Chapter 1
Introduction: An Overview of Host-Directed Therapies for Tuberculosis

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Host-Directed Therapy: Purpose and History

Despite the widescale success of the antibiotic era in mitigating a plethora of bacterial infectious diseases, tuberculosis (TB) "the white death" remains a public health scourge claiming approximately 1.3 million lives annually, with estimates of nearly a third of the world's population infected with its causative agent *Mycobacterium tuberculosis* (Mtb) [1]. While the first antibiotics, sulfonamides and penicillin, proved to be ineffective at controlling Mtb infection, the advent of streptomycin in 1943 created chemotherapeutic treatment options for this disease. Streptomycin and para-aminosalicyclic acid, the two effective anti-TB chemotherapeutic drugs, rapidly induced resistance by Mtb when either agent was given alone [2], a harbinger of the multidrug-resistant (MDR) TB strains that would eventually develop. Isoniazid (INH), developed a few years later, was a much more potent and caused fewer toxic side effects. The development of drug resistance is a recurring problem in TB treatment, as Mtb has developed ways to circumvent nearly every antibiotic.

Host-directed therapy (HDT) offers the potential to combat these drug resistance issues. First, by focusing on host, rather than bacterial targets, to empower the immune system to clear the mycobacterial infection, the agents do not directly apply selective pressure on the bacteria. Second, HDT agents may be employed in combination with standard anti-mycobacterial therapy potentially shortening treatment, and thereby improving adherence and limiting the emergence of resistance arising due to incomplete treatment. An added benefit of many of these HDT agents is they also have anti-inflammatory effects that ameliorate the lifelong inflammatory

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pulmonary tissue damage caused by active TB infection, improving the quality of life and possibly long-term survival, for cured patients [3–6].

HDT has its roots as some of the oldest TB therapy. Prior to the chemotherapeutic era, all TB treatments by necessity were "host directed." Ascertaining the impact on patients is difficult because no adequate comparison has ever been performed [7]. A systematic review of 564 patients admitted to New York State sanatoria found [8] a mortality rate of 37%, an improvement over models indicating a mortality rate between 53% and 86% [9] for TB cases not in sanatoria. The effect may be due to the host-directed benefits of a healthy diet, proper rest, mild exercise regimen, and sunlight often included in the sanatoria setting [10]. Indeed, evidence suggests that reclining in a supine position reduced Mtb bacilli growth [11].

The Antibiotic Era

By the mid-1950s, the development of effective TB drugs, like INH and PAS, the focus on the host diminished, and the sanatoria quickly closed. New classes of anti-TB drugs were discovered, and combination treatment regimens employed to impede the emergence of drug-resistant TB. However, increasingly drug-resistant TB remained a problem. By 2006, the first reports of extensively drug-resistant (XDR) TB appeared, revealing strains resistant to the two major first line TB drugs, INH and rifampicin, as well as aminoglycosides and quinolones [12, 13], highlighting the need for alternative treatment strategies for TB.

Complicating progress is a lack of funding for TB drug development, with the World Health Organization estimating $3.5 billion shortfall for TB implementation in 2018, and as much as a $2 billion per year research shortfall as well as limited profit motivation for pharmaceutical companies [14]. HDT strategies can take advantage of investments in other fields, such as in oncology and autoimmune diseases, to re-purpose drugs already in use or in development that may modulate the immune system to improve TB outcomes [15]. Therapies already proven safe and effective for other disorders have a streamlined and more cost-effective pathway to approval for TB clinical use. Understanding how Mtb dysregulates the host immune system to create a hospitable environment, and how HDT agents may improve immune functions to more rapidly cure TB and decrease excess tissue damage is the key to developing clinically impactful HDT.

Host Response to Mtb

The growth of Mtb in the lung has long been tied into the state of the immune response [16]. After the first few weeks of infection, as Mtb rapidly replicates within macrophages, its growth substantially decreases upon the arrival of T cells. A functional immune response controls, but does not eradicate Mtb, leading to a latent

infection classically defined by the formation of a granuloma and tuberculin reactivity. Active disease occurs when immunity is unable to control Mtb growth, either soon after infection, or after immunity is compromised during latency, leading to granuloma breakdown and bacterial proliferation in tissues [16]. While no proven HDT targets have been identified, many potential targets within several subsets of immune cells have either been proposed or are being tested. From these results, we can begin to home in on specific cellular pathway targets for optimal therapeutic benefit from HDTs.

