

Review

Zinc: An Emerging Axis of Host–Pathogen Interaction in Tuberculosis

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Abstract

Zinc is an essential micronutrient required by all forms of life, including *Mycobacterium tuberculosis* (Mtb), the etiological agent of tuberculosis. Mtb can persist within the host for years and requires a prolonged, multidrug treatment regimen for effective clearance. The sequestration of essential metals, including zinc, during bacterial infection is a key component of the host's innate immune response. In this process, metal-chelating proteins such as the neutrophil-derived protein, calprotectin, play a central role in nutritional immunity by limiting microbial access to critical metal cofactors. Despite its importance, the impact of nutritional immunity on Mtb pathogenesis remains incompletely understood. In this review, we summarize recent advances in our understanding of zinc-responsive adaptations in Mtb and propose that zinc limitation within the host contributes significantly to the long-term persistence of this pathogen.

Keywords: zinc; neutrophils; nutritional immunity; calprotectin; S100A8/A9

1. Introduction

The World Health Organization estimates that approximately one quarter of the global population is infected with *Mycobacterium tuberculosis* (Mtb), the causative agent of tuberculosis (TB) [1]. According to the Global Tuberculosis Report 2025, there were approximately 10.7 million cases of tuberculosis in 2024, with 1.23 million deaths [1]. One of the reasons for the staggering impact of TB on global public health is the extraordinary ability of Mtb to persist for months during chemotherapy, often without any clinical symptoms of disease [2,3]. A typical treatment regimen for tuberculosis entails daily administration of at least three antibiotics for 4–6 months [4]. Although bacterial load in the sputum appears to be reduced by over 90% within the first two weeks [5], and sputum conversion in the majority usually occurs by two months, an early withdrawal of antibiotics often leads to a high frequency of relapses [6,7]. Moreover, bacilli recovered from relapsed TB sputa have the same minimal inhibitory concentrations for the tested drugs as the strains cultured before the treatment [8], suggesting that the antibiotic tolerance of Mtb in the relapsed cases is an outcome of phenotypic variation across individual bacilli. Drug-tolerant subpopulations of Mtb cells have also been observed in multiple in vitro conditions, and



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are generally correlated with slow-growth and metabolic quiescence [9]. While the evidence for metabolically quiescent bacilli in hosts remains elusive, the two most extensively studied host-induced growth-restrictive conditions are low pH and hypoxia [10–18]. The acidification of phagolysosomes in Mtb-infected macrophages has been shown to restrict the growth of intracellular bacilli [19,20], thus supporting the hypothesis that the persister subpopulation could be harbored within phagolysosomes. Similarly, the obligate requirement of oxygen for Mtb growth and the presence of a hypoxic environment in TB granulomas together form the basis for host-induced hypoxic conditions as a key driver for the development of non-replicating drug-tolerant persisters in vivo [12,18]. However, the causal effect of low pH and/or hypoxia on the development of non-replicating persisters in vivo is yet to be demonstrated.

Recent findings from our studies and others reveal that the level of free zinc, an essential elemental micronutrient for all forms of life, is a crucial determinant of transcriptional and metabolic reprogramming in Mtb and other mycobacteria [21–28]. For example, a relatively modest decrease in the intracellular free zinc levels induces changes in the composition of the Mtb ribosome, which eventually undergoes hibernation upon further zinc depletion [25,26]. Ribosome hibernation is a highly conserved process across bacterial species, presumably to preserve the non-translating ribosomes in slow/non-replicating bacilli and enable them to restart protein synthesis during growth resuscitation [29]. Moreover, the evidence of zinc-limiting conditions in Mtb-infected host lungs [23,26,30], likely induced by the host innate immune system through a process commonly called nutritional immunity, raises the hypothesis that host sequestration of zinc from Mtb underlies the development of non-replicating persisters. Here, we present a literature review supporting this hypothesis.

