Immune Cell Regulatory Pathways Unexplored as Host-Directed Therapeutic Targets for *Mycobacterium tuberculosis*: An Opportunity to Apply Precision Medicine Innovations to Infectious Diseases

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The lack of novel antimicrobial drugs in development for tuberculosis treatment has provided an impetus for the discovery of adjunctive host-directed therapies (HDTs). Several promising HDT candidates are being evaluated, but major advancement of tuberculosis HDTs will require understanding of the master or "core" cell signaling pathways that control intersecting immunologic and metabolic regulatory mechanisms, collectively described as "immunometabolism." Core regulatory pathways conserved in all eukaryotic cells include poly (ADP-ribose) polymerases (PARPs), sirtuins, AMP-activated protein kinase (AMPK), and mechanistic target of rapamycin (mTOR) signaling. Critical interactions of these signaling pathways with each other and their roles as master regulators of immunometabolic functions will be addressed, as well as how *Mycobacterium tuberculosis* is already known to influence various other cell signaling pathways interacting with them. Knowledge of these essential mechanisms of cell function regulation has led to breakthrough targeted treatment advances for many diseases, most prominently in oncology. Leveraging these exciting advances in precision medicine for the development of innovative next-generation HDTs may lead to entirely new paradigms for treatment and prevention of tuberculosis and other infectious diseases.

Keywords. tuberculosis; host-directed therapy; precision medicine; immunometabolism; signaling pathways.

Despite identification of many potential bacterial targets, the current development pipeline for antimicrobial drugs against *Mycobacterium tuberculosis* (*Mtb*) is meager. Very few drugs of new classes are likely to enter clinical evaluation within the foreseeable future. In response, tuberculosis therapeutic research now includes efforts to identify adjunctive host-directed therapies (HDTs), with a focus on drugs already approved or in clinical development for other diseases [1]. Two important factors must help to guide this new research. First, responses to infections are governed by essential core regulatory mechanisms that have been conserved in all eukaryotic cells throughout the course of evolution, including all immune cells. Second, immune cells of any lineage must be able to function well as a cell in general before they can be effective in host defense. When the core regulatory mechanisms of cellular metabolism and other functions are pathologically disrupted, all cells, including immune cells, experience stress and their functions are compromised. In immune cells, the core regulatory mechanisms for metabolic and immune functions broadly intersect. The overlap and interactions between metabolic and immune regulation has been termed "immunometabolism" [2].

Table 1. Candidate Tuberculosis Host-Directed Therapeutic Agents

Drug Class/Target	Drug Examples	Probable Therapeutic Mechanism
MAPK cascade inhibitors [4] RAF-B MEK ERK JNK	Vemurafenib[a], dabrafenib Trametinib[a] [6] SCH772984 CC-930 [7], sitagliptin[a]	Varies: anti-inflammatory[b]/metabolic dysfunction – OR – interfering with tuberculosis pathogenic effect on signaling
Small GTPase inhibitors [8] Ras (RAF-MEK-ERK) Rho/ROCK [9]	Tipifarnib [10], salirasib [11], fasudil[c] [12], **statins**[a] [13], **metformin**[a] [14]	Same
Wnt inhibitors [15]	OMP-54F28 [16], tankyrase inhibitors [17], **clofazimine**[a] [18]	Same, but more complex
Protein kinase inhibitors Tyrosine kinase inhibitors [19, 20] c-abl, c-kit JAK/STAT VEGF EGFR Ser-thr kinase inhibitors SIK inhibitors	 **Imatinib**[a] [21, 22] and others **Tofactinib**[a] [23], ruxolitinib[a] **Pazopanib**[a] **[24]** **Gefitinib**[a] **[25]** Dasatinib[a], bosutinib[a] [26] (approved as TKIs)	 Increase autophagy and myeloid cell mobilization Anti-inflammatory Normalize vasculature in granulomas to improve drug penetration Increase autophagy, anti-inflammatory Anti-inflammatory and decrease M2 polarization
AMPK activators [27]	**Metformin**[a] [28], **AICAR** [29], AZD-769662 Berberine[a] [30], resveratrol[a] [31], **acetylsalicylic acid**[a]	Anti-inflammatory, increase autophagy, and improve DC, TH1 CD4 cell, and CD8 memory cell development
AMPA channel receptor blockers	Topiramate[a] [32], perampanel[a] [33]	Anti-inflammatory
PARP inhibitors [34, 35]	NAD intermediates (NAM[a], NR[a], NMN[a]), tetracyclines[a], olaparib[a], many in development	Anti-inflammatory, increase autophagy, improve effector T-cell function, and inhibit Tregs
Sirtuins Activators [36] Inhibitors [37]	 Resveratrol[a] [31], NAD intermediates, **statins**[a] [38], **metformin**[a], berberine[a] [30], and many STACs in development Sirtinol, cambinol, tenovin, others	 Anti-inflammatory and increase autophagy Increase Th1/Treg ratio
PI3K-AKT-mTOR pathway inhibitors [39,40] Direct mTOR inhibitors [41, 42]	Idelalisib[a], afuresertib [43], perifosine [44], MK-2206 [45], GSK-609693, [46], triciribine [47] Sirolimus[a], everolimus[a], ridaforolimus	Increase autophagy, decrease M2 polarization, and improve DC, Th1 CD4 cell, and CD8 memory cell development Same
PTEN activator	Resveratrol[a] [48]	Increase autophagy and decrease M2 polarization
p53 activator	Nutlin 3A [49]	Increase autophagy and decrease M2 polarization
Autophagy inducers [50]	**Imatinib**[a]/other TKIs, **metformin**[a], **statins**[a], **verapamil**[a], **selective serotonin reuptake inhibitors**[a], carbamazepine[a], sirolimus[a]	Increase autophagy: improve pathogen killing, clearance of proinflammatory organism components, and processing of antigenic material for T-cell presentation
Oxidative stress reduction agents [51]	Silymarin[a] [52], Tanshinone [53]	Anti-inflammatory and improve macrophage functions, including autophagy
ERS/UPR reduction agents Inflammasome inhibitors [54]	Phenylbutyrate[a] [55], ursolic acid[a] [56] Fasudil[c] [57], tauroursodeoxycholic acid[a] [58] β-hydroxybutyrate[a] [59], MCC950 [60], sitagliptin[a]	Anti-inflammatory and improve macrophage functions, including autophagy
LOX-1 and other scavenger receptor suppressors Angiotensin II receptor inhibitors [61]	Ellagic acid[a] [62], coenzyme Q10[a] [63] Docosahexaenoic acid[a] [64], sitagliptin[a], **statins**[a] [65], Tanshinone derivatives [66] Telmisartan[a] [67], others	Decrease M2 polarization/foam cell development, improve macrophage functions
Cathelicidin inducers [68]	**Vitamin D**[a], **phenylbuturate**[a], nicotinamide[a], resveratrol[a], pterostilbene[a]	Induction of antimicrobial peptides, improve lipid metabolism, and decrease M2 polarization
Dipeptide dipeptiase-4 inhibitors	Sitagliptin[a] [69], others	Anti-inflammatory/decrease inflammasomes, improve lipid metabolism and macrophage function, decrease M2 polarization, and preserve CXCL10 on effector T cells
Mevalonate metabolism inhibitors	Amino-bisphophonates[a], eg, zolandronate [70]	Enhance γδ T-cell activity and bridging between and innate and adaptive immunity
Highly pleiotropic agents	**Metformin**[a], **statins**[a], **phenylbutyrate**, Fasudil[c], berberine[a], sitagliptin[a]	

Table 1   continued.

