CHAPTER ONE

The multi-faceted roles of TGF-β in regulation of immunity to infection

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Advances in Immunology, Volume 150
ISSN 0065-2776
https://doi.org/10.1016/bs.ai.2021.05.001

Abstract

Transforming Growth Factor-β is a potent regulator of the immune system, acting at every stage from thymic differentiation, population of the periphery, control of responsiveness, tissue repair and generation of memory. It is therefore a central player in the immune response to infectious pathogens, but its contribution is often clouded by multiple roles acting on different cells in time and space. Hence, context is all-important in understanding when TGF-β is beneficial or detrimental to the outcome of infection. In this review, a full range of infectious agents from viruses to helminth parasites are explored within this framework, drawing contrasts and general conclusions about the importance of TGF-β in these diseases.

1. Introduction

Transforming Growth Factor-β is arguably the most fascinating, influential and pleiotropic of all cytokines (Li, Wan, Sanjabi, Robertson, & Flavell, 2006; Travis & Sheppard, 2014). It is implicated throughout development and adulthood in immune regulation, metabolism and homeostasis, through to fibrosis and wound repair (David & Massague, 2018). These multiple physiological roles result in a fundamental impact of TGF-β in all infection settings. Here, I focus primarily on its effects on the host immune system responding to and clearing pathogens, and offer an updated survey from those previously available in the literature (Li, Wan, et al., 2006; Reed, 1999; Sanjabi, Oh, & Li, 2017).

TGF-β is encoded as three separate genes in mammals, and together these comprise part of a much larger gene family including Activins, Bone Morphogenetic Proteins (BMPs) and similar growth factors (Chen & Ten Dijke, 2016; Hinck, Mueller, & Springer, 2016). The three isoforms, TGF-β1, -β2 and β3, share most functional properties, but play specialized roles particularly in regulation of differentiation and cellular behavior (Govinden & Bhoola, 2003), resulting in contrasting developmental phenotypes in mice lacking each isoform (Sanford et al., 1997). However, for all isoforms, protein expression and post-translational activation are tightly regulated through a

complex cascade of processing, sequestration in latent form, and release of active cytokine, involving cellular proteases and binding partners on cell surfaces (Shi et al., 2011). A corresponding family of membrane TGF-β receptors (TβRs) with cytoplasmic protein serine/threonine kinase domains, are widely expressed and transduce signals through the highly conserved Smad pathway (Batlle & Massagué, 2019; Derynck & Budi, 2019).

Genetic deficiencies in gene-targeted transgenic mice result in lethal inflammatory disorders within weeks of birth (Kulkarni et al., 1993; Shull et al., 1992), which are even recapitulated when T cells alone cannot express TGF-β (Li, Sanjabi, & Flavell, 2006; Marie, Liggitt, & Rudensky, 2006); consequently experimental manipulations employ more refined constructs such as mutated receptors with a dominant negative kinase domain (Gorelik & Flavell, 2000), conditional deletions targeted to specific lineages (Lewis, Wehrens, Labarta-Bajo, Streeck, & Zuniga, 2016), or pharmacological kinase inhibitors with preferential activity against individual TβRs (Inman et al., 2002; Wang, Chen, et al., 2020). A further invaluable experimental tool is the monoclonal antibody 1D11 which neutralizes all three isoforms of mammalian TGF-β (Dasch, Pace, Waegell, Inenaga, & Ellingsworth, 1989).

1.1 TGF-β and the immune system

TGF-β has profound effects on every compartment of the immune system (Kelly, Houston, Sherwood, Casulli, & Travis, 2017). The earliest effects of TGF-β on the developing immune system are in the thymus, providing survival signals to rescue T cells from apoptosis (Sanjabi et al., 2017); this is a harbinger of the pivotal, lifelong role in regulating the balance between tolerance and reactivity, acting directly on effector populations and through induction of regulatory T cells (Johnston, Smyth, Dresser, & Maizels, 2016; Rubtsov & Rudensky, 2007). Beyond T cells, TGF-β acts broadly across the mature peripheral immune system, including B cells (Tamayo, Alvarez, & Merino, 2018), dendritic cells (Seeger, Musso, & Sozzani, 2015), monocyte/macrophages (Tsunawaki, Sporn, Ding, & Nathan, 1988), natural killer (NK) cells (Viel et al., 2016), and innate lymphoid cells (Viant et al., 2016).

Within the T cell compartment, there is significant inhibition of cytotoxic T cells by TGF-β, particularly in the tumor setting (Chen et al., 2005; Thomas & Massague, 2005), which is of direct relevance to viral pathogens as explored below. However, in other key respects, TGF-β

signaling activates important effector cell subsets, including T follicular helper (TFH) cells that are required to drive B cell affinity maturation and isotype switching in germinal centers (Marshall et al., 2015), and tissue-resident memory T cells that develop following (Mani et al., 2019). TGF-β has also been widely characterized as a factor promoting Th17 cell differentiation (Veldhoen, Hocking, Atkins, Locksley, & Stockinger, 2006), although most recently a distinction has been made between nonpathogenic TGF-β-induced Th17, and pathogenic Th17 driven by other ligands such as SAA and Activin A (Lee et al., 2020).

Among "non-professional" cells playing important roles in the immune system, those at barrier surfaces such as the airways (Branchett & Lloyd, 2019) and the intestinal tract (Bauché & Marie, 2017) are strongly modulated by TGF-β, with further induction of epithelial or endothelial cells to transform into fibroblasts, in the critical epithelial-to-mesenchymal transition (EMT) that underpins fibrosis (Pardali, Sanchez-Duffhues, Gomez-Puerto, & Ten Dijke, 2017; Sebe et al., 2008).

So while TGF-β is appropriately described as a double-edged sword, anti-inflammatory as well as pro-fibrotic, it can also be considered to be a remarkably multi-dimensional mediator able to exert effects in almost any setting. Moreover, these effects are highly context-dependent according to tissue, dose, the accompanying cytokine milieu, and the activation or differentiation state of cells exposed to the same mediator. In this review, I focus on the role of TGF-β in promoting, modulating or inhibiting specific immune mechanisms, rather than implications that it is directly pathogenic beyond the immune system, for example, causing pulmonary fibrosis or cardiac myopathy (de Oliveira et al., 2012).

1.2 TGF-β in infection

The prominent immunosuppressive effects of TGF-β cause, in many infectious diseases, a weakening of resistance or immunity, for example, through promoting regulatory T cell activity (Maizels & Smith, 2011). However, as detailed below, there are numerous examples in which TGF-β can protect the host, if not from infection then from the consequences of infection. Importantly TGF-β frequently acts in a modifying role to restore the steady state, and ensuring a healthy resolution once infection is overcome. An important point to consider is that activation is often invoked as a negative feedback mechanism, so that elevated TGF-β in infection does not necessarily signify a causal role in susceptibility or pathology, but reflects a homeostatic reaction to inflammation.

In the complex host-pathogen interplay, there are many examples of invading organisms exploiting the TGF-β pathway to modulate, deviate or suppress host immunity and permit pathogen establishment, for example, through proteases which activate latent TGF-β, or even mimics of the protein that drive the signaling pathway without the need for host cytokine, as discussed below in Section 8. In intracellular infections (viruses, some bacteria and protozoa) there are also ample examples of modulation of downstream intracellular signaling pathways, either within immune cell populations, or in stromal tissues that may contribute to more widespread pathogenic effects including fibrosis and tumorigenesis. These will be mentioned in the following sections that deal sequentially with the full range of infectious agents that challenge the immune system.