1.1. Zinc: An Essential Elemental Nutrient for All Forms of Life, Including Mtb

Zinc is a vital micronutrient and is essential for various metabolic and enzymatic functions across all life forms, including DNA polymerase, RNA polymerase, tRNA synthetases, and enzymes responding to oxidative stress [31]. In prokaryotes, it is estimated that zinc is bound to approximately 5–6% of cellular proteins, with roughly 50% identified as catalytic enzymes, and 20% requiring zinc as a structural component [32–34]. In addition to structural and catalytic roles, zinc acts as a regulatory signal that modulates gene expression and stress responses in bacteria [31,35]. Although the total intracellular concentration of zinc ranges from 0.1 to 1 mM, the majority of zinc is closely associated with various metalloproteins, while the pool of free zinc ions remains limited to the picomolar range [32,35,36]. The essential role of zinc in bacterial systems is further highlighted by the conserved evolution of dedicated zinc homeostatic pathways, which ensure optimal zinc levels for metabolism [31,35–38].

Zinc homeostasis in bacteria: The biological consequences of zinc pose a fundamental challenge, requiring bacteria to precisely balance zinc concentrations to maintain adequate intracellular levels that sustain vital cellular functions while preventing excessive accumulation and toxicity [39,40]. The need to balance and maintain intracellular zinc levels led to the evolution of sophisticated influx, distribution, and efflux systems that regulate zinc homeostasis [39,40]. In prokaryotes, zinc homeostasis is regulated by three interconnected pathways: influx systems that take up zinc from the extracellular environment, efflux systems that export zinc to prevent zinc toxicity, and regulatory networks that monitor intracellular zinc concentrations to modulate zinc transporter expression [34,41]. High-affinity ATP-binding cassette (ABC) transporters such as ZnuABC and low-affinity ZIP family permeases facilitate zinc uptake [39]. P-type ATPases, such as ZntA, cation diffusion

facilitators (CDF), and resistance-nodulation-division (RND) family pumps, facilitate zinc efflux [42].

The expressions of zinc influx and efflux systems are often controlled by zinc-regulated metalloprotein transcription factors [33–35]. Examples of these zinc-responsive transcriptional repressors include Zur (zinc uptake regulator, Fur family), AdcR (MarR/SlyA family), and SmtB (ArsR family), while examples of zinc-responsive transcriptional activators include: ZntR (MerR family), ArsR/SmtB families, and SczA [34,37,43–48]. Interestingly, and unique to mycobacteria, SmtB and Zur are encoded within a single operon, whereas most bacteria encode them separately [44]. Zur and SmtB diametrically oppose each other. While zinc-bound Zur binds to the promoter regions of its target genes and represses the transcription of zinc influx systems, zinc-unbound SmtB binds to the promoter regions of its target genes and represses transcription of zinc efflux systems [44]. Thus, Zur acts as a transcription repressor under zinc-replete conditions while SmtB acts as a repressor under zinc-limited conditions [43,44].

Zinc-responsive transcriptional repressors such as Zur and AdcR bind zinc ions and, in their fully metalated and hemimetalated states, inhibit transcription of their respective zinc uptake systems by binding to promoter regions and repressing transcription [37,43,44,47,49]. The region in which Zur binds is known as the *zurbox* and consists of a conserved AT-rich region of 18–30 base pairs [50,51]. During zinc limitation, zinc-free Zur and AdcR lose their affinity for their respective DNA sequences, leading to de-repression and robust transcription of their respective zinc uptake systems [43,44,47,49].

Conversely, transcriptional activators upregulate zinc efflux or storage systems to mitigate toxicity from excess zinc [43,44,52]. For example, SczA in *S. pneumoniae* binds upstream of a palindromic DNA sequence when zinc is limited, thereby blocking RNA transcription of the *czcD* zinc exporter [37,38]. When bound to zinc, SczA binds to a distinct region upstream of the *czcD* promoter, inducing its transcription [37,38]. Another efflux pump activator is ZntR, which binds to DNA in both the presence and absence of zinc [43,48,53]. The binding of zinc by ZntR induces a conformational change in the DNA double helix, enabling access for RNA polymerase and robust transcription of the P-type ATPase and efflux pump, ZntA [43,48,53].

Although the total cellular zinc concentration is estimated to be in the millimolar range, studies in *E. coli* have determined that changes in femtomolar concentrations of free zinc can trigger either Zur-mediated zinc uptake or ZntR-dependent zinc efflux [43,44,54].