Drug Class/Target	Drug Examples	Probable Therapeutic Mechanism
Combinations	Fasudil[c] and **statins**[a] (ROCK inhibition) [71] **Vitamin D**[a] **and phenylbutyrate**[a] [72] (cathelicidin induction) Tipifarnib and **statins**[a] [73] (RAS-ERK pathway inhibition)	

Bold text indicates that agent has been evaluated for potential tuberculosis host-directed therapeutic activity in a published study.

Abbreviations: AICAR, 5-Aminoimidazole-4-carboxamide ribonucleotide; AKT, serine/threonine protein kinase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPK, adenosine monophosphate-activated protein kinase; DC, dendritic cell; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; ERS, endoplasmic reticulum stress; JAK, Janus tyrosine kinase; JNK, c-Jun N-terminal kinase; LOX-1, lectin-like oxidized low-density lipoprotein receptor 1; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; NAM, nicotinamide; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; PARP, poly(ADP-ribose) polymerase; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatidylinositol-3, 4, 5,-trisphosphate 3-phosphatase; RAF, rapidly accelerated fibrosarcoma; RAS, Rat sarcoma protein; ROCK, Rho-associated coiled-coil containing kinase; SIK, salt-inducible kinase; STACs, sirtuin activating compounds; STAT, signal transducers and activators of transcription; TKI, tyrosine kinase inhibitor; UPR, unfolded protein response; VEGF, vascular endothelial growth factor.

[a] US Food and Drug Administration approved or available over the counter.

[b] Decreasing inflammatory reaction may allow improved drug and immune cell access to lesions; decrease tissue damage; possibly allow "wake and whack" strategies to improve antimicrobial response by allowing activation of nonreplicating bacilli with low metabolism levels.

[c] Approved in other countries with stringent regulatory authorities.

Although cytokines and interferons are essential for host immunity, none alone can prevent or eradicate *Mtb* infection. Immune responses must be viewed in the context of key genetic/epigenetic programmed regulatory pathways that are being progressively uncovered by basic molecular biology research. These discoveries are being applied for the development of an amazing spectrum of new targeted therapeutics for many diseases, most notably in oncologic, autoimmune, and metabolic disorders. Although the connections between core immunometabolism regulation and *Mtb* have only begun to be established, many studies have documented modification of some cell signaling pathways by *Mtb* to facilitate its survival. Lack of knowledge of the interactions between *Mtb* infection and the central cellular regulation pathways operating in immune cells constitutes a major scientific gap. This review will provide a broad, but not nearly exhaustive, overview of core immunometabolism regulation, the known and probable connections with *Mtb* pathogenesis, and the many opportunities to leverage new interventions being developed for precision medicine treatment of diseases now known to result from dysfunction of these fundamental core control processes.

PREVIOUSLY STUDIED TUBERCULOSIS IMMUNE MECHANISMS WITH NEW HDT RESEARCH OPPORTUNITIES

MAPK Signaling and the RAS/RAF/MEK/ERK Cascade

Mitogen-activated protein kinases (MAPKs) regulate several cellular processes, including stress responses, apoptosis, autophagy, metabolism, inflammation, and immune cell development with nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) as a significant downstream activation target. Innate immune cells recognize pathogen-associated molecular pattern (PAMPs), through pattern recognition receptors (PRRs). These receptors signal through a variety of pathways with dual functions in regulation of inflammation/immunity and metabolism. PAMP-PRR interaction–initiated signaling pathways include MAPKs. The 14 human MAPKs include extracellular signal-regulated kinase (ERK), c-Jun N terminal kinase (JNK), and p38, serine/threonine kinases that regulate transcription factor activity and have regulatory cross-talk with several other pathways. MAPK signaling is a progressive cascade that begins with activation of MAP3K kinases (by upstream kinases, small GTPases, or PRR-related adaptors) activating MAP2K kinases that then activate MAPKs, which have many downstream substrates [3].

Mtb adversely affects immune cell regulatory and effector functions by interaction with many of these interconnected signaling nodes and pathways. Several well-characterized *Mtb* ligands modulate immune cells through PAMPs to facilitate survival in phagocytes [4]. The PRRs of innate immune cells recognize *Mtb* PAMPs, including lipoarabinomannan and lipoproteins, which modulate MAPK signaling for enhancing *Mtb* survival in several ways. For example, prolonged ERK signaling through Toll-like receptor (TLR) activation by an *Mtb* lipoprotein induces interleukin (IL)-10 production while suppressing IL-12 secretion and T-helper (Th) 1 cell activation [5]. Inhibitors for several members of the MAPK family and related cascades are now US Food and Drug Administration (FDA)-approved or in clinical evaluation for therapy of malignant, inflammatory, and hyperimmune diseases.

See Table 1 for a list of some potential candidate tuberculosis HDT drug classes and specific agents with various molecular targets.

Small Molecule GTPase Superfamily

Small GTPases include the highly complex Ras, Rho, Rab, Ran, and ARF (ADP ribosylation factor) superfamilies. The Ras superfamily in particular has extensive crosstalk with MAPKs to regulate immunometabolic functions [74]. *Mtb* infection inhibits some GTPases and activates others. *Mtb* nucleoside diphosphate kinase binds to and inactivates the small GTPase Rac1 (a Rho kinase) in the macrophage, causing a defect of both NOX2 assembly and antimicrobial reactive oxygen species (ROS) production [75]. Some Rho GTPases activate Rho-associated coiled-coil–containing kinase (ROCK) as a downstream effector to regulate several different metabolic and immune functions [76]. Overactive Rho/ROCK signaling occurs in pathologic inflammatory conditions, including postischemic damage and diabetic complications. The ROCK-specific inhibitor, fasudil, is approved in some countries for treatment of vasospasm and decreasing stroke damage [9]. Alone, or in combination with rosuvastatin, fasudil can decrease inflammation by reducing downstream NF-κB signaling and tissue damage, for example, in animal models of cerebral ischemia [71].

During mycobacterial infection, Rheb (Ras family kinase) inhibits autophagy, and host cells attempt to utilize microRNA-155 to reverse this inhibition and limit bacterial growth [77]. Mevalonate pathway metabolism can upregulate the activity of Ras small GTPases through farnesylation. Some Ras members are involved with upregulation of inflammation caused by various etiologies, including in a rheumatoid arthritis model based on heat-killed *Mtb*. In this model, the Ras inhibitor farnesylthiosalicylic acid had significant anti-inflammatory activity [78]. Tipifarnib, another drug that disrupts Ras farnesylation, suppresses Ras/ERK signaling and NF-kB induction with synergistic effects in combination with simvastatin [73]. Selective targeting of GTPases has been suggested for HDT against *Mtb*, but this approach has not yet been studied.