2. Viral infections

In viral infections, neutralizing antibodies together with NK and $CD8^+$ cytotoxic T cells are the primary defense modes of the immune system. While TGF-β has direct effects on each of the effector cell subsets, and arguably the greatest impact is through Tregs (Veiga-Parga, Sehrawat, & Rouse, 2013), there is a generalized immunosuppression seen across numerous viral infections.

As an exhaustive description of all these is beyond the scope of this review, I focus on selective examples which illustrate the importance of TGF-β in determining the course or outcome of viral infection, two of which (Influenza and LCMV) provide informative animal models, two chronic human infections (Hepatitis B and HIV), and one emerging through the latest Coronavirus pandemic.

2.1 Influenza virus

Influenza virus infection of mice induces a measurable increase in TGF-β activity within 24 h (Schultz-Cherry & Hinshaw, 1996), an effect attributed to the ability of neuraminidase to activate TGF-β (see Section 8 below). Over-expression of TGF-β, by intranasal administration of a recombinant plasmid, markedly reduced inflammatory responses to infection, but permitted faster viral outgrowth, demonstrating the double-edged nature of this cytokine in viral infection (Williams et al., 2005). Subsequent studies validated the protective role of TGF-β, in reports that mice treated with 1D11 anti-TGFβ antibody suffered accelerated mortality from influenza infection, while adenoviral-mediated supplementation of TGF-β *in vivo* delayed death

(Carlson et al., 2010). Similar mortality was seen in mice lacking ADAP, an upstream intracellular adaptor protein that promotes TGFβ expression (Li, Jiao, et al., 2015).

The protective effects of TGF-β were also documented in mice that were infected with influenza virus following induction of airway allergic responses; in this model of asthma, mice are sensitized and challenged with ovalbumin, but then survive viral doses which are lethal to control animals. Survival is due to expression of high levels of TGF-β in the lung that temper inflammatory cytokine levels and minimize tissue damage, and is lost in mice lacking TβRII expression, using a tamoxifen-inducible deletion construct to avoid embryonic lethality of the global knockout (Furuya et al., 2015). In this case, TGF-β did not alter the overall viral load in infected mice. Interestingly, this study also measured the inactive, LAP-associated form of TGF-β, which was higher in control, pathology-prone mice indicating a high degree of *in vivo* conversion to the active form during the allergic response.

Notably, infection of mice in which only the bronchial epithelial cells are unable to express TGF-β, shows enhanced protection from pathology, due to uninhibited Type 1 interferon release (Denney, Branchett, Gregory, Oliver, & Lloyd, 2018). Thus, in mice at least, the highly context-specific role of TGFβ appears to dampen the local inflammatory response to the detriment of the host, while controlling systemic reactions that may protect the host from mortal outcomes.

2.2 LCMV virus

Lymphocytic choriomeningitis virus (LCMV) offers an elegant model to track antigen-specific T cell responses *in vivo*. Exogenous TGF-β given at the outset of infection greatly suppressed the generation of $CD8^+$ cytotoxic T lymphocytes (CTLs) that mediate protection, and resulted in higher virus titers in infected mice; however, animals benefitted by amelioration of the local inflammatory reaction to virus in the footpad (Fontana et al., 1989). Moreover, TGF-β also inhibited NK cell activation during LCMV infection (Su, Leite-Morris, Braun, & Biron, 1991). In contrast, mice whose T cells express the dominant negative TβRII are able to rapidly clear infection, generating greater numbers of virus-specific CTLs that constituted a long-term memory population (Tinoco, Alcalde, Yang, Sauer, & Zuniga, 2009). Lineage-specific deletion of TβRII in $CD4^+$ T cells also resulted in protection against LCMV (Lewis et al., 2016) although, in the

same model, anti-TGF-β treatment had no effect on the outcome of LCMV infection (Boettler, Cheng, Ehrhardt, & von Herrath, 2012).

2.3 Hepatitis B virus

HBV exposure of Kupffer cells *in vitro* promotes TGF-β expression over pro-inflammatory (IL-1, IL-6 and TNF) cytokine production (Li et al., 2012) which, if occurring *in vivo* could explain fibrotic liver disease in the absence of overt inflammation. TGF-β, which is at higher serum levels in HBV patients (Flisiak, Prokopowicz, Jaroszewicz, & Flisiak, 2005), negatively effects NK cell activation, prolonging hepatitis B infection (Sun et al., 2012). However, it also renders hepatocytes less susceptible to viral replication as a result of multiple transcriptional changes (Hong et al., 2012; Li, Liu, Tian, & Chen, 2016), which may help balance out its overall effect on infection with this virus.

2.4 HIV infection

Although no causal data exists for the impact of TGF-β expression during HIV infection, it has been noted in independent studies that symptomatic patients have elevated serum TGF-β which negatively correlated with T cell counts, and that levels were higher in those with progressive disease (Maina et al., 2016; Wiercinska-Drapalo, Flisiak, Jaroszewicz, & Prokopowicz, 2004). Moreover, even with antiretroviral therapy, TGF-β can remain high and may contribute to greater susceptibility both to opportunistic infections, and to comorbidities such as fibrosis and chronic obstructive pulmonary disease (Theron, Anderson, Rossouw, & Steel, 2017).

Interestingly, SIV infection of African green monkeys is nonpathogenic but elicits a similar rise in TGF-β at very early time-points, suggesting that initially that upregulation is beneficial, limiting T cell hyperactivation and thereby viral spread (Kornfeld et al., 2005). However, in humans, as infection progresses, the effects of TGF-β appear to be increasingly detrimental, facilitating infection of myeloid cells, impeding viral-specific $CD8^+$ cell activation and promoting fibrotic pathology (Dickinson et al., 2020).

2.5 Coronavirus infections

The role of TGF-β in infections with coronaviruses (particularly SARS and SARS-CoV-2 or Covid-19) has yet to be fully defined. Several groups have reported elevated serum or lung TGF-β cytokine or mRNA, and circulating TGF-β-expressing lymphocytes, in coronavirus infection (Ferreira-Gomes

et al., 2021; Noroozi et al., 2020; Wang, Su, et al., 2020; Xiong et al., 2020). Whether increased TGF-β acts to block the protective response, or to restrain the life-threatening hyperinflammatory reaction, is not established, but one recent study suggests it is deleterious due to diverting antibody-producing B cells into nonprotective IgA secretion (Ferreira-Gomes et al., 2021). Serum TGF-β levels are higher in both SARS (Lee et al., 2004) and severe SARS-Cov-2 (Ghazavi, Ganji, Keshavarzian, Rabiemajd, & Mosayebi, 2021), although a more mixed profile was observed in MERS (Min et al., 2016). In a SARS cohort, severe disease cases showed higher TGF-β levels but at relatively late stages, suggesting that it may be a consequence, rather than a cause, of the earlier cytokine storm (Huang et al., 2005). It should be noted that most data represent serum or plasma levels, rather than the intensity of TGF-β activation in the infected airways. Here, a sudden surge of TGF-β in the lung would correlate with edema and fibrosis in severe disease which might be treatable with blocking antibodies or inhibitors (Chen, 2020).

While TGF-β activation could result purely from dysregulation of endogenous pathways, there may also be specific induction by SARS products. For example, the papain-like protease (Plpro) of SARS upregulates TGF-β gene expression both in human epithelial cells *in vitro*, and when injected into the lungs of mice (Li, Wang, et al., 2016; Wang et al., 2017). A further amplification of TGF-β can be mediated by the SARS nucleocapsid protein (N protein) binding Smad3, to promote fibrosis while minimizing apoptosis (Zhao, Nicholls, & Chen, 2008). Whether similar action by the homologous SARS-CoV-2 protease and N protein can cause acute localized activation of TGF-β in the airways remains to be determined.