To combat zinc toxicity, bacteria utilize three main types of efflux pumps: P-type ATPases, CDF (cation diffusion facilitators) proteins, or RND (resistance and nodulation) tripartite efflux pumps [34,38,43,44,55,56]. Furthermore, P-type ATPases can be divided into two subgroups: the monovalent Cu^+ and Ag^+ subgroup, and the divalent Zn^{2+} , Cd^{2+} , Pb^{2+} subgroup [55]. Of the multiple P-type ATPases encoded by *M. tuberculosis*, CtpC (Rv3270) is the only characterized zinc-efflux pump; it is induced by high zinc concentration to confer resistance against zinc poisoning, and requires a metallochaperone, PacL (Rv3269), for its activity [57,58]. However, the transcription regulator of CtpC and PacL is yet to be identified.

To increase intracellular zinc concentrations under zinc-limiting conditions, two important ABC-transporters, AdcABC and ZnuABC, are encoded by prokaryotes [30,33,38,39,44,48,49,52]. AdcABC is primarily encoded by Gram-positive bacteria [59,60], and ZnuABC by both Gram-positive and Gram-negative bacteria [61–63]. In the AdcABC system, AdcA is a zinc-binding extracellular subunit, AdcB is a permease, and AdcC is an ATPase [52,59]. While the AdcABC influx system has mainly been studied in the *Streptococcus* genus, the ZnuABC system has been studied in many bacterial species, including mycobacteria [34,43,47,49,55,64,65]. The ZnuABC transporter is transcriptionally regulated by Zur

and comprises three proteins: the soluble ZnuA, which resides in the periplasm, and which binds and delivers zinc to the ZnuB channel, which then transports zinc into the cytoplasm, and the ZnuC ATPase that provides the energy needed to transport the zinc ions across the inner membrane [36].

Mycobacterium smegmatis contains two *znuABC* operons: *znuABC1* (*Msmeg_6045-6047*) as the primary zinc uptake system, and *znuABC2* (*Msmeg_6049-6051*) [44,64], which is predicted to either be a backup importer or activated at lower zinc concentrations than *znuABC1* [64]. In fact, stepwise de-repression of Zur-controlled genes in multiple phases has been observed [44,64]. Mtb contains a reduced form of *znuABC* comprising only *Rv2059* (*znuA*) and *Rv2060* (*znuB*) with only three transmembrane domains [64]. Beyond zinc influx transporters, Zur also regulates several other genes involved in zinc homeostasis [66]. In Mtb, thirty-two genes, presumably in sixteen operons, were upregulated in a Δ *zur* strain [66]. Taken together, a complex hierarchical network of gene expression is dedicated to maintaining zinc homeostasis in bacteria, highlighting the importance of zinc in bacterial physiology.

Zur is the master regulator of zinc homeostasis in bacteria: Zur belongs to the Fur (ferrous uptake regulator) superfamily of transcription factors that can reversibly bind zinc, exhibiting binding sites with a femtomolar affinity for the metal [67–69]. The crystal structure identifies three distinct domains of Zur: an N-terminal DNA-binding domain (DB), a C-terminal dimerization domain (D), and an interdomain hinge that contains the metal-binding M-site, which binds to one zinc ion [65,67]. The D-site, on the surface of the D domain, and the C-site, at the C-terminus, are the second and third zinc-binding sites, respectively [65,67]. The C-site acts as a structural zinc-binding site, while the M- and D-sites serve as regulatory zinc sensors [65,67]. The M-site acts like an on-off switch, while the D-site modulates and fine-tunes Zur repression, leading to a stepwise de-repression of Zur-regulated genes [65,67]. Zur is constitutively dimeric, but is loosely organized in an “open” state in the absence of zinc, while zinc binding induces conformational changes into a “closed” state that enables high-affinity DNA binding [65,67,70]. Zinc-bound Zur binds to the *zurbox*, thereby obstructing RNA polymerase and functioning as a repressor [49,65,68]. The affinity of Zur for different *zurbox* sequences in the genome can be differentiated by the number of zinc atoms in the dimer: while some *zurbox* sequences remain occupied by a partially metalated Zur, others are de-repressed [71], thus allowing stepwise expression of genes during the gradual depletion of intracellular zinc [71]. This stepwise expression may expand the scope of Zur-regulated transcriptional reprogramming from binary to modular, thereby enabling bacteria to mount a broader range of responses to zinc starvation.