Wnt Signaling Pathway

Signaling by Wnt (19 known ligands) and their 10 different G-coupled Frizzled (Fz) receptors has pivotal roles in immune responses to many pathogens [79] and is often induced through TLR/NF-κB signaling. Downstream Wnt signaling is either canonical (through β-catenin) or noncanonical (through $Ca2^+$, JNK, or Rho GTPase signaling). Wnt signaling regulates several aspects of immunity, including lymphocyte development, dendritic cell (DC) differentiation, and cytokine production and has extensive interactions with other major signaling families, including PRR-initiated pathways [80]. Pro- or anti-inflammatory effects may result, depending on interaction of particular combinations of the many possible Wnt and Fz ligand–receptor pairings.

The highly complex role of Wnt signaling in tuberculosis has begun to be explored [81–83]. However, further research is needed to understand the specific effects of different Wnt signaling components at different stages of *Mtb* infection. Therapeutic use of Wnt pathway inhibitors has been slow because of toxicity issues, but new drug classes may prove to have therapeutic benefit [15]. Interestingly, clofazimine inhibits canonical Wnt signaling in vitro, has several immunomodulatory effects observed in clinical use, and is in evaluation for treatment of Wnt-dependent cancers [18].

PROMISING INNOVATIVE TUBERCULOSIS HDT AGENTS IN PRECLINICAL STUDIES

Protein Kinase Signaling Inhibition: Imatinib

Tyrosine kinases (TKs), both receptor and nonreceptor, are involved in signaling pathways controlling most cellular processes. In many cancers, TKs are dysregulated and targeted by new-generation anticancer drugs [19]. Imatinib targets Abl kinase and effectively treats chronic myelogenous leukemia. In a murine macrophage cell line, imatinib reduced *Mtb* intracellular survival and bacterial loads with no direct effect on *Mtb* [21]. Mechanisms of action are not proven, but likely involve enhancing autophagy and phagosomal acidification [84, 85]. Imatinib also boosts the number of mobilized myeloid progenitor cells in a murine tuberculosis model [22], possibly by inhibition of c-kit or other TKs, resulting in "emergency hematopoiesis." Imatinib is currently being evaluated as a treatment adjuvant in a rhesus macaque tuberculosis model.

Other TKs possibly involved with tuberculosis pathogenesis include Janus tyrosine kinase (JAK)/signal transducers and activators of transcription (STAT) [23], vascular endothelial growth factor receptor (VEGFR) [24, 86], and epidermal growth factor receptor (EGFR) [25]. Inhibitors continue to be developed for these and many other classes of kinases, and several are now available for clinical use [19, 20]. Other kinase families are involved in immune/inflammatory and/or angiogenesis regulation. For example, inhibition of salt-inducible kinases enhances immune functions of macrophages and DCs in vitro [87].

AMP-Activated Protein Kinase Activators

Adenosine monophosphate (AMP)–activated protein kinase (AMPK) senses low cellular adenosine triphosphate (ATP) levels and initiates signaling to increase ATP by decreasing anabolism and inducing catabolism [88]. The AMPK/peroxisome proliferator–activated receptor γ coactivator-1alpha (PGC-1α) pathway is a key mechanism of antimicrobial defense by activating autophagy and can also reduce inflammation [29]. AMPK intersects with several signaling pathways, including blocking ERK activation and inhibiting the Ras family GTPase Rheb and its downstream signaling partner mechanistic target of rapamycin (mTOR) complex 1 (mTORC1), an autophagy inhibitor [88]. Metformin (MET) has been a useful type 2 diabetes

Table 2. Location and Function of the Poly-(ADP-Ribosyl) Polymerase and Sirtuin Families

Name	Enzymatic Activity	Cellular Location	Biologic Function Examples
PARP1	Poly(ADP-ribosyl)transferase	Nuclear	DNA repair, inflammation, metabolic regulation antiviral, cell differentiation and death
PARP2	Poly(ADP-ribosyl)transferase	Nuclear/cytoplasmic	DNA repair, inflammation, metabolic regulation
PARP3	Mono(ADP-ribosyl)transferase	Nuclear/cytoplasmic	Cell cycle regulation, DNA repair
PARP4	Poly(ADP-ribosyl)transferase	Nuclear/cytoplasmic	Cellular defense to toxins, tumorigenesis
PARP5a tankyrase 1	Poly(ADP-ribosyl) transferase	Cytoplasmic/stress granules	Antiviral, inflammation, metabolic regulation, telomere maintenance
PARP5b tankyrase 2	Poly(ADP-ribosyl)transferase	Cytoplasmic	Inflammation, metabolic regulation, Telomere maintenance
PARP6	Unknown	Cytoplasmic	Cell proliferation, DNA repair
PARP7	Unknown	Unknown	Antiviral, cytosolic RNA processing
PARP8	Unknown	Unknown	Unknown
PARP9	Inactive	Nuclear/cytoplasmic	Cell migration
PARP10	Mono(ADP-ribosyl)transferase	Cytoplasmic	Antiviral, cell proliferation, cytosolic RNA processing
PARP11	Unknown	Unknown	Unknown
PARP12	Mono(ADP-ribosyl)transferase	Cytoplasmic/golgi/stress granules	Antiviral, cytosolic RNA processing
PARP13	Inactive	Cytoplasmic/stress granules	Antiviral, cytosolic RNA processing
PARP14	Mono(ADP-ribosyl)transferase	Nuclear/cytoplasmic/stress Granules	Nuclear RNA processing, inflammation, metabolic regulation
PARP15	Unknown	Stress granules	Cytosolic RNA processing
PARP16	Mono(ADP-ribosyl)transferase	Cytoplasmic	Unfolded protein response
SIRT1	Deacetylase	Nuclear/cytoplasmic	Metabolic regulation, anti-inflammatory, Stress response, cell senescence
SIRT2	Deacetylase	Cytoplasmic	Cell cycle regulation
SIRT3	Deacetylase	Mitochondrial	Mitochondrial metabolism and respiration
SIRT4	Mono(ADP-ribosyl)transferase /lipoamidase	Mitochondrial	Metabolic regulation
SIRT5	Deacetylase	Mitochondrial	Metabolic regulation
SIRT6	Mono(ADP-ribosyl)transferase /deacetylase	Nuclear	Metabolic regulation, DNA repair/PARP1 activation
SIRT7	Deacetylase	Nucleolar	Cellular homeostasis regulation, stress response, epigenomic maintenance

Abbreviations: PARP, poly(ADP-ribose) polymerase; SIRT, sirtuin.

mellitus (T2DM) treatment for 50 years and is in extensive clinical evaluation for cancer and cardiovascular disease [89]. MET both directly and indirectly increases AMPK activity. MET also has AMPK-independent effects that enhance functions of many immune cell types, including macrophages [90].