A further dimension is the interaction of SARS-CoV-2 with the ACE-2 receptor, which degrades angiotensin-II (AngII); in SARS, infection selectively down-regulated levels of ACE-2 while increasing AngII (Kuba et al., 2005). AngII has been implicated in driving lung epithelial cell production of TGF-β in sterile inflammation (Molteni et al., 2007), although this has yet to be demonstrated in the viral setting. It is thus plausible that a further circuit may be invoked by the virus to increase levels of TGF-β during infection (Zuo, Zhao, & Chen, 2010).

2.6 Viral infections in general

These cases exemplify why, in the arena of viral infections, no generalized picture emerges for the effects of TGF-β. The role of this cytokine is so context-dependent, cell-specific and pleiotropic that each viral pathogen

represents a unique case in which the influence of TGF-β will depend on timing, tissue and exposure of the virus to immune surveillance. Although discussing a selected few viral infections, similar patterns of impaired immunity, enhanced viral growth but dampened inflammatory pathology mediated by TGF-β are also seen in Respiratory Syncytial Virus (Williams et al., 2005) and Rhinovirus (Bedke et al., 2012; Thomas et al., 2009), as well as in Hepatitis C virus (Alatrakchi et al., 2007; Rowan et al., 2008), although in the latter case TGF-β is further implicated in the pathology of liver fibrosis and carcinogenesis (Meindl-Beinker & Dooley, 2008).

One level at which it is possible to generalize is the extent to which viruses have adapted to manipulate the TGF-β pathway. As discussed in Section 8, specific viral proteins can activate latent TGF-β, and induce its expression in a variety of host cells. Reciprocally, the innate immune system has developed mechanisms to restrain TGF-β expression in the event of viral infection. Ligation of intracellular RIG-I-like receptors (RLRs) with double-stranded viral RNA results in activation of the transcription factor IRF3, which has a structural similarity with Smad3. IRF3 both inhibits Smad3 association with the TGF-β receptors, and interferes with its nuclear localization following receptor binding (Xu et al., 2014).

3. Bacterial infections

As with viral infections, TGF-β plays the most prominent role in the setting of prolonged, chronic infection; hence this section focusses on mucosal bacterial pathogens and tuberculosis, in which TGF-β is generally immunosuppressive. However, in the mucosal context, the pivotal antibody isotype IgA which regulates populations of both pathogenic and commensal bacteria, is promoted by the effects of TGF-β on B cells (Borsutzky, Cazac, Roes, & Guzman, 2004; Coffman, Lebman, & Shrader, 1989). Hence, again TGF-β acts on both sides of the fence, restraining and promoting different pathways involved in the control of infectious agents.

3.1 Gram-negative bacteria

A widely used model of enteric bacterial infection studies *Salmonella typhimurium* in mice. Early work suggested that TGF-β administration protected from lethal infection, with enhanced IFNγ and nitric oxide production, and reduced bacterial loads (Galdiero et al., 1999). The human enteric pathogen *Yersinia enterocolitica* can also be modeled in mice; here TGF-β treatment, particularly when combined with IL-12, reduced bacterial loads (Bohn et al., 1998), while anti-TGF-β antibody reduced survival of infected

animals (Zhong, Cantwell, & Dube, 2010). However, these studies did not investigate whether a Th17 response stimulated by TGF-β could contribute to its protective effect. A more recent study in mice contrasted *S. typhimurium*, in which TGF-β may also benefit the host through reducing inflammation and promoting repair, with *Citrobacter rodentium* which interferes with TGF-β signaling through down-regulation of the TGF-β receptors with highly pathogenic consequences (Zhang et al., 2018).

Mice infected with *Neisseria gonorrhoeae* show upregulated TGF-β expression across a variety of immune cell types in a model of vaginal infection, in which susceptibility can be reversed by anti-TGF-β antibody treatment (Liu & Russell, 2011), a result which led these authors to subsequently demonstrate direct induction of TGF-β by bacterial products (Liu, Islam, Jarvis, Gray-Owen, & Russell, 2012), as discussed in Section 8.

A particularly interesting model for the role of TGF-β is that of *Helicobacter pylori*, which infects both humans (in which it can cause gastric ulcers and lead to cancer) and laboratory mice (Li, Xie, & Lu, 2015). TGF-β is induced in gastric epithelial cells during infection, and these cells when co-cultured with $CD4^+$ T cells can drive regulatory T cell differentiation (Beswick, Pinchuk, Earley, Schmitt, & Reyes, 2011). *In vivo*, TGF-β from dendritic cells is also important; studying mice with CD11c-Cre-driven deletion of TGF-β from DCs, Treg levels were lower, and *Helicobacter* establishment greatly reduced; interestingly, mice on a RAG-deficient background were also more resistant if DCs lacked TGF-β, demonstrating an innate pathway through which TGF-β can increase susceptibility (Owyang et al., 2020). Furthermore, it is possible that TGF-β also enhances Th17 responses in gastritis, and in the longer term predisposes to cancer susceptibility, so overall plays a highly deleterious role (Li, Xie, & Lu, 2015).

3.2 Gram-positive bacteria

The inhibitory effects of TGF-β on the protective anti-bacterial response were first shown in a mouse model of *Staphylococcus aureus* infection, in which cytokine administration resulted in expanded bacterial load, while antibody depletion had the converse effect (Lowrance, O'Sullivan, Caver, Waegell, & Gresham, 1994). *Listeria monocytogenes* is an intracellular bacterium which is countered by a classical Type 1 immune response involving IFNγ and other inflammatory cytokines. However, in this case TGF-β promotes survival in mice, with administration of protein rescuing mice from lethal doses, while antibody treatment renders mice more status (Nakane

et al., 1996). *Clostridium* is a taxon which encompasses both commensals (see Section 7) and pathogens such as *C. difficile*; in the latter setting, intense intestinal inflammation from bacterial toxins can occur, which is ameliorated by the action of TGF-β; interestingly cytokine release is specifically elicited by one of the toxins, TcdA (Tinoco-Veras et al., 2017).

3.3 Mycobacterium tuberculosis

M. tuberculosis is a chronic bacterial infection with profound immunomodulatory effects which delay and impair the host immune system (Ellner, 2010; Toossi & Ellner, 1998; Urdahl, 2014), including expansion of $Foxp3^+$ regulatory T cells (Scott-Browne et al., 2007; Shafiani, Tucker-Heard, Kariyone, Takatsu, & Urdahl, 2010) and muted effector T cell responses (Hirsch et al., 1996) that both can result from TGF-β signaling. TGF-β is elevated (alongside IL-10) in patients with active disease, as measured in blood monocytes, lung lavage and granulomas (Bonecini-Almeida et al., 2004; Olobo et al., 2001; Toossi, Gogate, Shiratsuchi, Young, & Ellner, 1995) as well by *in vitro* release by peripheral T cells; drug treatment reduces levels *in vivo*, and inhibition of TGF-β signaling increases T cell response measures *in vitro* (Hirsch, Ellner, Blinkhorn, & Toossi, 1997). Furthermore, TGF-β may render cells intrinsically more susceptible to mycobacterial colonization (Hirsch et al., 1997; Hirsch, Yoneda, Averill, Ellner, & Toossi, 1994) and lead to the reactivation of latent bacteria in granulomas (Arbues et al., 2020). In a nonhuman primate model with *Cynomolgus* macaques, TGF-β is conspicuous in the developing lung granulomas, corresponding to observations on established granulomas in patients; interestingly, downstream Smad2/3 signaling is impaired in macaque granulomas through a mechanism yet to be investigated (DiFazio et al., 2016).