Zur-regulated ribosome remodeling in Mtb under moderate zinc starvation: Zinc limitation induces Zur-dependent de-repression of the ribosomal protein paralogues lacking the zinc-binding CXXC motif [24,72,73]. During ribosome assembly, these proteins, which are called C- for the lack of the motif, kinetically outcompete their C+ counterparts with the CXXC motif, thereby remodeling the ribosome from C+ to C- composition. Overall, 7 of the 54 core ribosomal proteins possess C+/C- paralogue pairs in bacteria [72]. These include S14, S18, L28, L31, L32, L33, and L36, with each C+/C- paralogue pair sharing 30–60% protein sequence identity [67,72]. *Streptomyces coelicolor* has previously been shown to contain all seven paralogous pairs [74]. Studies in *S. coelicolor* and *Bacillus subtilis* demonstrate step-wise de-repression of C- ribosomal paralogues [49,65,71,75]. In *S. coelicolor*, using binding kinetics studies, Shin et al. determined that Zur had a greater binding affinity for the promoter of the *l33c-* gene than the *l32c-* gene [49,65]. Previous work in *B. subtilis* reported three distinct de-repression stages of zinc-regulated ribosomal protein paralogues, L31, L33, and S14 [75]. The hemi-metalated form Zur_2Zn_3 de-represses *l31C-* and *l33C-* in the first stage, followed by *znuABC*, and the metallochaperone *yciC* in the second stage [75]. Lastly,

the fully unmetalated $Zur_2:Zn_2$ results in the de-repression of *s14C*- [75]. Importantly, S14C-incorporation requires de novo ribosome assembly as it is an essential factor for ribosome biogenesis [75].

The genes encoding C- ribosomal proteins in mycobacteria are usually organized in Zur-regulated operons [22–25]. While *M. smegmatis* and its closely related rapidly growing mycobacteria encode five C+/C- paralogues (S18, S14, L33, L28, and L31) [22,24,25], *Mtb* encodes four such pairs, S18, S14, L33, and L28 [23,24]. Notably, *Mtb* seems to possess a lineage-specific duplication of L28C-, thus potentially encoding two L28 C- ribosomal proteins for a single C+ paralogue [21,23,24], although only one of these (encoded by Rv2058c) is usually detected in the C- ribosomes isolated from most in vitro zinc-starved *Mtb* cultures. The mycobacterial C+/C- paralogues exhibit 35–60% amino acid sequence identity [22,24,25], implying that their substitutions could potentially impact the structure and function of the ribosome [28].

Multiple independent studies have demonstrated that *Mtb* and *M. smegmatis* respond to zinc starvation by inducing transcription of C- ribosomal proteins in a Zur-dependent manner [22–25,28], and mutations in the encoding genes lead to growth impairment under zinc starvation [22,25], indicating that ribosome remodeling serves as an adaptive mechanism of zinc homeostasis in mycobacteria—similar to the findings in *B. subtilis* [21–25,66,76,77]. Furthermore, Prisic et al. demonstrated that the addition of calprotectin—a metal-chelating agent released by neutrophils in necrotic granulomas—to *Mtb* growth media enhances the expression of C- ribosomal proteins, suggesting that *Mtb* bacilli residing within the extracellular environment of neutrophil-rich necrotic granulomas likely induce C-ribosomes, while those residing intracellularly within zinc-rich phagosomes of macrophages predominantly produce C+ ribosomes [23–25]. Consistent with this model, infection of C57BL/6 mouse with a strain of *Mtb* expressing a fluorescent reporter from the promoter of the C- ribosomal protein exhibited reporter expression in ~60–70% of bacilli at 14 weeks post-infection, while only 10% of bacilli expressed the reporter at 4 weeks post-infection when cells were predominantly replicating intracellularly [25]. Interestingly, *Mtb* cells cultured in zinc-limiting conditions appear to be more virulent than their zinc-rich counterparts [23]. Moreover, transcriptomic analyses of sputum from tuberculosis patients have illustrated zinc-starvation responses in *Mtb* bacilli, suggesting a zinc-limiting microenvironment in the hosts [30,78]. Taken together, these findings offer compelling evidence for zinc-responsive ribosome remodeling as a key adaptive mechanism in *Mtb* during its growth in vivo and possibly during transmission [78].