AMPK regulates effector T-cell differentiation during responses to infections by control of a glucose-sensitive metabolic immune checkpoint to maintain cell energy levels and viability through modulating metabolism. T cells lacking AMPK displayed reduced mitochondrial bioenergetics and cellular ATP production in response to pathogenic challenge in vivo. AMPK is essential for Th1 and Th17 cell development and effective primary T-cell responses to viral and bacterial infections in vivo [91]. Also, AMPK monitors energy stress related to glucose levels and facilitates CD8 T-cell memory development by controlling the transition of metabolically active (primarily

utilizing glycolysis) effector CD8 T cells to metabolically (primarily lipid oxidation) quiescent memory T cells during the contraction phase of the immune response [92].

In *Mtb*-infected mouse models, increasing AMPK activity by MET and other agents improves autophagy and mitochondrial function and decreases *Mtb* growth [28, 29]. Singhal et al demonstrated that this effect may be mediated by increased macrophage production of ROS upon mitochondrial recruitment to phagosomes to kill intracellular bacteria [28]. MET also suppressed inflammation by an AMPK-dependent mechanism with decreased pulmonary damage. Several new AMPK pathway signaling activators are in development.

Statins: Pleiotropic HDT Effects
Statins inhibit 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase to modify cholesterol levels and have well-known

anti-inflammatory and oxidative stress reduction effects independent of lipid alterations [93]. Statins are highly pleiotropic, causing a wide spectrum of effects on immune cells, including suppressing Rho/ROCK and other Ras GTPase pathways to decrease vascular inflammation [13, 94], improve dysregulated macrophage lipid metabolism, downregulate matrix metalloproteinases (MMPs), and enhance autophagy [95]. Simvastatin added to a standard tuberculosis regimen in a murine model significantly enhanced bacillary killing in lung tissue [96]. Choices of an optimal statin and its dosing regimen for clinical evaluation remain to be established.

LEVERAGING INNOVATIVE ADVANCES IN PRECISION MEDICINE FOR TUBERCULOSIS HDT BASED ON TARGETING CORE REGULATORY PATHWAYS

The "NAD World" Concept

Nicotinamide adenine dinucleotide (NAD) and related metabolites have essential roles in regulation of a vast range of critical cell functions [97, 98]. The ratio between the oxidized (NAD^+) and reduced (NADH) forms is a critical regulator of energy physiology for all eukaryotic cells. Additionally, NAD^+ is a substrate for enzymes that utilize the molecule to either catalyze covalent modifications of target proteins and/or convert NAD^+ into active signaling metabolites. These enzymatic processes, more than redox mechanisms, can quickly deplete cellular NAD^+ levels. Knowledge of NAD biology has played a critical role in the recent advances in understanding the pathogenesis of and in developing innovative targeted therapeutics for many diseases.

Three core cell regulatory enzyme families utilize NAD^+. Membrane-bound CD38 (ADP-ribose cyclase/NAD glycohydrolase) hydrolyzes NAD^+ into cyclic ADP-ribose (cADPR). cADPR triggers calcium mobilization (via transient receptor potential cation channel, subfamily M, member 2 [TRPM2] and other channels), leading to immune cell activation and proliferation and is involved with many immune and inflammatory processes [99]. Inhibitors of CD38 enzymatic activity are in preclinical evaluation [100]. The other two enzymes, poly-(ADP-ribosyl) polymerases (PARPs) and sirtuins, will be a focus of this review due to their connections with many essential regulatory signaling pathways and available therapeutic interventions.

ADP-Ribosylation: Poly-(ADP-Ribose) Polymerases

All eukaryotic cells have PARPs or equivalent enzymes that form polymers of ADP-ribose (PAR) from NAD^+ that are attached to a substrate protein [98, 101]. The mammalian PARP family includes 17 members (Table 2); the most thoroughly studied are PARP1 and PARP2 [102]. Despite the nomenclature, only 6 members synthesize PAR. PAR chains are typically composed of up to 200 linked ADP-ribose units with extensive branching coupled onto target proteins. Five other members

add only a single ADP-ribose onto a targeted protein [103]. Chromosome structure/chromatin modification, epigenetic gene expression regulation, RNA processing, telomere maintenance, cell differentiation, aging, and cell cycle control are among the many key functions of PARP family members.

LPS induces PARP1 activity through MAPK signaling, causing an increase in inflammatory mediators, including tumor necrosis factor alpha (TNF-α), IL-1β, IL-6, interferon gamma (IFN-γ), inducible nitric oxide synthase, MMPs, and adhesion and chemotaxis molecules [104], largely driven through NF-κB signaling. PARP1 and ERK stimulate each other in a positive feedback cycle during responses to stress inducers [105]. Increased PARP1 activity occurs in a variety of pathologies including infections, diabetes, cancer, and neurodegenerative conditions and increases inflammation and suppresses autophagy [106–110]. PARP activity can also become dysregulated in stressful conditions caused by buildup of free radicals/oxidative stress and misfolded proteins, triggering endoplasmic reticulum stress. PARP activation increases expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor triggering ion channels in many cell types [111], and in a macrophage cell line, AMPA receptor activity increases TNF-α levels and generation of ROS [112].

PARPs are known to be involved in regulation of host defenses and in pathogenic mechanisms of several infectious organisms. Some pathogens activate PARP1 to modulate host cell signaling during infection to their advantage. For example, *Helicobacter pylori* induces intracellular PAR production during infection of gastric epithelial cells, playing a role in *H. pylori*–mediated chronic inflammation and disease [108]. *Trypanosoma cruzi* induces the ROS-PARP1-RelA pathway for upregulation of cytokine expression in cardiomyocytes, resulting in sustained inflammation [113]. *Mycoplasma fermentans* inhibits host DNA topoisomerase I by activation of PARP1 via the induction of MAPK signaling [114]. In contrast, *Chlamydia trachomatis* causes degradation of PARP1, most likely to downregulate inflammation [115]. Several PARPs have key roles in antiviral defenses by inhibiting transcription and translation [116, 117].

A connection between *Mtb* and PARPs has yet to be established, but *Mtb* is known to modulate MAPK activity and other pathways regulated by or regulating PARPs. One potential link is the recent report that *Mtb* produces tuberculosis necrotizing toxin, a NAD^+ glycohydrolase, depletes host cellular NAD^+ levels, and causes macrophage cell death [118]. Production of a NAD^+ glycohydrolase by *Streptococcus pyogenes* causes death of infected cells primarily by NAD/ATP depletion. However, an early burst of PARP1 activity causes PARylation leading to release of the damage-associated molecular pattern molecule, high mobility group box 1 protein (HMGB1) from the nucleus that contributes to cell death. This release of HMGB1 appears to be dependent on PARP1 activity [119].

HMGB1 is released during experimental tuberculosis [120]. One direct connection of these pathways with mycobacterial infection is a recent finding that Wnt/β-catenin signaling can inhibit Bacillus Calmette-Guerin (BCG)-induced macrophage necrosis by increasing the production of glutathione to scavenge ROS in part through repression of PARP1/AIF signaling [121]. Also, PARP1 regulates functions of many types of immune cells, including DCs, macrophages, and T and B lymphocytes and influences Th1 and Th2 differentiation [122]. PARPs downregulate Treg cells and function [123].