In animal models, if T cells express the dominant-negative TβRII receptor, mice show enhanced resistance to *M. tuberculosis* (Raghuvanshi, Sharma, Singh, Van Kaer, & Das, 2010); a similar phenotype is seen in lineage-specific (Lck-Cre driven) deletion of TβRII in T cells, with increased IFNγ responses particularly within the granuloma (Gern et al., 2021). When the dnTβRII transgene was expressed on a background unable to respond to IL-4 (STAT6-deficient), the animals became highly resistant, a phenotype that could be replicated with the pharmacological TβRI kinase inhibitor SB431542, combined with a STAT6 inhibitor (Bhattacharya et al., 2014). In contrast, a combination of dnTbRII with T-bet deficiency failed to protect animals, arguing that in wild-type mice, both TGFβ and IL-4 restrain the development of the

protective Th1 effector subset. Recently, it has been proposed that ILC3s provide critical early immune responses that protect against *M. tuberculosis* (Ardain et al., 2019); it will be interesting to determine if the reported activity of TGF-β in inhibiting ILC3 differentiation (Viant et al., 2016) represents another pathway through which this cytokine acts to facilitate mycobacterial infection.

Although TGF-β is thus strongly associated with promoting susceptibility to tuberculosis (Rook, Hernandez-Pando, & Zumla, 2009), and Th17 responses are not generally considered critical to protection (Domingo-Gonzalez, Prince, Cooper, & Khader, 2016; Mayer-Barber & Sher, 2015), a clear consensus has yet to emerge as to whether it is an appropriate target for treatment of tuberculosis. Its role in fibrotic granuloma formation might strengthen the case that it should be so considered, or at least, as originally suggested by Toossi and Ellner (1998), argue that TFG-β neutralization could be an effective adjunct to optimize either drug or immunotherapy.

4. Fungal infections

Candida albicans is a common yeast which can be pathogenic, particularly in immune deficiency; patients with chronic disseminated candidiasis were found to express high levels of TGF-β in the liver, and production was notably from monocytes and hepatocytes (Letterio, Lehrnbecher, Pollack, Walsh, & Chanock, 2001). In a mouse model, however, TGFβ played a more protective role, as its administration delayed disease progression while anti-TGF-β antibody treatment blocked resistance (Spaccapelo et al., 1995). Recovery from infection was associated with a stronger Th1 response, that in this setting was promoted by TGF-β at the expense of IL-4 and IL-10. More recent work has established the critical role of Th17 in protection against *C. albicans* (Conti et al., 2009), and in this light it would be interesting to re-examine the effects of TGF-β in yeast infection.

Cryptococcus neoformans is a respiratory fungal infection which in mice elicits a Th2-dominated eosinophilic response; in animals receiving a TGF-β-expressing plasmid in the airways (as used in influenza and RSV experiments, see Section 2.1), lung eosinophilia was strongly inhibited while fungal replication greatly enhanced (Williams et al., 2005). In a longer-term rat model, a distinction was made between treatment at the time of infection, which increased levels of fungi in the lung. or after 1 month infection which was protective; in the latter setting, TGF-β inhibited the respiratory burst of

macrophages while stimulating release of lysozyme, a known anti-fungal mediator (Shao, Rivera, Niang, Casadevall, & Goldman, 2005).

5. Protozoal parasite infections

Most protozoal pathogens of humans occupy intracellular niches, including the Apicomplexan parasites (malaria and *Toxoplasma*), as well as *Leishmania* species causing kala-azar, and the etiologic agent of Chagas' disease, *Trypanosoma cruzi*. The African trypanosomes (e.g., *Trypanosoma brucei*) are extracellular. In many of these infections, serum TGF-β levels are elevated although whether this reflects an immunosuppressed status or a response to inflammatory damage is often not clear.

5.1 Leishmania

Leishmaniasis is an intracellular protozoal parasite which establishes a long-term infection when Th1 responses are insufficient, in particular where activation of inflammatory pathways in macrophages is muted. TGF-β expression at the early stages of response restrains Th1 development, favoring an inappropriately dominant Th2 response to this parasite. During chronic infection, TGF-β also acts through regulatory T cells, IL-10 and the direct down-modulation of macrophages infected with the parasite (Peters & Sacks, 2006).

Multiple species of *Leishmania* differ in host range, tropisms and consequent pathology. Murine macrophages infected with a pathogenic cutaneous *L. amazonensis* form sharply up-regulated their TGF-β expression *in vitro*, while mice normally resistant to this species and to *L. braziliensis* were rendered susceptible by administration of exogenous TGF-β (Barral-Netto et al., 1992). *L. braziliensis* similarly induced TGF-β production by human macrophages (Barral et al., 1995). In the mouse model, pathology of cutaneous lesions was also exacerbated by administration of TGF-β or alleviated by the anti-TGF-β monoclonal 1D11, corresponding to the ability of TGF-β to increase Th2/IL-10 and inhibit the protective IFNg response (Barral et al., 1993). Clearance of *L. tropica* parasites, however, required treatment with antibodies to both TGF-β and IL-10 (Anderson et al., 2008), indicating that depending on the species of *Leishmania*, additional regulatory mechanisms are in place.

In infection with visceralizing *Leishmania* species (such as *L. chagasi*/*L. infantum*, and *L. donovani*), TGF-β levels rise in both mice and humans (Gantt et al., 2003). Mouse strains of differing susceptibility to *L. chagasi*/

L. infantum show contrasting TGF-β responses, which are high in susceptible strains (e.g., BALB/c, B10.D2) but low in resistant C3H or C57BL/10 mice (Gomes-Pereira, Rodrigues, Rolao, Almeida, & Santos-Gomes, 2004). As with the cutaneous *Leishmania* species, resistant mice can be converted to susceptibility by forced expression of TGF-β through a adenoviral vector (Wilson, Young, Davidson, Mente, & McGowan, 1998). Again, the ability of macrophages to kill intracellular *L. infantum* parasites was impaired by TGF-β (Gantt et al., 2003), indicating that this is an all-encompassing factor allowing parasite persistence *in vivo*.

TGF-β is known to directly compromise the intracellular defense pathways of macrophages (Vodovotz, Bogdan, Paik, Xie, & Nathan, 1993). To counter this, *in vivo* anti-TGF-β antibody blockade in mice elevated Leishmanicidal nitric oxide production within lesion macrophages, leading to more rapid resolution even though no change in the overall Th1/Th2 balance was observed (Li, Hunter, & Farrell, 1999). More recently, monocyte-derived macrophages from human cases of *L. donovani* infection were shown to have down-regulated TLR4 and up-regulated A20 (TNFAIP30) which is a pivotal inhibitor of inflammatory signaling; similar changes could be effected by the addition of TGF-β, highlighting an upstream pathway through which immunity to *Leishmania* may be abrogated (Das et al., 2012).

As protective immunity requires classical interferon-γ-mediated activation of macrophages, an important question has been whether TGF-β directly blocks production of this cytokine from Th1 cells, or other cellular sources. Within the $CD4^+$ subset, for example, it is known that TGF-β blocks induction of the key transcription factor T-Bet, thereby precluding Th1 differentiation (Gorelik, Constant, & Flavell, 2002); the same authors then demonstrated that mice with T-cell-specific expression of the dominant negative TbRII (dnTbRII, driven by the CD4 promoter) responded to *L. major* infection with significantly enhanced cytokine production and ameliorated lesion size (Gorelik et al., 2002). The same dnTβRII expressed under the CD11c promoter resulted in rescue of IFNγ responses to *L. major*, with greatly reduced parasite loads and footpad lesion size (Laouar, Sutterwala, Gorelik, & Flavell, 2005); this study then identified the key origin of IFNγ as NK cells, confirming this population as a critical TGF-β-sensitive source of Th1-promoting cytokines in *Leishmania* infection (Bogdan, 2012; Laskay, Diefenbach, Röllinghoff, & Solbach, 1995).