T cells are vitally important to the control of Mtb pathogenesis, although the exact mechanisms remain unclear. While IFN-γ production was thought to be of primary importance in T cell functionality [17], recent studies have suggested that it is not required and likely detrimental to control Mtb growth within the lung [18]. Without a deeper understanding of how T cells control TB, knowing how to target them with HDTs is difficult. Immunomodulatory agents used to treat autoimmune disorders are well known to increase the risk of reactivation in latently infected TB patients. Work with the immune checkpoint inhibitor PD-1 has also shown that immune activating agents can lead to detrimental results during TB disease [19, 20]. Initial murine studies utilizing PD-1 knockout mice showed significantly increased lethality during Mtb infection. Knockout mice had increased cytokine levels and inflammatory cells present in the lung, indicating that maintaining balanced negative regulation of T cell immunity is essential to control TB. TB reactivation has been subsequently reported in several cancer patients being treated with a PD-1 checkpoint inhibitor [21]. Further supporting the role of the T cell response during TB disease is a recent study that reported harmful effects when T cell metabolism was modulated [22]. Initially thought to be an ameliorative HDT target due to its role in Mtb-induced necrosis in macrophages [23], knockout studies of the mitochondrial matrix protein cyclophilin D, had heightened T cell responses that increased cytokine levels without a change in Mtb burden, and led to the death of most of the mice within 3 months of Mtb challenge.

The Inflammatory Response

One of the drivers of utilizing HDTs is a desire to lessen the inflammatory and tissue damaging effects caused by active TB on the host. Even after successful TB treatment, Mtb infected patients are at an increased risk to develop chronic pulmonary dysfunctions (COPD) [24] making immuno-modulatory agents candidates for HDT development. Corticosteroids were one of the first agents evaluated as an HDT for TB. While benefits have been observed as an adjunctive therapy for tuberculous meningitis, non-physiological concentrations were required for an effect on pulmonary TB with serious adverse events reported at lower concentrations [25]. Several non-steroidal anti-inflammatory drugs have been, or are currently, being tested as potential HDTs ranging from over the counter drugs (e.g. aspirin or ibuprofen) to prescription arthritis medications [5]. While targeting acute inflammation mediators

has been therapeutically beneficial for some autoimmune disorders, there is an open question on whether stopping inflammation is the best course of action in infectious disease induced inflammatory situations as these interventions may not have favorable effects in treatment of infections. The inflammatory process has three stages: onset, resolution, and post-resolution [26]. The resolution phase occurs after the onset of acute inflammation when apoptosis of inflammatory cells occurs, cytokines and other mediators are removed from the extracellular environment through decoy receptors, pro-inflammatory signaling pathways are turned off, and macrophages are reprogrammed to produce anti-inflammatory cytokines and pro-resolution mediators. Instead of only inhibiting inflammation, an alternative course of action could be enhancing resolution. For example, eicosanoids, including prostaglandins and resolvins, promote resolution by suppressing TLR and NF-κB signaling [27]. Prostaglandins are specifically involved in the cross-regulation of IL-1 and Type I interferon during TB disease. Prostaglandins are synthesized from arachidonic acid via cyclo-oxygenase (COX) that competes with 5-lipoxygenase (5-LO) for available arachoidonic acid. Zileuton, an inhibitor of 5-LO, increases prostaglandins synthesis and when administered 1 month after Mtb infection, when the onset of inflammation has likely dissipated, can significantly increase survival in mice [28]. A key factor for the development of HDTs is timing: a therapeutic agent that has beneficial affects during the early stages of Mtb infection may have no benefit, or even be harmful, during latency or late stages of infection.

A key component of resolution is the induction of apoptosis and the clearance of dead cells. Neutrophils, primary drivers during the onset of inflammation, are induced to go through apoptosis by a series of pro-apoptotic factors and then phagocytosed by macrophages by efferocytosis [29]. When this process is perturbed during uncontrolled inflammation, neutrophils instead go through necrosis, a poorly regulated form of cell death. Necrotic cells release damage-associated molecular patterns (DAMPs) and other pro-inflammatory molecules that further exacerbate pathogenesis. Mtb actively induces necrosis of infected cells and blocks apoptosis. Several studies have shown that infected apoptotic neutrophils activate macrophages leading to phagosomal maturation and significantly decreased Mtb burden [30, 31]. Mtb, by way of ESAT-6 and its secretion system ESX-1, instead induces necrosis of neutrophils, releasing viable Mtb into the extracellular environment where it can be phagocytosed by neighboring macrophages. An attenuated strain of Mtb lacking ESX-1 secretion system stays within the apoptotic neutrophil as it phagocytosed by the macrophage unable to block phagosome maturation [31]. Better understanding the mechanisms of Mtb-induced necrosis in order to identify potential HDT targets is a priority. Two that have been identified are reactive oxygen species (ROS) that are required for Mtb induced necrosis in neutrophils, and peroxisome proliferator-activated receptor (PPAR)γ a nuclear receptor known to be necessary for Mtb pathogenesis by limiting apoptosis. Early *in vitro* studies of inhibitors of ROS and Mcl-1, a downstream effector of PPARγ, in macrophages have decreased Mtb levels compared to untreated controls [31, 32].