PARP Inhibitors

PARP inhibitors (including NAD$^+$ intermediates, nicotinamide [NAM], nicotinamide riboside [NR], and nicotinamide mononucleotide [NMN]) can decrease lipopolysaccharide (LPS)–induced inflammation and are being studied for treatment of many inflammatory diseases [34, 35]. Targeted PARP inhibition with newer drugs has been successful in cancer treatment, and the FDA has approved olaparib for BRCA-mutated advanced-stage ovarian cancers [124]. The PARP inhibitor 3-aminobenzamide attenuated progression of heat-killed *Mtb* adjuvant-induced arthritis in a mouse model [125]. Pyrazinamide's (PZA) structure is similar to NAM, and PZA may possibly be a PARP inhibitor.

Sirtuins

The other posttranslational protein modification requiring NAD$^+$ is deacetylation by sirtuins (SIRTs). SIRTs have similarities with histone deacetylases (HDACs), but SIRTs also have many nonhistone substrates, are not inhibited by drugs targeting HDACs 1, 2, and 4, and their activity levels are highly NAD$^+$ dependent [98, 126]. SIRTs are also activated by cyclic adenosine monophosphate (cAMP)/PKA-AMPK signaling independent of control by NAD$^+$ levels to deacetylate some substrates [127]. Seven human SIRTs have been identified, distinguished by their subcellular locations and deacylation targets [128]. Some SIRTs have additional nondeacetylase activities (Table 2). SIRT1 is the most studied and has a major role in regulating transcription. Histone deacetylation by SIRT1 leads to increased compaction of chromatin and decreased gene transcription. Also, SIRT1 represses transcription on a continuing basis by recruitment of nuclear enzymes involved in histone methylation and DNA methylation, suggesting a broad role for SIRT1 in epigenetic gene regulation [129].

SIRT1 also deacetylates a broad range of transcription factors to regulate target gene expression both positively and negatively. The promoters for several transcription factors of genes involved in metabolism, inflammation, and oxidative stress, including NF-kB, FOXO1, p53, COX-2, and hypoxia-inducible factor (HIF) 1α, are SIRT1 substrates, making SIRT1 signaling a vital linkage between energy availability and innate immunity [128, 130]. In general, activation of SIRT1 results in reduction of cell stress, inflammation, apoptosis, and rate of senescence [131]. Disruption of the antagonistic SIRT1 interactions with NF-kB causes increasing severity of inflammatory and metabolic disorders, including increased risk of diabetes, atherosclerosis, and aging-related diseases [132, 133]. SIRT1 activation upregulates expression of phosphatidylinositol-3, 4, 5,-trisphosphate 3-phosphatase (PTEN), an antagonist of phosphatidylinositol 3-kinase (PI3K)–serine/threonine protein kinase (AKT)–mTOR signaling to enhance autophagy [48].

SIRT1 regulates immune cell differentiation by multiple mechanisms, including shifting metabolic activity from glycolysis to fatty acid oxidation in monocytes progressing from the hyperinflammatory stage to the hypoinflammatory stage of sepsis [134, 135]. SIRT1 switches the cell energy source by enhancing downstream peroxisome proliferator-activated receptor gamma (PPAR-γ) activity through deacetylating PGC-1α. SIRT1 is a key downregulator of the IL-12/IL-23 balance in human DCs [136] and also maintains T-cell immune tolerance [137].

The roles of the SIRT family in *Mtb* infection remain unexplored. However, SIRTs are involved with host defenses against pathogens, including as evolutionarily conserved broad-spectrum antiviral host factors [138]. In contrast, SIRT activity may be modified by pathogens to achieve a survival advantage. Human immunodeficiency virus (HIV) Tat inhibits SIRT1 deacetylase activity resulting in hyperactivation of NF-kB, causing chronic activation of infected cells [139]. Herpes simplex virus type 1 modulates the AMPK/SIRT1 axis differentially during the course of infection [140]. During *Listeria monocytogenes* infection, SIRT2 plays a critical role in an epigenetic mechanism to reprogram host responses to enhance infection by deacetylating a specific histone locus in the presence of bacterial factor InlB [141]. *Leishmania infantum* hijacks the SIRT1-AMPK axis to switch macrophage mitochondrial metabolism from glycolytic metabolism to oxidative phosphorylation crucial for parasite survival in vitro and in vivo [142].

Sirtuin Modulators

To take advantage of SIRT's protective effects against inflammation, oxidative stress, and degenerative diseases observed in a wide range of animal models of diseases, many pharmacologic activators have been developed [36]. Resveratrol is a natural polyphenol being studied for treatment of several disorders involving dysregulated metabolism and inflammation/immunity, degenerative diseases, and malignancies. Resveratrol has many mechanisms of action including SIRT1 activation, and the relative importance of each mechanism is unclear [31]. Resveratrol induces cAMP signaling by suppressing cAMP phosphodiesterase to modulate inflammation and further activate SIRT1 [143]. To target SIRT directly, many SIRT activating compounds (STACs) are in development [36]. One, SRT1720, decreased

the severity of pulmonary, renal, metabolic, and cardiovascular diseases in animal models [144]. Simvastatin attenuates TNF-α–induced apoptosis via the upregulation of SIRT1 [38]. Overall, therapeutically increased SIRT activity has been associated with improved health and a longer lifespan in several experimental models.

SIRT1 inhibition can improve T-cell–mediated antimicrobial function by enhancing HIF1α activity in DCs to decrease transforming growth factor beta (TGF-β) expression and increase DC-derived IL-12 and Th1/T-regulatory cell balance [130] and increase inflammatory microbial responses. SIRT1 inhibition could potentially be useful when enhanced immunity is essential (eg, very early during infection) in persons with suboptimal defensive responses, and possibly for improving vaccine effectiveness. Several SIRT inhibitors are in clinical trials. Conversely, drug stimulation of SIRT1 activity might be useful to reduce tissue damage during the later stage of infections or with a hyperinflammatory response.

PARP-SIRT-AMPK Interactions

SIRT1 and PARP1 have extensive regulatory crosstalk [98]. Both require NAD$^+$ to function, but PARP1 binds with a higher affinity and can deplete NAD$^+$ when highly active, suppressing SIRT1 activity. Also, intermediates and enzymes of the NAD$^+$ salvage pathway contribute to regulating PARP and SIRT activity by inhibiting PARP1 while boosting SIRT1 [145, 146]. To counteract PARP1 suppression, SIRT1 interacts with and deacetylates PARP1 to inhibit PARP1 activity and maintain cellular NAD$^+$ levels and its own activity. In contrast, SIRT6 increases PARP1 activity by mono-ADP-ribosylation to promote DNA repair under stress [147]. Notably, PZA directly inhibits SIRT6 activity [148].

AMPK can cross-regulate SIRT and PARP activity. PARP activation depletes NAD$^+$ and ATP levels. In response, AMPK is activated and induces autophagy, preventing PARP-induced necrotic cell death. AMPK also phosphorylates PARP1, causing PARP1 disassociation from intron binding sites of several genes [149]. SIRT1 and AMPK are cross-activating signaling partners [150]. SIRT1 is required for AMPK activation through deacetylation of liver kinase B1 (LKB1). Activated AMPK increases NAD$^+$ levels, enhancing SIRT activity.