Hence, TGF-β looms large in the biology of *Leishmania* due to its ability to modulate both early and late phases of infection through interactions with multiple innate and adaptive cell types.

5.2 Malaria

Malaria (*Plasmodium* spp.) is a Apicomplexan protozoan which, in humans, is transmitted through hematophagous mosquitoes, and following multiplication in the liver, invades red blood cells. As well as fevers, malaria can cause lethal brain inflammation; mouse models can replicate blood-stage infection and, to a limited degree, cerebral malaria. A number of field-based studies in malaria-endemic areas have indicated reduced TGF-β levels in infected patients, generally inversely correlating with severity of disease (recently reviewed by Drewry & Harty, 2020). For example, in one recent study in Uganda, cerebral malaria cases showed ∼70% reduction in serum TGF-β compared to healthy controls; patients also suffered from thrombocytopenia which may have deprived them of an essential source of the cytokine (Hanisch, Bangirana, Opoka, Park, & John, 2015).

A new perspective in malaria is offered by the advent of controlled human infections, either in the context of vaccine trials, or to provide a clearer analysis of how the immune response to this parasite evolves. In an early trial, TGF-β was one of the first cytokines to be upregulated in infection, and across the cohort levels positively correlated with parasite intensity (Walther et al., 2005, 2006). A more recent controlled malaria infection group was dichotomous, with raised levels only in one subset which proved to have less severe symptoms (de Jong et al., 2020). Hence, there is strong circumstantial evidence for a protective role of TGF-β against severe disease, although in the setting of long-term repeated infection in endemic areas, the cytokine may also be facilitating ongoing transmission.

In the mouse models, TGF-β depletion with antibodies strongly aggravates pathology, as mice which can normally clear *P. yoelli* succumb to lethal infection, and death is hastened in those given the more virulent *P. berghei* species; conversely, recombinant TGF-β1 extended survival more than twofold in *P. berghei* infected animals (Omer, Kurtzhals, & Riley, 2000; Omer & Riley, 1998). However, timing was important in this model, as mice able to resolve infection did not produce TGF-β until day 5 of infection, while those expressing it from the first 24 h of infection delayed the protective pro-inflammatory response, and suffered a more severe outcome (Omer, de Souza, & Riley, 2003). In another model, with non-lethal *P. chabaudi*, exogenous TGF-β not only failed to protect, but subjected recipient mice to a lethal income (Tsutsui & Kamiyama, 1999). While seemingly contradictory, the essential point is that TGF-β levels are very finely

tuned in each genetic combination of host and parasite strains; in some expression will be deficient and rescued with exogenous cytokine; in others, TGF-β activity is well-calibrated, and immunity becomes dysregulated when levels are manipulated in either direction (Drewry & Harty, 2020).

5.3 Toxoplasma

Toxoplasma gondii is, like malaria, an Apicomplexan intracellular parasite, but able to invade a wide variety of cells and host species, and mostly studied in the setting of macrophage infection, in which the parasite promotes TGF-β production (Bermudez, Covaro, & Remington, 1993). This in turn renders macrophages more susceptible to infection, primarily by blocking TNF production so that the host cells fail to activate appropriately; in the presence of exogenous TNF, TGF-β can no longer promote infection or inhibit nitric oxide generation (Langermans, Nibbering, Vuren-Van Der Hulst, & Van Furth, 2001). As with *Leishmania*, innate immunity through NK cells is important in resistance, but is down-regulated by TGF-β, so that anti-TGF-β antibody treatment of SCID mice raises IFN-γ responses and prolongs survival following *T. gondii* infection (Hunter, Bermudez, Beernink, Waegell, & Remington, 1995).

An interesting facet of *T. gondii* is the role of IL-17, as well as IFNγ, in resistance (Kelly et al., 2005); TGF-β can promote Th17 differentiation, but NK cells can also contribute to the IL-17 response. *In vitro*, the ability of NK cells to produce IL-17 required not only IL-6 and IL-23, but also TGF-β (Passos et al., 2010). Hence TGF-β acts in parallel to dampen and promote different arms of the immune system during this infection.

In vivo, *Toxoplasma* parasites disseminate to many tissues and infect diverse cell types, provoking a range of pathological outcomes (Gaddi & Yap, 2007). In particular, the intestinal epithelium is targeted by $CD4^+$ T cells, causing inflammatory ileitis, which may be countered through TGF-β released by the epithelial cells (Buzoni-Gatel et al., 2001). In a mouse model, transfer of epithelial cells alone prevented development of ileitis in *T. gondii* infection, in a manner which could be abrogated by anti-TGF-β antibody (Mennechet et al., 2004). Hence the lymphocyte and epithelial compartments play opposing roles in *T. gondii* infection, with the outcome determined by TGF-β expression.

A similar scenario was found in the brain, which is a major niche for dormant bradyzoite cyst formation, and where encephalitis can ensue, particularly in neonates infected transplacentally. However, rather than dampen

inflammation, TGF-β administration sharply increased mortality, due to greater parasite replication, and the loss of an effective immune response (Schluter et al., 1998). Hence as with many other infectious settings discussed here, TGF-β can play both beneficial and detrimental roles in Toxoplasmosis (Zare-Bidaki et al., 2016).

5.4 Trypanosoma cruzi

An early indication of a role for TGF-β in infection by *T. cruzi*, the etiological agent of Chagas' disease, was the finding that either TGF-β receptor expression, or activation of the pathway, were required for successful infection of mink lung epithelial cells by the parasite (Ming, Ewen, & Pereira, 1995). However, *T. cruzi* does not appear to directly ligate those receptors, but activates host TGF-β signaling to facilitate cell entry and replication within the cell (Hall & Pereira, 2000). Hence, anti-TGF-β antibody can inhibit *T. cruzi* infection of murine cardiomyocytes, a highly relevant cell targeted in human disease (Waghabi, Keramidas, Feige, Araujo-Jorge, & Bailly, 2005). It is also not yet clear whether this is a universal pathway for parasite infection, as *T. cruzi* has an extraordinarily promiscuous range of target cells, and can exploit multiple, alternative receptor pathways in widely differing host species (Epting, Coates, & Engman, 2010). Moreover, *T. cruzi* products actually inhibit downstream TGF-β gene activation in dermal fibroblasts (Mott, Costales, & Burleigh, 2011) and alter cardiomyocyte TGF-β receptor distribution (Calvet, Silva, De Melo, De Araújo-Jorge, & Pereira, 2016); such effects may reflect tissue-specific nuances by which *T. cruzi* optimizes its parasite niche *in vivo*.

In mouse models, infection promotes TGF-β production by spleen cells, while administration of exogenous TGF-β exacerbates disease and mortality (Silva, Twardzik, & Reed, 1991), an effect correlated with it dampening macrophage activation *in vitro*. Chagas' disease patients show markedly higher serum TGF-β, levels of which correlate with severity of myocardiopathy (Araujo-Jorge et al., 2002; Perez et al., 2011). Administration of SB431542 and GW788388, which inhibit TGF-β receptor kinase activity, reduced peak parasitemias and prolonged survival in similar models (de Oliveira et al., 2012; Waghabi et al., 2007). However, mice expressing the dnTβRII under the CD2 promoter were actually more susceptible to *T. cruzi* infection (Martin, Postan, Lucas, Gress, & Tarleton, 2007), suggesting that when blockade is more complete, underlying protective functions of TGF-β may also be lost.

In view of reports that *T. cruzi* antigens can directly induce production of TGF-β *in vivo* and *in vitro* (Hansen et al., 1998), and that live parasites activate latent TGF-β (Waghabi, Keramidas, Feige, et al., 2005), this parasite may have evolved to amplify the TGF-β pathway to facilitate its establishment, with deleterious long-term consequences for the host. A further co-adaptation is suggested by the finding that replicating intracellular parasites (amastigotes) internalize TGF-β, as shown by specific antibody binding, possibly as a cue for development to the disseminating trypomastigote form (Waghabi et al., 2005).