Ribosome hibernation is induced by zinc-starvation in mycobacteria: In zinc-starved mycobacteria, single-particle cryo-EM structures at 3.3 Å have revealed that the C- ribosome is the preferred target of the protein Y homolog called Mpy (mycobacterial protein Y), which binds to the decoding center on the 30S subunit and inactivates the 70S C- ribosomes into hibernating monosomes [25–27].

Ribosome hibernation in bacteria refers to the stress-induced reversible inactivation of bacterial ribosomes, in which active 70S are converted into inactive 100S dimers or 70S monosomes [79–91]. This process employs various specific factors, of which RMF, short and long HPF, and protein Y homologs are the most widely studied candidates and bind to the decoding center of the ribosome [79,81–91]. More recently, new atypical members of ribosome hibernation factors called Balon or Ribosome Tunnel Occlusion Factor (RTOF) have also been discovered, which bind either to the vacant A-site or to the nascent polypeptide exit tunnel (NPET), respectively [85,92]. Ribosome hibernation is highly conserved across the bacterial kingdom and has also been observed in eukaryotes [68–78]. The process of hibernation is hypothesized to preserve the cytosolic pool of associated ribosomes by preventing subunit dissociation caused by unfolded proteins, thereby making

them resistant to degradation by nucleases and facilitating the resumption of translation following periods of stress [29].

Like other members of the protein-Y family of ribosome hibernation factors, Mpy contains a unique $\beta\alpha\beta\beta\alpha$ RNA-binding topology [25]. The N-terminus of Mpy binds to the 30S ribosomal subunit proteins S3 and S9 at the head region and interacts with the 16S rRNA helices h18, h24, h44, h31, and h34, and h28, blocking translation while the C-terminus is disordered [25–27]. This binding site coincides with the binding region of other pY family proteins that hibernate the ribosome [25]. Mpy inactivation of non-translating 70S C-ribosomes by binding to the decoding center helps to prevent their degradation [24–26].

Although Mpy is constitutively expressed, its binding to the 70S C- ribosome is facilitated by the Mpy recruitment factor (Mrf), whose transcription and post-transcriptional stability are regulated by zinc. Mrf is located within the C- operon in *M. smegmatis* (MSMEG_6069) and adjacent to the second L28 C- paralogue in Mtb (Rv0106) [24–26]. Mrf contains the zinc-binding CXXC motif, suggesting that its stability is controlled by zinc and that the protein is post-transcriptionally regulated in a zinc-dependent manner [26]. Zinc-bound Mrf is turned over by the Clp protease system [26]. When zinc-bound Mrf is turned over, Mpy recruitment remains low at the zinc concentration that induces its transcription and ribosome remodeling [26]. Using a CRISPRi inducible knockdown system, Li et al. demonstrated that knocking down the ClpP1P2 protease resulted in Mrf stability in zinc-replete conditions [26]. Furthermore, Ziemski et al. performed a genome-wide screening of ClpC1 targets in Mtb and determined Mrf (Rv0106) as a likely candidate of ClpC1, the chaperone associated with ClpP1P2 protease [93]. ClpS has been shown to interact with ClpC1 as an adaptor for ClpP1P2 [26,94]. Li et al. could detect Mrf-ClpS interaction only under zinc-replete conditions [26]. These findings together suggest that when zinc is abundant, zinc-bound Mrf readily interacts with ClpS-ClpC1 and is degraded by the ClpP1P2 protease system, presumably through ClpC1 [26]. In zinc-starved conditions, a zinc-free form of Mrf no longer interacts with the ClpP1P2 protease system, thereby stabilizing the protein and inducing Mpy recruitment [26].

Taken together, the adaptive responses induced by zinc-starvation, including ribosome remodeling and hibernation, likely impact the physiology and metabolism in Mtb in ways that could change the growth and/or drug sensitivity of the pathogen. However, the relevance of these changes in a host depends on the extent to which zinc is sequestered from Mtb during infection.