Immunosupression

An important question needing to be addressed by HDT is whether negative regulatory immune cells and pathways utilized by Mtb to subvert host immunity and by the host to protect against deleterious inflammatory responses can be targeted therapeutically. As highlighted above, blocking or removing brakes, "checkpoint inhibition"- on T cell responses has had no beneficial effect on Mtb burden, but increases inflammation and tissue damage in the lung [19, 20, 22]. The concept of "disease tolerance" whereby the host dampens the inflammatory and adaptive immune response to the presence of a persistent infectious pathogen so as to protect against tissue damage has started to be explored in the context of TB [33]. Utilizing HDTs that are meant to induce host immunity in this context may have deleterious effects, particularly in the absence of an effective antimicrobial agent. An example of this is a recent study testing a matrix metalloproteinase (MMP) inhibitor as a single therapy HDT for TB [34]. Expecting to observe decreased pulmonary cavitation, the authors instead reported an increased cavitation, heightened immunopathology, and decreased survival. A second study that used other MMP inhibitors and included antibiotics was able to show a significant decrease in bacterial burden in mice given antibiotics with MMP inhibitors compared to antibiotics alone [35]. Thus, the context of when and how an HDT is used is an essential component of their development.

Myeloid-derived suppressor cells (MDSCs) are a regulatory cell population that acts to resolve inflammation and return to homeostasis [36]. They produce anti-inflammatory cytokines (e.g. IL-10), generate ROS and nitric oxide, suppress T cell proliferation by removing arginine from the extracellular environment, and recruit Tregs. The cancer field has been at the forefront of MDSC research, identifying new phenotypic markers, describing cellular functions, and identifying ways that they are used by tumors to grow and metastasize [37]. Initial observations during Mtb infection have found that MDSC levels rise in the blood during active disease and decrease after successful therapy [38]. Intriguingly, Mtb may be phagocytosed by MDSCs and can evade host immunity within these cells [39]. As a potential HDT target, all-trans retinoic acid (ATRA) differentiates MDSCs into mature macrophages, DCs, and neutrophils, decreased Mtb burden, and improved lung function in mice. While extensive research is needed to characterize the role of MDSCs at different stages of infection, exploring them as a potential HDT target has a strong rationale.

Immunometabolism

All cells require energy to function and replicate and immune cells are no exception. Over the past few years, there has been a renewed interest and appreciation in the metabolic activity of immune cells and how its directly intertwined with their functionality [40, 41]. A naïve T cell upon activation requires the energy and biosynthetic

molecules needed for proliferation, while a long-term resident memory T cell lives in a more quiescent state with energy requirements focused on long-term metabolic stability. Proliferating T cells utilize aerobic glycolysis for their energy needs that is an inefficient source of ATP but allows for the synthesis of needed biomolecules (e.g. amino acids, fatty acids). Memory cells use the more efficient oxidative phosphorylation as their energy source. Other immune cells, including macrophages and dendritic cells, go through similar metabolic reprogramming in response to immune function changes. Primary drivers of this metabolic programming are the signaling molecules mTOR and AMPK. Signaling through mTOR places the cell in an anabolic state, while AMPK alerts the cell to low ATP levels and reprograms the cell into a catabolic state [42]. The role of these signaling molecules, and their potential as HDT targets, is currently being studied with both an mTOR inhibitor targeting drug (everolimus) and metformin a drug with several reported mechanisms including AMPK activation.

Additional aspects of immunometabolism are also being tested as HDT targets. Tryptophan is an essential amino acid that humans obtain through diet and is needed by proliferating T cells [43]. To suppress T cell activity tryptophan can be removed and metabolized by neighboring cells. Tryptophan deprivation has been proposed as a driver of immune suppression in the tumor microenvironment. Indoleamine-2,3-dioxygenase (IDO) produces kyneurenine among other metabolites from tryptophan and has become the focus of therapeutically targeting tryptophan metabolism [43]. In Mtb granulomas, IDO levels are elevated, and studies have indicated a link between bacterial burden and IDO levels [44]. In macaques, the use of the IDO inhibitor 1-methyl-tryptophan resulted in decreased Mtb growth, improved pulmonary pathology, and increased T cell numbers [45]. Also, granulomas were reorganized, allowing for T cells to migrate into the granuloma. The results suggest that HDTs that allow for improved penetration into granulomas may be promising agents.