Taken together, these findings argue that TGF-β plays a sharply negative role in Chagas' disease, starting from impairment of prompt protective immunity through to chronic myocardial pathology which is the cause of high mortality in *T. cruzi* Infection. Consequently, therapies targeting TGF-β are being actively pursued in this parasitic disease (Araujo-Jorge, Waghabi, Bailly, & Feige, 2012; Ferreira et al., 2019).

5.5 African trypamosomes

Unlike the intracellular *T. cruzi*, African trypanosomes are extracellular and bloodstream forms are thought to primarily evade immunity by rapid antigenic variation, but involving other mechanisms such as hypergammaglobulinaemia. However, mice infected with *T. congolense* were significantly protected by the administration of TGF-β, reducing not only pathological measures, but switching the mode of immunity toward Th1 and reduced B cell hyper-activation, perhaps thereby permitting the host to mount a more coherent response to infection (Namangala, Sugimoto, & Inoue, 2007).

6. Helminth parasite infections

Helminth worm parasites are extremely prevalent in less developed countries, establishing in many cases long-term chronic infections which reflect either, or both, antigen-specific and more generalized immune suppression (McSorley & Maizels, 2012). The latter is often evident in dampened inflammatory responses to third-party antigens such as allergens, autoantigens and vaccines (Weinstock & Elliott, 2014). Although multiple modulatory pathways are certainly involved, given the wide diversity of helminth species and their immune evasion strategies, in many instances there is evidence that implicates TGF-β in determining the mode and measure of immune responses to these parasites. In one remarkable example, elevated T cell TGF-β production was found among multiple sclerosis

patients in Argentina who had acquired intestinal helminth infections and whose disease entered remission (Correale & Farez, 2007); in patients subsequently treated with anthelminthic drugs, levels of TGF-β-producing cells then declined while disease symptoms relapsed (Correale & Farez, 2011).

Human helminth infections can also compromise vaccine responses (Elias et al., 2005); in a striking interventional study, a cohort pre-treated with anthelminthic drugs showed higher IFNγ and IL-12 responses following BCG vaccination than those given placebo; but the untreated group expressed significantly higher levels of TGF-β in response to PPD restimulation (Elias, Britton, Aseffa, Engers, & Akuffo, 2008). These indications that TGF-β function is accentuated in helminth infections are further supported by studies finding higher circulating TGF-β levels in infected Ethiopian individuals (Leng, Bentwich, & Borkow, 2006) while *in vitro* secretion of TGF-β by cultured peripheral blood cells from Cameroonian children increased in proportion to intensity of infection (Turner et al., 2008).

Helminths encompass a spectrum of invasion strategies, developmental programs, and final tissue niches. While some studies (such as those mentioned above) aggregate cases with different helminth infections, finer analysis requires individual parasite-host combinations; hence the sections below highlight two sets of nematodes (roundworms)—the vector-borne filarial parasites, and the soil-transmitted intestinal helminths—and two groups of platyhelminthes (flatworms), the trematode flukes and cestode tapeworms. An interesting topic outside the scope of this review is the role of TGF-β family members in the immune response of insects to nematode parasites (Ozakman & Eleftherianos, 2019), and their role in resistance of free-living nematodes (e.g., *C. elegans*) to microbial infection (Zugasti & Ewbank, 2009).

6.1 Filarial nematodes

Filarial nematode infections frequently induce a state of parasite-specific immune hyporesponsiveness, in which peripheral blood lymphocytes fail to react to filarial antigens *in vitro* (Nutman, Kumaraswami, & Ottesen, 1987; Sartono, Kruize, Kurniawan-Atmadja, Maizels, & Yazdanbakhsh, 1997), due at least in part to regulatory T cells and cytokines, including TGF-β and IL-10 (Metenou & Nutman, 2013). A causal link between host TGF-β and immune suppression was established by *in vitro* T cell experiments with PBMC from patients with onchocerciasis (Doetze et al., 2000) and lymphatic

filariasis (Babu, Blauvelt, Kumaraswami, & Nutman, 2006; King et al., 1993), in which antigen-specific T cell hypo-responsiveness was reversed with anti-TGF-β antibodies. In contrast, some patients are fully reactive to parasite infection, and develop various forms of pathology leading to lymphedema and elephantiasis; TGF-β and other regulatory markers are diminished in such cases (Babu et al., 2009). However, the influence of TGF-β is not entirely one-sided in lymphatic filariasis, as it is also implicated in development of pathogenic Th17 responses in patients with clinical symptoms (Anuradha et al., 2014).

In human *Onchocerca volvulus* infections, adult worms establish in subcutaneous nodules, encysted by immune cells which stain intensely with anti-TGF-β (Korten, Kaifi, Büttner, & Hoerauf, 2010), as found also for a related parasite *Dirofilaria repens* (Brattig, Racz, Hoerauf, & Buttner, 2011), suggesting the possibility that these parasites can induce localized host TGF-β as part of an immune-suppressive strategy. In such cases, high levels of skin microfilariae (the transmission stage) are tolerated. As in lymphatic filariasis, there is a contrast between those patients with high parasite loads and immune hyporesponsiveness, mediated in part by TGF-β (Doetze et al., 2000), and others who develop a hyper-responsive state with very low microfilariae, and reduced host cell expression of TGF-β around the parasite nodules (Korten, Hoerauf, Kaifi, & Büttner, 2011). Such hyper-reactivity is associated with severe dermatitis attributed to killing of the skin-dwelling microfilariae, that may be alleviated by TGF-β in asymptomatic cases.

In an animal model of filariasis, the rodent nematode *Litomosoides sigmodontis* is able to block the development of Type 1 Diabetes in NOD mice, irrespective of the presence of IL-4, but dependent on TGF-β as shown by antibody depletion experiments (Hübner et al., 2012). Using dnTβRII mice, the same parasite was shown to activate a host regulatory cell which imposed hyporesponsiveness on TCR-transgenic target cells, although that suppression was not necessarily TGF-β-mediated (Hartmann, Schramm, & Breloer, 2015); however, evidence that TGF-β is acting on the physiological hyporesponsive Th2 cell population was obtained by gene expression analysis of such cells from infected mice (Knipper, Ivens, & Taylor, 2019).

6.2 Intestinal nematodes

In global numbers, human helminth infections are dominated by four soil-transmitted intestinal nematode species that collectively infect over one billion people: the roundworm *Ascaris lumbricoides*, the hookworms

Ancylostoma duodenale and *Necator americanus*, and the whipworm, *Trichuris trichiura* (Bethony et al., 2006). As mentioned above, children infected with these parasites show elevated TGF-β responses (Turner et al., 2008). However, none of these organisms productively infect laboratory animals, and hence experimental studies focus on rodent parasites, principally *Heligmosomoides polygyrus bakeri* and *Nippostrongylus brasiliensis* (both related to hookworms), and the mouse whipworm *T. muris*.