1.2. Zinc Transport and Immune Regulation by Host

Like bacteria, zinc has a critical role in human biology: approximately 10% of the human proteome, including essential enzymes and transcription factors, binds zinc [95,96]. Zinc deficiency has a detrimental effect on the host's ability to control respiratory infections [97–99], and it is understood that zinc is a necessity for the homeostatic maintenance and function of immune cells [97,100,101]. Broadly, inflammatory pathways including toll-like receptor activation and cytokine signaling have been shown to influence the surface expression of zinc transporters, modulating intracellular and extracellular zinc availability [102]. ZIPs or Zrt and Irt-like proteins (zinc- and iron-regulated transporters, respectively) increase cytosolic zinc by importing from extracellular and phagosomal spaces. In contrast, ZnTs (Zinc Transporters) decrease cytosolic zinc by exporting into extracellular and phagosomal spaces [102]. The modulation of both ZIP and ZnT expression in response to infection has been observed in many immune cells, including dendritic cells [103], T cells [104,105], monocytes [106,107], mast cells [108], and neutrophils. For example, bacterial lipopolysaccharide (LPS), a powerful pro-inflammatory immunological stimulator, can induce toll-like receptor activation in dendritic cells and has been shown to downregulate

ZIP6 and ZIP10, thereby decreasing intracellular zinc and driving cellular maturation [103]. In contrast, ZIP8 was observed to be upregulated as a consequence of T-cell receptor activation in vitro [109]. ZIP4 mutations were also observed in systemic zinc deficiency leading to loss of Langerhans cells—epidermal macrophages—disrupting barrier function and homeostasis [110]. The effects of differential inflammatory responses to an infection result in pathway-specific zinc mobilization. Moreover, these specific responses directly affect zinc availability and storage in cell-specific instances (Table 1). While zinc bioavailability has been established as a requirement for normal immune cell function [101], it is equally important for immune effectors to limit pathogens from accessing zinc [111], and the means by which this is accomplished are extensive.

Nutritional immunity specifically refers to host strategies that restrict pathogens' access to essential nutrients, particularly metal cofactors required for microbial metabolism and virulence [112]. Broad pro-inflammatory signaling pathways sequester zinc locally at infection sites as well as systemically [111,113,114]. For example, pro-inflammatory stimulation appears to induce blood serum secretion of the pro-inflammatory cytokine IL-6, thereby upregulating zinc importer ZIP14 (slc39A14) in hepatocytes [114]. This ZIP14 upregulation likely contributes to hepatocyte scavenging of zinc and decreased concentration of zinc in serum [114]. Moreover, intraperitoneal challenge with LPS and the subsequent systemic inflammatory response result in increased zinc uptake by ZIP14 expression in gastrointestinal cells and hepatocytes [115]. Furthermore, in comparison to the parent wild-type strain, a polymicrobial sepsis model in a ZIP14-deficient mouse produced increased levels of IL-6 and other pro-inflammatory cytokines, while reducing zinc concentration in the liver [116]. Taken together, these studies provide compelling evidence of systemic zinc sequestration during infection. Although the ultimate purpose of systemic zinc sequestration appears to be to restrict its availability to pathogens, the influence of zinc redistribution on immunological precursor cell lineage commitment likely alters the course of broader immune response.

Table 1. The effect of inflammation on zinc availability and lineage commitment.

Inflammatory Source	Experimental Set-Up	Target	Zinc Modulation Effect	Citations
Lipopolysaccharide (LPS); TLR4 stimulation	In vitro; in vivo	BM Dendritic Cells; Splenic CD11c + DCs	Decreased intracellular free zinc Decreased ZIP6 + 10 expression; increased Znt-1 and -4 expression.	[103]
Monocyte-derived DCs + TSST-1 superantigen; TCR stimulation	In vitro	CD4 + T Cell Receptor	3-fold increase in intracellular free zinc via ZIP6 Upregulated ZIP8 expression localized in the lysosome	[104,109]
IL-2 stimulation	In vitro	CTLL-2 Cytotoxic T Cells	Zinc concentrated in intracellular lysosomal compartments	[105]
Lipopolysaccharide (LPS)	In vitro	PBMC differentiated MΦ	15-fold increase in intracellular free zinc over 40 min	[106]
LPS-injection induced systemic IL-6	In vivo; systemic	Hepatocyte and GI cell zinc transporters	Upregulated ZIP14 on GI cells + hepatocytes during acute response; Increased zinc uptake; serum zinc reduced; Reduced ZIP upregulation in IL-6 ^{-/-} mice	[114,115]

Table 1. Cont.