PI3K-AKT-mTOR Pathway

In human cell-based screening systems, inhibition of the kinase AKT (within the PI3K-AKT-mTORC1 pathway) significantly decreased growth of *Mtb* [151]. This key pathway also mediates polarization of monocytes to M2 macrophages [152, 153], and selective inhibition of AKT/mTOR signaling promotes autophagy [154]. mTORC1 and AMPK have an antagonistic relationship with both able to regulate the other and having opposite functions in several cellular processes [155]. TLR4 signaling can induce HIF1α expression by activating MMP9 to cleave

AMPK leading to mTORC1 activation [156]. Since *Mtb* is known to interact with TLR4 it may utilize this pathway to suppress AMPK activity in infected macrophages. PI3K-AKT-mTOR pathway activity also can interfere with DC, CD4, and CD8 T-cell maturation and development.

Several approaches are available to manipulate this pathway, including sirolimus inhibition of mTORC1. Sirolimus enhances *Mtb* killing in macrophages by increasing autophagy and possibly by other mechanisms [157]. Inhibition of mTORC1 has been used to improve vaccine effectiveness for many types of antigens in animal models [158], including one for BCG, with enhanced Th1 responses [159]. Inhibition of mTORC1 has improved generation of antigen-specific memory CD8$^+$ T cells with vaccinations or viral infections during both the expansion and contraction phases of response in animals. These cells had higher proliferation, improved function, and increased longevity. Many newer mTOR inhibitors are in development. Combined PI3K/mTOR inhibitors are now in clinical evaluation and may be more effective than sirolimus [160].

PTEN and p53 are cooperating tumor suppressor proteins that have key roles in macrophage polarization [161, 162] and enhancing autophagy [163]. PTEN is a phosphatase that antagonizes AKT/mTOR signaling, has regulatory roles in innate immune cell activation [164], inhibits BCG infection of several cell lines [165], and is induced by resveratrol [48]. AMPK stimulates PTEN to negatively regulate inflammation [166]. p53 expression is downregulated in BCG-infected cell lines [167]. p53 expression activators are now in clinical evaluation for cancer treatment [49].

See Figures 1 and 2 for interactions and outcomes of activation of these core signaling pathways.

Autophagy

Xenophagy is the form of autophagy that disposes of foreign materials, enhances efficiency of pathogen killing, clears proinflammatory organism components, and processes antigenic material for T-cell presentation. The relevance of xenophagy in host immunity to *Mtb* is well established [168]. However, the metabolic sensors and signaling pathways that induce autophagy and the optimal pharmacological intervention targets for infections are not fully characterized. Many of the signaling pathways discussed in this review modulate autophagy, including AMPK and mTOR as focal points [169]. For example, glycogen synthase kinase 3-β (GSK3-β), in tandem with AMPK, inhibit mTORC1. Canonical Wnt signaling blocks GSK3-β activity leading to increased mTORC1 signaling and decreased autophagy [155].

SIRT1 may influence autophagy by deacetylation of key components of its induction network, including autophagy-related proteins 5, 7, and 8. SIRT1 also induces expression of autophagy components through activation of FoxO family transcription factors [170]. Enhancement of autophagy to increase clearance
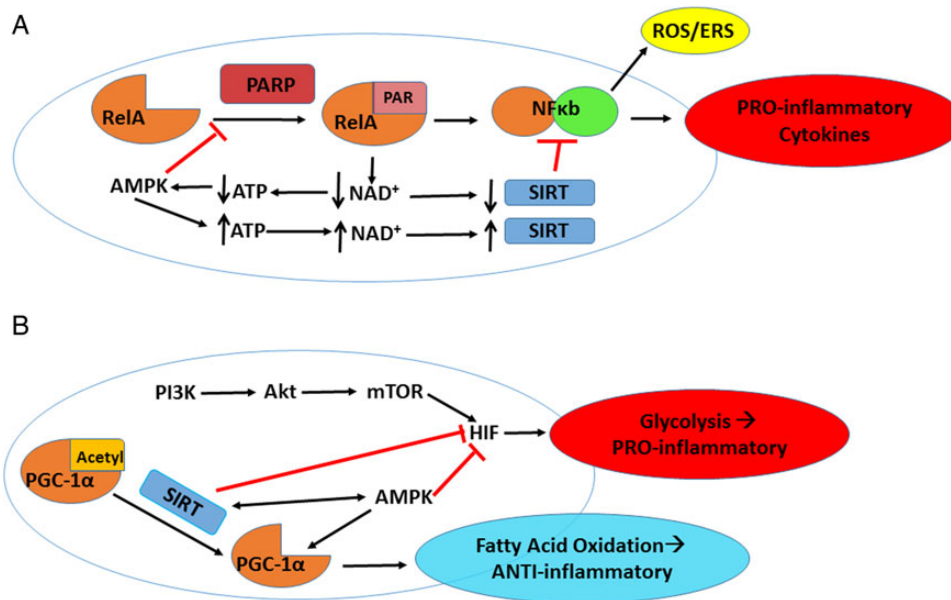
Figure 1. Signaling pathways of immunometabolism and its dysregulation. Growth receptors (including receptor tyrosine kinases) and pattern recognition receptor (PRRs) induce mechanistic target of rapamycin (mTOR) and poly(ADP-ribose) polymerase (PARP) activation through phosphatidylinositol 3-kinase (PI3K)/serine-threonine protein kinase (AKT) and c-Jun N-terminal kinase (JNK)/extracellular signal-regulated kinase (ERK) signaling, respectively, to stimulate inflammation, largely by upregulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). Phosphatidylinositol-3, 4, 5,-trisphosphate 3-phosphatase (PTEN) directly inhibits PI3K activation. Sirtuin (SIRT) and AMP-activated protein kinase (AMPK) cross-activate each other. SIRT dampens inflammation by blocking PARP directly. SIRT signaling also downregulates NF-kB activation. AMPK inhibits PARP through suppression of ERK signaling. AMPK stimulates PTEN, blocks mTOR and induces autophagy. Increased reactive oxygen species (ROS)/oxidative cellular stress induces ERK signaling and PARP activation, and endoplasmic reticulum stress (ERS) increases PARP activation. Both types of stress lead to inflammation, cell damage, and death, and damage-associated molecular pattern (DAMP) molecule release. DAMPs further increase these signaling patterns, resulting in a vicious cycle of progressive inflammation and cell death. The stress responses also lead to increased uptake of oxidized low-density lipoprotein (ox-LDL) in macrophages via scavenger receptors. Increased ox-LDL causes lipid droplet formation that may lead to foam cell development. Foamy macrophages are most often M2 polarized, producing a hypoinflammatory response and increasing susceptibility to *Mycobacterium tuberculosis* infection. β-Adrenergic and some G-protein–coupled receptors can activate adenylate cyclase that in turn increases protein kinase A (PKA) and SIRT activities. SIRT activation can also inhibit cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE).

of *Mtb* and decrease excess inflammation and cellular damage is an exciting new area for HDT research.