In *H. polygyrus*-infected mice, T cell expression of TGF-β rises following infection (Finney, Taylor, Wilson, & Maizels, 2007; Ince et al., 2005) and plasma levels increase two- to fivefold over 28 days of infection, but drop to baseline levels with a week of drug-induced worm clearance (Su, Segura, Morgan, Loredo-Osti, & Stevenson, 2005). Anti-TGF-β antibody (1D11) treatment of mice, commencing at day 9 of infection, resulted in an eventual reduction in adult worm burden that was not evident until week 6 of infection (Doligalska, Rzepecka, Drela, Donskow, & Gerwel-Wronka, 2006). A later study with the TβRI kinase inhibitor SB431542 induced more rapid expulsion of *H. polygyrus* (Grainger et al., 2010), a finding that may reflect the production by this parasite of a functional parasite mimic that activates the TGF-β pathway (see Section 8 below), that would not have been neutralized by 1D11 antibody. Further evidence for the importance of TGF-β signaling in this parasite model comes from dnTβRII mice, which fail to control the inflammatory reaction to infection that is precipitated by incoming larval parasites breaching the epithelial barrier, and exacerbated by deficiency in regulatory T cells. Consequently, dnTβRII mice mount excessive IFNγ responses that prevent development of a protective Th2 response required for worm expulsion (Ince et al., 2009; Reynolds & Maizels, 2012).

H. polygyrus is a widely used platform to study immunomodulation, for example in immune inflammation and co-infection. In a model of Graft-*vs*-Host disease (GvH) driven by infusion of allogeneic T cells, inflammation and mortality was reduced in *H. polygyrus*-infected mice, alongside induction of $Foxp3^+$ Tregs and TGF-β, but not if the donor cells were unresponsive to TGF-β through expression of the dnTβRII (Li, Chen, et al., 2015). In a co-infection model, *H. polygyrus*-infected mice are more susceptible to *M. tuberculosis* with diminished anti-mycobacterial responses; *in vitro*, anti-PPD responses are inhibited by parasite secreted products (HES, see Section 8), but rescued by the TβRI inhibitor SB431542 (Obieglo et al., 2016). Interestingly, in study of *M. tuberculosis* in humans, those co-infected with an intestinal nematode (*Strongyloides stercoralis*) had higher TGF-β levels which were reduced by anthelmintic therapy

(Anuradha et al., 2017), suggesting that this cytokine may play an important role in helminth-mycobacterial interactions.

Another rodent model, *Nippostrongylus brasiliensis*, follows the hookworm life cycle of initial skin penetration, and migration through the lung, trachea and esophagus to the intestinal tract. In this system, damage to the lung can be extensive which requires repair by TGF-β activated macrophages. Hence, the loss of TβRII expression on myeloid cells (though a $LysM^{Cre} \times TGF\text{-}\beta RII^{flox}$ system) aggravated lung pathology. However, mice lacking TGF-β-stimulated macrophages also expelled gut parasites more quickly, illustrating the trade-off between tissue repair and effective anti-helminth immunity (Heitmann et al., 2012).

In the establishment of chronic infection with *Trichuris muris*, TGF-β is activated by intestinal dendritic cells expressing $\alpha_v\beta_8$ integrin, and then acts to directly repress the protective Th2 response, without invoking regulatory cell suppression; mice lacking this integrin are resistant to infection, as are wild-type mice treated with TGF-β-neutralizing antibody (Worthington et al., 2013).

6.3 Schistosomes and liver flukes

Schistosoma mansoni trematode infection presents a complex picture in which adult worms in the periportal vasculature release eggs that must egress through the gut lumen for transmission, yet are often trapped in the liver causing fibrosis alongside more widespread inflammatory reactions in the spleen, intestinal tract and portal veins. Mouse models can replicate the early inflammatory reactions, which are not significantly heightened by anti-TGF-β antibody treatment alone, but are greatly exacerbated when given in combination with anti-IL-10, revealing overlapping mechanisms to control pathology (Herbert, Orekov, Perkins, & Finkelman, 2008). In baboons repeatedly infected with *S. mansoni*, the degree of fibrosis in the portal vasculature correlated strongly with level of TGF-β production by peripheral blood lymphocytes challenged *in vitro* with *Schistosoma* egg antigen (SEA) (Farah et al., 2000). However, TGF-β was also the only cytokine to correlate with down-regulation of liver granulomas in chronic infection (Mola et al., 1999), indicating opposing costs and benefits in different tissues of the infected host. Another pathological sequel of infection is pulmonary arterial hypertension, which may be exacerbated by thrombospondin-1 activation of TGF-β in a IL-4/IL-13-stimulated macrophage-dependent pathway (Mickael & Graham, 2019).

In contrast to these studies on the role of TGF-β in the pathogenesis of schistosomiasis, surprisingly little is understood about its impact on

protective immunity. In a mouse model of vaccine-induced immunity, expression of TGF-β negatively associated with protection, in part by de-activating type 1 macrophages that express nitric oxide synthase in protected mice (Williams et al., 1995). Interestingly, when testing administration of either TGF-β, or anti-TGF-β, which resulted in stronger Th17 or Th1/2 responses respectively, both were found to reduce adult worm and egg burdens in two different strains of mice (Tallima, Salah, Guirguis, & El Ridi, 2009), suggesting that in steady-state infection TGF-β levels are regulated to minimize potentially pathogenic immune responses of any effector mode.

Fasciola hepatica is a large liver fluke trematode prevalent in livestock, in which TGF-β plays a particularly prominent role (Musah-Eroje & Flynn, 2018), for example, dampening *in vitro* responses of lymphocytes from infected cattle (Flynn & Mulcahy, 2008). Infection of mice sharply increases TGF-β levels (Chung, Bae, Yun, Yang, & Kong, 2012), and induces DC and T cell production of TGF-β, which can be recapitulated *in vitro* with parasite secretory products (see Section 8) (Walsh, Brady, Finlay, Boon, & Mills, 2009). In the same study, *F. hepatica* infection was shown to suppress autoimmunity in a model of multiple sclerosis (experimental autoimmune encephalomyelitis), in a manner sensitive to anti-TGF-β antibody treatment. Another trematode of clinical significance is *Clonorchis sinensis*, which causes liver fibrosis in South-East Asia; infected mice showed increased plasma TGF-β, heightened liver TβR expression, and physiological markers of fibrosis (Yan et al., 2015).

6.4 Tapeworms

Cestodes, or tapeworms, include the highly pathogenic hydatid organism, *Echinococcus granulosus*, which in humans grows into large cysts treatable only by surgery. The failure of the immune response to eliminate this parasite is associated with increasing levels of TGF-β over the course of infection with an increasing Treg:Th17 ratio over time (Pang et al., 2014), although a Th9 population also emerges that is dependent on TGF-β signaling (Pang et al., 2018). In humans with the related *E. multilocularis*, recent evidence suggests that the parasite also produces ligands that activate the TGF-β pathway (see Section 8) (Nono, Lutz, & Brehm, 2020).

7. Commensal microbiome

The commensal microbiota maintain a profound and interdependent relationship with the host immune system (Hooper, Littman, & Macpherson, 2012), in which TGF-β plays a major part (Ihara, Hirata, & Koike, 2017).

TGF-β-deficient mice are born healthy, but die of fulminant intestinal inflammation within a few weeks of birth due to hyperreactivity to microbial species (Kulkarni et al., 1993; Shull et al., 1992). Reflecting this, many commensal microbes have been found to promote TGF-β expression or signaling. In a noted example, *Clostridium* bacteria can drive TGF-β epithelial cell expression, expand colonic Tregs and dampen colitis (Atarashi et al., 2011). One member of this bacterial assembly, *Clostridium butyricum*, directly induces TGF-β expression in lamina propria dendritic cells, which is further amplified by autocrine stimulation, to drive Treg differentiation (Kashiwagi et al., 2015). A possible mechanism for TGF-β induction, in epithelial cells at least, was established by screening bacterial metabolites on a reporter cell line, identifying the short-chain fatty acid butyrate as an active factor, which may be acting by inhibition of the histone deacetylase that down-regulates TGF-β expression (Martin-Gallausiaux et al., 2018).