How the metabolic activity of an immune cell correlates with its functionality is an open and important question for immunometabolism, although the mitochondria and the generation of ROS are known to be involved [46]. Some metabolites may also directly signal within the cell. For example, the TCA metabolite itaconate inhibits the release of both IL-1β and Type I Interferons linking itaconate to the known role of the two cytokines in the regulation of inflammation during TB [47]. Studies with immune-responsive gene 1(Irg1), a mitochondrial enzyme that produces itaconate, indicate that in the absence of itaconate mice quickly succumb to Mtb infection with increased levels of inflammation and pathology [48].

The Modern HDT Clinical Pipeline

For an HDT agent to go into clinical development, animal data showing an improvement in bacterial load, immunopathology, and overall survival should be necessary. The question of exactly which animal model(s) are most appropriate is an open debate. The vast majority of *in vivo* HDT research has been done in small animal models, particularly murine. Imatinib, statins, metformin, MMP inhibitors, --the

phosphodiesterase-4 (PDE-4) inhibitor CC-3052, and zileuton have all been studied in mice with some also tested in guinea pigs. Only a few potential HDTs have been studied in non-human primates (NHPs) while several have gone on to clinical development without NHP data. Furthermore, the zebrafish model has also identified a few potential HDTs [49, 50]. None of the models produce an infection identical to what is observed in human tuberculosis, thus determining what type of animal studies should be necessary for further development as an HDT is difficult. Many questions remain unanswered. If a potential HDT does not show a benefit in small animal models, should the agent not be studied in the costlier NHP model? What criteria should be used to advance agents to clinical studies? As research into HDTs develops and allows correlation of findings from clinical trials with animal models, we will be better able to answer these questions.

The current pipeline of HDT development has three segments. Agents (a) in clinical development (b) being tested in small vertebrate animals and monkeys or (c) being tested *in vitro*. The HDTs in some form of clinical development include statins, imatinib, metformin, everolimus, and CC-3052. How this group was first identified and tested is enlightening for how future HDTs may be developed. Metformin was originally identified based off an *in vitro* screen of 13 autophagy and AMPK-activating drugs in BCG challenged THP-1s, a human macrophage cell line. While metformin was not the only drug screened found to have an ameliorative effect on bacterial burden, it has been in wide clinical use for decades, so it was selected for further development [51]. Statins were initially tested in human PBMCs and macrophages and then in mice because of the known role of host cholesterol in Mtb pathogenesis, and statins immunomodulatory capabilities [52]. Imatinib was identified through a focused analysis of the role of receptor tyrosine kinases in TB [53]. As a well described targeted anti-inflammatory, CC-3502 was tested *in vivo* in the presence of INH [54]. Everolimus was also initially tested as a well-established anti-inflammatory and inducer of autophagy [55]. Clinical evaluation of these drugs for TB treatment is ongoing, thus extrapolating on their ultimate effectiveness as HDTs is not possible. However, these studies have laid a foundation for how potential HDTs can be identified and developed for clinical testing.

Most of the current HDTs in clinical development were chosen from an *in vitro* testing, either as a targeted study of a specific drug or class, or from a screening of several drug classes. These studies usually utilize either monocyte-derived macrophages from humans or mice, or a macrophage cell line, primarily human (e.g. THP-1s). While these assays have resulted in identification of promising candidates, several have produced false positive results (23). Reliance on monocellular *in vitro* assays to establish initial evidence on the potential of HDT is problematic and should be replaced with multicellular assays. Several *in vitro* human granuloma models have been developed and are starting to be used to test antibiotics and HDTs [56]. While these assays do not completely recapitulate the *in vivo* human granuloma environment, they do provide additional complexity over standard *in vitro* models through the addition of multiple types of human immune cells, and fibroblasts. Thus, making them an extremely useful model for HDT development. They may aid in improving the translational quality of *in vitro* discoveries.

When to stop developing a potential HDT is a pertinent question for determining the progression of drug candidates into clinical development. Selecting agents approved as safe for use for other diseases will help mitigate risk. However, understanding the impact of drug-drug interactions between the HDT agent and TB and HIV treatment drugs is also critical. Positive or negative results for an HDT agent given without concomitant TB treatment should not be used to make critical decisions concerning further evaluation.

Conclusion

Mtb actively disrupts host immune cellular pathways to create a favorable environmental niche as it establishes infection. The overarching goal of HDT is to reverse or compensate for this immune dysregulation to allow the host immune system to improve TB treatment outcomes. As you will read throughout this book, HDT candidates represent a broad spectrum of agents targeting a variety of cells and pathways, complicating their clinical development and direct comparison. They all are intended to restore balanced regulation among immune cell metabolic pathways, between pro- and anti-inflammatory pathways, necrosis and apoptosis, and activation and inhibition of specific immune cell populations. Achieving such balance is the key to harnessing the potential of HDT for infectious diseases.

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