13 via IL-22/ JAK1.[81]

As noted, efficient clearance of nematode infection requires STAT6, where deletion of the IL-4Rα delays goblet cell expansion and slows parasite expulsion. Initial epithelial injury by parasites stimulates the release of the alarm cytokines IL-25 and IL-33, promoting Th2 lymphocyte expansion and elevated levels of IL-4, IL-5, IL-9, and IL-13. Specifically, IL-13 is required for these responses since exogenous IL-25 administration, which mimics mucosal responses to nematode, does not occur in IL-13 knockout mice.[79] Furthermore macrophages and dendritic cells, stimulated by glycans and glycolipids on the parasites surface, amplify the Th2 cytokines, as well as eosinophils and basophil expansion.

Paneth cells, in contrast to goblet cells, remain at the base of the intestinal crypts near the stem cells and secrete numerous antimicrobial compounds, including lysozyme, secretory phospholipase A_2(sPLA$_2$), RegIIIγ, Angiogenin4, and defensins (cryptidins in mice).[82] Interestingly, Paneth cells also contain elevated levels of TNF-α, IL-17, and IL-23 and are implicated in acute mucosal inflammation. During systemic TNF-α challenge, Paneth cells release large amounts of IL-17 into the mucosal immune system, making this cell type an interesting target for understanding systemic vs. mucosal immune compartmentalization. The release of Paneth cell antimicrobial compounds into the intestinal lumen have broad spectrum activity against gram-positive and gram-negative bacteria and are the major strategy for regulation microbiome composition. Murine studies demonstrate IL-13 is also required for increased Paneth cell antimicrobial expression, where absence of IL-13$^{-/-}$ or IL-4R$^{-/-}$ inhibits responsiveness.[83]

Recently, we demonstrated intravenous nutrition—with a lack of enteral feeding—results in decreased tissue and luminal levels of IL-4 and IL-13, associated with reduced STAT6 phosphorylation, and decreased levels of both the Paneth cell product sPLA$_2$ and the goblet cell product MUC2. These effects were reversible with the addition of intravenous IL-25 during intravenous feeding,[84] similar to the mucosal response to nematode infection. Interestingly, our ex vivo studies demonstrate that the loss of Paneth and goblet cell products during intravenous feeding are associated with increased susceptibility to bacterial enteroinvasivness, however, these effects are reversible when intravenously fed animals are administered IL-25.[84]

JAK-STAT Mutations in Health

Inflammatory bowel disease. JAK-STAT signaling plays crucial roles in epithelial proliferation, differentiation, and apoptosis. States of intestinal hyper-inflammation, such as the inflammatory bowel diseases (IBD) ulcerative colitis (UC), Crohn disease (CD), and ankylosing spondylitis (AS), are associated with elevated STAT signaling.[85] Since the epithelial barrier is comprised of non-hematopoietic derived cells which are in close proximity to the hematopoietically derived lymphocytes in the lamina propria, knockout studies were needed to elucidate epithelial specific STAT signaling.

Murine enterocyte specific STAT5 deletion, which is normally activated by IL-22/JAK1, increases severity of DSS-colitis

and delays wound healing following intestinal injury, perhaps through the loss of NFκB inhibition.[86] In this model, epithelial STAT5 was required for tight junction barrier integrity. Similarly, epithelial deletion of STAT3, normally activated by IL-6/JAK2, results in greater DSS-colitis severity and impaired cellular stress responses related to epithelial restitution.[87] Global knockout of STAT6 results in increased inflammation and crypt damage following DSS challenge, characterized by elevated nitrite/nitrate levels. While it remains unclear if hyperregulation of respective STAT pathways in these processes contribute toward or protect against epithelial pathogenesis in IBD, characterization of JAK-STAT signaling during the development and treatment of these intestinal diseases will further our understanding of the molecular signaling involved.

Hyper-IgE syndromes. Another disease associated with altered STAT signaling is hyperproduction of IgE. Production of IgE by plasma cells normally remains under tight regulation through stimulation by IL-4, IL-13, and IL-21 and suppression by IFN-γ, IL-10, and TGF-β. IL-4 binding of the IL-4R stimulates STAT6, leading to moderate production and release of IgE. Binding of IL-10 or IFN-γ to the IL-10R or IFN-γR stimulate STAT3, which inhibits STAT6 through STAT3 dependet mechanisms. The more recently identified role of IL-21 in IgE production in human B cells also signals through STAT3 and leads to more prominent IgE release than IL-4 or IL-13 under normal conditions.[88] However, since STAT3 also has suppressive effects upon STAT6 mediated IgE production, STAT3 mutations lead to augmented IgE production by STAT6 and is characterized by hyper-IgE pathologies in humans. Patients carrying STAT3 mutations suffer from skin allergies, lung infections, elevated serum IgE, and abnormalities in connective tissues, skeletal muscle, and the vascular system. IFN-γ therapy in these patients produces mixed results.[89]

Therapeutic Interventions

Studies continue to define the role of the JAK-STAT signaling mutations and subsequent effects upon human health and disease, including immune diseases, cancer, and inflammatory disorders. These studies have identified mechanisms and pathways that may be amendable through pharmacologic intervention.

Current clinical trials investigate the efficacy of inhibiting JAK protein signaling to ameliorate disease. However, one pediment remains the vast cross talk between diverse cytokines and JAK-STAT signaling machinery. Many therapies are not unique to a particular JAK resulting in unintended clinical consequences. Nevertheless, JAK inhibitor drugs that proved effective in laboratory studies are currently in phase I and II clinical trials. An example is the use of baricitinib, which targets JAK1/JAK2, in rheumatoid arthritis patients, and pacritinib, which targets advanced myeloid malignancies and chronic idiopathic myelofibrosis.

Conclusions

JAK-STAT signaling is one of the principal signaling pathways utilized by cytokine receptors. Since the discovery of this pathway, many studies elucidated the role of this pathway in many processes including cell development, growth and survival. We've described several roles of JAK-STAT signaling the intestinal mucosal immune system and its response to challenge by bacteria, viruses, and antigens found in intestinal lumen. Our studies on the route and type of nutrition have demonstrated reduced JAK-STAT signaling associated with loss of adaptive and innate mucosal immune function, which is reversible with exogenous stimulants. The JAK-STAT pathway is vital to T cell differentiation, B cell maturation and development, secretion of sIgA, and mucus and antibody production, which are required to maintain anti-viral and anti-bacterial defenses at the mucosal surface. Further elucidation of JAK-STAT signaling under normal and pathological conditions will better complete our understanding of intestinal immunity and homeostasis.

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