Another example is that of *Bacterioides fragilis*, a commensal which induces host regulatory T cells through its Polysaccharide A (Mazmanian, Liu, Tzianabos, & Kasper, 2005). The bacteria were given to germ-free mice, which in steady-state express low levels of TGF-β within their T cell compartment; colonization with wild-type *B. fragilis* induced higher TGF-β levels than even in mice with a fully conventional microbiota, but only if they expressed Polysaccharide A, as a mutant PSA-negative strain had no effect (Round & Mazmanian, 2010).

8. Pathogen exploitation of TGF-β

Across the diversity of pathogen organisms, many take advantage of the immunomodulatory effects of TGF-β, and have adaptively evolved to interact with the TGF-β pathway. Through varied strategies, pathogens may locally activate latent TGF-β and/or potentiate the downstream signaling cascade (Section 8.1), induce key host cell types to upregulate or activate the cytokine (Section 8.2), or even elaborate their own ligands to bind the TGF-β receptors independently of the host cytokine (Section 8.3).

8.1 Activation and potentiation of host TGF-β

A number of pathogens produce mediators that activate latent TGF-β. For example, influenza recombinant neuraminidase (NA) does so by removing sialic acid moieties from the latent complex (Schultz-Cherry & Hinshaw, 1996), although it is uncertain whether proteolytic release is then required

for full activation (Carlson et al., 2010). Among the protozoa, proteolytic cleavage by parasite enzymes is invoked, as in the case of *Leishmania chagasi* promastigotes in human macrophage cultures, which required cysteine protease activity (Gantt et al., 2003). Likewise, *Trypanosoma cruzi* parasites, as well as soluble extracts of these organisms, activate latent TGF-β *in vitro* (Waghabi, Keramidas, Feige, et al., 2005), through the action of a major cysteine protease, cruzipain (Ferrao et al., 2015).

In the case of *M. tuberculosis*, there is enhanced TGF-β activation but most likely through an indirect mechanism, as release is primarily from monocytes and macrophages, and is reduced by a plasmin inhibitor (Aung, Wu, Johnson, Hirsch, & Toossi, 2005). A sequential process is indicated in malaria, as extracts of red blood cells infected with three different *Plasmodium* species, all activate latent TGF-β, inhabitable with antibodies to specific proteins (thrombospondin and TRAP) but also requiring a metalloprotease (Omer, de Souza, Corran, Sultan, & Riley, 2003).

Intracellular pathogens, in particular viruses, have every opportunity to modulate TGF-β expression and signaling. Hepatitis B virus pX protein, for example, interacts with Smad4, a transcription factor downstream of TβRI, to stabilize it, promote its nuclear translocation and thereby augment the transcriptional response to TGF-β ligation (Lee et al., 2001).

Hepatitis C virus (HCV) core protein upregulates TGF-β1 transcription in human HepG2 hepatoma cells, potentially through general activation of MAP kinases (Taniguchi et al., 2004), while potentiating a large number of TGF-β-regulated genes when expressed as a transgene in mouse livers (Benzoubir et al., 2013). In addition, the nonstructural NS4 protein from HCV can induce TGF-β expression by monocytes from uninfected donors (Rowan et al., 2008).

8.2 Induction of host cell TGF-β production

Mycobacterial PPD (Toossi, Young, et al., 1995) and lipoarabinomannan (Dahl, Shiratsuchi, Hamilton, Ellner, & Toossi, 1996) induce TGF-β from human monocytes in a manner that could not be prevented by endotoxin inhibitors. Soluble extracts of *H. pylori* induce TGF-β from epithelial cells and monocytes, but no further characterization of the protein responsible was reported (Wu et al., 2007). In a more defined system, the BAD1 protein from the dimorphic fungus *Blastomyces dermatitidis*, was found to evoke TGF-β release from murine neutrophils and macrophages, with resulting suppression of inflammatory pathways such as TNF production (Finkel-Jimenez, Wuthrich, & Klein, 2002).

Among the helminth parasites, the hookworm Anti-Inflammatory Protein (AIP) also promotes TGF-β production, as part of broader counter-inflammatory effects in the colon (Ferreira et al., 2017). Schistosome lipids induce human eosinophils to produce TGF-β (Magalhaes et al., 2018), while SEA from the Schistosome eggs evokes host TGF-βto induce Foxp3$^+$ regulatory T cells (Zaccone et al., 2009). In a similar manner, the excretory/secretory products of *F. hepatica* (FHES) can induce mouse bone marrow DCs to produce TGFβ (Finlay et al., 2015).

Many of the older studies of activation or induction did not progress to precise mechanism, and these would repay new analysis, which apart from confirming original reports, may reveal novel molecular interactions that could be exploited pharmacologically to control TGF-β.

8.3 Pathogen homologs and mimics

Helminth parasites are primitive members of the metazoa, multicellular animals, and hence encode homologs of TGF-β which are required across a range of developmental and physiological processes; for example, the free-living nematode *C. elegans* encodes four distinct homologs with multiple developmental functions (Gumienny & Savage-Dunn, 2013). A TGF-β homolog (TGH-2) from the filarial parasite *Brugia malayi* was found to trigger signaling in a mink lung reporter cell line (Gomez-Escobar, Gregory, & Maizels, 2000). Similar family members from other nematodes (McSorley et al., 2010) and schistosomes (Freitas, Jung, & Pearce, 2009; Liu et al., 2013) have been described, but functional interaction with mammalian receptors was not reported. However, in the trematode *F. hepatica*, three TGF-β homologs were identified, one of which (FhTLM) induced Smad signaling in bovine macrophages, with a switch toward an M2-like phenotype (Sulaiman et al., 2016). Additionally, an *Echinococcus multilocularis* activin-like molecule was discovered which synergizes with host TGF-β to induce Foxp3$^+$ Tregs (Nono et al., 2020).

A very different evolutionary strategy is that of *H. polygyrus* which has elaborated a novel mimic of TGF-β (named TGM) which functionally replicates its immune modulatory capacity, inducing both murine and human Foxp3$^+$ Tregs, despite bearing no sequence similarity to the mammalian cytokine (Johnston et al., 2017). While active TGF-β comprises a processed C-terminal fragment of ~110 amino acids, dimerized through an interchain disulfide bond, TGM is a monomer that requires no processing or activation, and consists of five domains homologous to the Complement Control

Protein (CCP) module, of which three are essential for triggering TGF-β signaling (Smyth et al., 2018).

It is likely that many other parasites have adopted similar strategies, although the active principles have yet to be identified: secreted products of the sheep intestinal nematode *Teladorsagia* stimulate TGF-β-responsive cells (Grainger et al., 2010) and extracts of *L. sigmodontis* activate TβR signaling in a manner that cannot be blocked by anti-TGF-β antibodies (Hartmann et al., 2015).

9. Conclusion

Our insight into the significance of TGF-β across the myriad of infectious diseases is at best incomplete, and very often superficial; this mediator too often defies any neat classification as beneficial or detrimental, requiring a nuanced understanding of the environmental milieu and kinetic context in which it may act. Moreover, in both laboratory and clinical research, measurement of an agent that exists in latent and active forms, generally sequestered in specific tissue sites, and with an outcome highly dependent on the status of recipient cells, presents both logistical and interpretative obstacles. Nevertheless, as opportunities arise with novel activators or inhibitors of TGF-β signaling, and the ability to deliver these in highly directed manner, so new possibilities will arise to treat many infectious diseases, in particular chronic conditions refractory to conventional chemotherapy, which should richly repay investigation.

Acknowledgments

I thank the Wellcome Trust for funding through an Investigator Award (Ref 219530), and the Wellcome Trust core-funded Wellcome Centre for Integrative Parasitology at the University of Glasgow (Ref: 104111). I also thank Orhan Rasid for critical review of the manuscript. The author declares no competing financial interests.

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