CELLULAR STRESS RESPONSES

Cell stress may be caused by harmful oxidants/oxidized molecules and misfolded proteins. Cells attempt to reverse these stresses by initiating inflammatory responses that further disrupt normal cell functions, and if unsuccessful, will cause apoptosis. Many pathologies, including diabetes, cancer, and infectious diseases, cause such stress responses that are primarily initiated by signaling pathways described in this review [171, 172].

Oxidative Stress and *Mtb* Infection
Reactive oxygen species are byproducts of energy metabolism and have an important role in signaling pathways and as antimicrobial effectors [173]. However, high levels of ROS lead to

DNA, lipid, and protein damage that must be limited. Cells control activity of ROS-generating enzymes and normally produce sufficient antioxidants to limit damage [174]. Molecular damage caused by excess ROS results in cellular oxidative stress. Lipid peroxidation products are elevated and antioxidant levels are decreased in myeloid cells obtained from tuberculosis patients, resulting in oxidative stress [175, 176]. However, the full role of oxidative stress in *Mtb* pathogenesis and the effects of new agents to reverse oxidative stress have not been well studied.

Endoplasmic Reticulum Stress/Unfolded Protein Response and *Mtb* Infection
Newly synthesized proteins are transported to the endoplasmic reticulum (ER) for posttranslational modification, proper folding, and secretion to their ultimate location. Accumulation of misfolded proteins in the ER disrupts cell function and

Figure 2. Poly(ADP-ribose) polymerase (PARP) and sirtuin (SIRT) effects on immunometabolism. *A*, PARP "PARylates" many substrates including RelA for activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in an oxidized nicotinamide adenine dinucleotide (NAD+)–dependent manner, leading to elevated reactive oxygen species (ROS)–oxidative stress/endoplasmic reticulum stress (ERS) and proinflammatory cytokine production. PARP hyperactivity also causes chronic inflammation by depleting NAD+ that subsequently decreases SIRT activity and lowers adenosine triphosphate (ATP) concentrations. SIRT can counteract NF-κB activation through deacetylation of the RelA/p65 subunit of NF-kB. Depleted ATP activates AMP-activated protein kinase (AMPK), which in turn increases ATP and NAD+ levels, leading to increased SIRT activity and suppressed PARP activity that may bring the cell back to equilibrium. *B*, SIRT regulates immune cell metabolic activity largely through regulation of hypoxia-inducible factor (HIF1α) and peroxisome proliferator–activated receptor γ coactivator (PGC-1α). Increased phosphatidylinositol 3-kinase (PI3K)/serine-threonine protein kinase (AKT)/mechanistic target of rapamycin (mTOR) signaling activates HIF to convert cell energy production mechanism to aerobic glycolysis during immune activation enhancing T-helper 1 cell differentiation. SIRT, along with AMPK, converts T-cell energy metabolism to fatty acid oxidation by blocking HIF activity and activating PGC-1α to enhance differentiation toward memory T cells and T-regulatory cells.

induces the unfolded protein response (UPR) [177]. UPR utilizes ER-localized transmembrane proteins to restrict protein synthesis and influx into the ER, while activating transcription of chaperone proteins to facilitate unfolded protein removal. If ER stress still progresses, C/EBP-homologous protein (CHOP) is activated to induce apoptosis. *Mtb*-induced ER stress (ERS) in infected granuloma macrophages correlates with increased apoptosis, and contributes to *Mtb* survival [178–182]. Testing of therapeutic agents known to reduce ERS for use as tuberculosis HDTs should be greatly expanded.

Cell stress induces many proinflammatory effectors, including NF-κB. Targeting NF-κB directly is limited by intrinsic pathway complexity, cross-talk with other pathways, and poor drug specificity. Efforts to improve NF-κB targeting are ongoing and may involve multimodal therapies [183]. Most NF-κB signaling inhibitors in development are IκB kinase ε (IKKε) inhibitors [184]. Inflammasomes are stress-induced protein complexes that form around intracellular Nod-like receptors and upregulate IL-1β and IL-18 production, leading to further

inflammation [54]. Inflammasomes can be inhibited by drug therapy.

OTHER INNATE IMMUNE CELL TYPES AND MEVALONATE METABOLISM

The recent review by Bhatt et al clearly presents the pressing need to study key signaling pathways, master regulators, and cellular stresses/reactions in other immune cells besides myeloid to determine how they are affected by tuberculosis and investigate potential interventions [185]. For example, γδ T cells have been hypothesized to play important roles in host defense against *Mtb* infection as early infection detection sentinels bridging innate and adaptive immunity. Human Vg9Vd2 T cells are activated by prenyl pyrophosphates produced by mevalonate metabolism [186]. Drugs targeting the mevalonate pathway by inhibiting farnesyl pyrophosphate synthase cause upstream accumulation of the cognate antigen, isopentenyl pyrophosphate, and can rapidly activate Vg9Vd2 T cells [70]. Whether drugs

enhancing γδ T-cell function by this mechanism may be effective for tuberculosis HDT is an unanswered question.

LIPID METABOLISM AND *MTB* INFECTION

Release of free radicals from stressed or damaged cells causes formation and release of oxidized low-density lipoproteins (ox-LDLs) and other oxidized lipids. Macrophages express several scavenger receptors, including CD36, lectin-type ox-LDL receptor 1 (LOX-1), and SR-1A, that transport ox-LDL into cells [187]. Scavenger receptor expression is regulated by Wnt, PPAR-γ, and SIRT signaling [188, 189] and induced by ERS [190]. Increased ox-LDL within macrophages causes accumulation of lipid droplets and development of foam cells. Foam cells often become polarized into M2 macrophages with suppressed IL-12 production and increased IL-10 expression, and are permissive for growth of mycobacteria. Also, a recent study in a cancer model demonstrated that ERS-induced accumulation of abnormal lipid bodies within DCs inhibits T-cell activity by interfering with antigen presentation and immunostimulatory activity, suggesting that targeting ER stress response may be a unique approach to enhance anticancer immunity [191]. Angiotensin II type 1 receptor activity also upregulates the expression of LOX-1 in several cell types [192] and initiates TLR4 signaling, resulting in oxidative stress [193]. CD36 and LOX-1 expression are elevated in *Mtb* animal models, whereas in CD36-deficient mice, tuberculosis infection is attenuated [194, 195]. Several agents are available to evaluate for reversal of these abnormalities.

VITAMIN D, PHENYLBUTYRATE, AND OTHER ANTIMICROBIAL PEPTIDE INDUCERS

Vitamin D plays an essential role in modulation of lipid metabolism abnormalities and related inflammation and has a prominent role in cellular immune function [196]. Activated vitamin D enhances expression of antimicrobial peptides [197, 198] including cathelicidin [199]. Clinical trials of adjunctive vitamin D in tuberculosis treatment have not shown consistent benefit [200]. However, effects of vitamin D in combination with other HDT drugs have only begun to be explored. Sodium phenylbutyrate (NaPB) is an FDA-approved agent for treatment of urea cycle disorders that is also an HDAC inhibitor increasing cathelicidin expression. The combination of vitamin D and NaPB results in additive enhancement of cathelicidin levels in cell lines [72]. A pilot clinical trial of this combination as adjunctive therapy for tuberculosis treatment demonstrated safety but no difference in 8-week culture conversion [201]. Determination of the most effective dose for NPB may need further study. NaPB also relieves ERS as a protein chaperone. Addition of resveratrol, pterostilbene, or nicotinamide to vitamin D

causes synergistic induction of cathelicidin and other antimicrobial peptides in cell lines [68].

TUBERCULOSIS AND DIABETES MELLITUS: UNFORTUNATE PATHOGENIC SYNERGY

T2DM is both a metabolic and inflammatory disease with complications caused by many inputs, including high levels of PAMP-initiated signaling related to the formation of advanced glycation end products (AGEs) that are ligands for many PRRs, including receptors of AGE (RAGE) [202]. Other inputs include oxidative stress, ERS/UPR/inflammasome activity, dysregulated lipid metabolism, oxidized lipid accumulation/foam cell formation, M2 polarization, increased PARP activation, and decreased SIRT activity. Poorly controlled T2DM causes macrophages to produce more inflammatory cytokines and chemokines as part of the ongoing positive feedback loop of chronic "metaflammation" [203].

T2DM increases the likelihood of active tuberculosis disease, slower treatment response, and death [204, 205]. Macrophages from patients with T2DM have reduced phagocytosis and antimicrobial peptide production, and highly increased ROS and proinflammatory cytokine secretion. These altered innate immune responses also delay development of adaptive immunity responses with IFN-γ–producing T cells arriving at infection sites almost a week later in the presence of T2DM than without T2DM. After arrival, these T cells produce increased levels of Th1 and Th17 cytokines and are likely to cause increased pulmonary tissue damage. Several parallels exist between the pathogenic mechanisms of T2DM and *Mtb*, leading to ineffectiveness of macrophage and DC functions (eg, impaired chemotaxis, phagocytosis, autophagy, antigen processing), cell necrosis/apoptosis, and tissue damage. T2DM and tuberculosis have common and additive mechanisms that disrupt cell regulatory signaling that are very likely to play prominent roles in the worsened course of tuberculosis infection with T2DM.

Given these common features, interventions designed to prevent or decrease diabetic metabolic dysfunctions, pathogenic mechanisms, and resulting complications may also be useful for *Mtb* HDT with and without concurrent T2DM. These include metformin, other AMPK and SIRT1 activators, imatinib, and PARP and dipeptidyl peptidase-4 inhibitors (DPP-4I). DPP-4Is are in wide clinical use and potently inhibit inflammation in mononuclear cells obtained from patients with diabetes by downregulating NF-kB expression through TLR2/4 and JNK signaling [69], and decreasing inflammasome formation and foam cell development [206, 207]. DPP-4Is can enhance effector T-cell trafficking to improve antitumor immunity in mice by preserving the active form of the chemokine CXCL-10. Sitaglipitin inhibits posttranslational processing (cleavage) of CXCL-10 by DDP-4 that also produces an antagonistic

derivative. This derivative binds to its receptor, CXCR3, but does not induce chemotaxis [208].

CONCLUSIONS AND THE WAY FORWARD

A revolution based on advances in innovative targeted molecular interventions and precision medicine is rapidly progressing in other medical research areas with rich pipelines of potential interventions that must be leveraged if progress is to be accelerated for tuberculosis HDT research. In the face of increasing antimicrobial drug resistance, the movement for developing tuberculosis HDT is growing rapidly and overlaps with innovative new approaches to develop more effective tuberculosis vaccines. New approaches can be based on better understanding of the master/core controllers of all cells (including immune cells), how to strengthen host defense mechanisms, and how to reverse the disruptive effects, as is being done for other diseases. However, the roles of the master regulator pathways of cellular metabolism and immunity and their linkage (immunometabolism) in *Mtb* infection have barely been explored. Only two references were identified addressing the roles of PARPs or SIRTs in tuberculosis pathogenesis by a recent literature review [121, 209], and only a few have addressed the roles of AMPK and mTOR. Improving knowledge of the effects of cellular dysfunction in immune cells (eg, ERS and oxidative stress) caused by infections is also critically important for advancing tuberculosis HDT research.

Complexity of the myriads of cell signaling, metabolic, and immune effector interactions is a huge challenge, and some targeted interventions to modulate fundamental cell regulatory mechanisms may have unexpected adverse effects. Research must proceed to determine which HDT targets are most promising and how to best use the potential interventions to be effective and safe for improving tuberculosis therapy, as is being accomplished in oncology. Ongoing development of pathway inhibitory and activating agents that are highly specific for individual molecules—for example, active for only 1 of the PARPs or SIRTs (instead of acting on several of them)—will be important advances. Oncology trials indicate that many of the new agents that modulate key pathways are quite tolerable. Only short-term (8–12 weeks or less) use of these agents may be needed as adjuvants for tuberculosis treatment. Of course, even with short-term drug use, long-term safety is unknown and will remain a concern to be carefully addressed in all future HDT clinical research. Safety endpoints must include possible worsening of tissue damage/pulmonary function, tuberculosis treatment response, and HIV replication status.

Hundreds of drugs are approved or in various stages of development for modulation of regulatory signaling pathways, and more are being approved for clinical use at a rapid rate. Selected drugs from the relevant classes that are now approved or in clinical trials can be screened for activity to restrict *Mtb* growth in appropriate cell lines. To help address issues regarding feasibility of application in nations most impacted by tuberculosis and of patient drug tolerance and adherence, none of the agents listed in Table 1 are biologic, parenteral, or highly toxic traditional chemotherapeutic agents. Even if only a few of these new-generation HDT agent classes can be repurposed for clinical use against *Mtb*, the number of drugs in the tuberculosis therapeutic pipeline would be greatly expanded. Also, repurposing allows avoidance of the vast majority of drug development costs. As with antiretroviral therapy and some other essential/life-saving medicines, the initially high costs of these agents for use in developing nations will significantly decrease over time. Prices of these drugs drop most rapidly after generic versions can be manufactured in or imported by countries within the regions impacted most by tuberculosis. Such lower-priced generics now undergo review by the FDA for "tentative approval" to allow US government funding to be used for their purchase and distribution to low-income countries.

To quote the Director of the US National Institutes of Health, Dr Francis Collins, precision medicine interventions are ". . . drugs and antibodies designed to counter the influence of specific molecular drivers. Many targeted therapies have been (and are being) developed, and several have been shown to confer benefits, some of them spectacular" [210]. Many pathogens clearly produce specific molecular drivers to subvert the same core cellular regulatory mechanisms that are modulated by malignancies. Because precision medicine agents are aimed at fundamental immune cell regulatory mechanisms, they are likely to also be effective for treatment of HIV and many other pathogens. A wide spectrum of new knowledge, research tools, and candidate therapies await adaption for tuberculosis HDT development and should advance powerful and innovative approaches to fundamentally transform antimicrobial therapy.

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