Inflammatory Source	Experimental Set-Up	Target	Zinc Modulation Effect	Citations
Polymicrobial sepsis	In vivo	Serum cytokines; liver zinc	ZIP14 ^{-/-} mouse had comparatively higher pro-inflammatory cytokines (including IL-6); Lower hepatocyte zinc versus WT	[116]
Systemic LPS inflammation and G-CSF injections	In vivo; mice and humans	Common myeloid progenitors; TLR signals	Inflammatory conditions favor lineage commitment towards immunoregulatory neutrophil-like monocytes (Ym1 ⁺ Ly6C ^{hi}) which suppress T-cell proliferation; expansion of classical monocytes	[117,118]
GM-CSF Supplementation	In vitro	Stimulated and infected MΦ	Significant increase in total cellular zinc; 60-fold increase in ZIP2 zinc importer; 2- and 4-fold increase in ZnT-7 and -4; GM-CSF mobilized zinc through STAT-3 and -5; reversible w/zinc supplementation	[119]

Zinc as a regulator of immune cell function: In the context of local zinc modulation at the site of infection, extracellular zinc is sequestered from both pathogens and host cells alike, primarily by the actions of activated infiltrating neutrophils (and to a lesser extent, monocytes) through the zinc-chelating heterodimer, calprotectin (S100A8/S100A9) [111,120,121]. Notably, calprotectin constitutes ~46% of all neutrophil cytosolic protein [122]. Further, neutrophils compose 50–70% of an individual's circulating white blood cells [123]. Neutrophils extravasate into infected tissues and perform a number of first-line immune functions characteristic of the innate immune response. These include the degranulation of antimicrobial proteins and proteolytic enzymes, phagocytosing of pathogens and debris, secretion of immunomodulatory proinflammatory cytokines, and undergoing a specialized apoptotic process called NETosis [124]. Neutrophil extracellular traps (NETs) are bactericidal webs of chromatin, histones, and a variety of pro-inflammatory molecules which can be induced by a number of mechanisms, including toll-like receptors and inflammatory signals [125]. Notably, NETosis results in the release of approximately 60% of total intracellular calprotectin: ~30% in the NET complex and another ~30% into the extracellular space [126]. In addition to its ability to sequester zinc, calprotectin is known to bind other crucial transition metals including iron, copper, and manganese [127,128]. The metal sequestration properties of calprotectin, in conjunction with other S100 proteins, demonstrate their powerful immunomodulatory and microbicidal function, frequently at host–pathogen interfaces in the epithelia [129–132].

In addition to directly restricting pathogenic growth, zinc sequestration by activated neutrophils also impacts the function of other immune cells. A number of in vitro studies utilizing *N,N,N',N'*-tetrakis (2-pyridinylmethyl)-1,2-ethanediamine (TPEN), a membrane-permeable zinc-selective metal chelator, examined the effects of zinc deprivation on cellular function in a variety of cells [107,114,133]. In one study, monocyte precursor cells differentiated in low-zinc conditions displayed enhanced monocyte lineage commitment [107]. TPEN altered multiple core monocyte functions specifically during differentiation, including enhanced pro-inflammatory tumor necrosis factor cytokine secretion, phagocytosis, and oxidative burst capabilities [107]. Importantly, these could be reversed by adding

supplementary zinc to the culture [107]. These enhanced phagocytic and oxidative burst capabilities were subsequently observed in low-zinc human-blood-derived monocytes while in the presence of bacteria in vitro [117]. While inflammation affects zinc mobilization in the host, zinc availability and transportation in turn impacts lineage commitment, cell membrane fluidity, and the consequent immune response, thereby amplifying the modulatory function of zinc on the immune system. These effects are summarized in Table 2.

Table 2. The effect of zinc modulation on immune cells.

Zinc Altering Factors	Experimental Set-Up	Target Cells	Effects	Citations
ZIP-6 overexpression	In vitro	BM Dendritic Cells	Prevented LPS-induced reduction in intracellular free zinc; MHCII upregulation	[103]
Zinc chelator TPEN	in vitro	CTLL-2 Cytotoxic T Cells	Zinc removed from zinc fingers; ERK-pathway blocked; cytoplasmic free zinc is required for IL-2-induced ERK signaling and T-cell proliferation	[105]
ZnSO ₄ supplemented cell culture (5 min)	In vitro	PBMC differentiated MΦ	Increased intracellular zinc	[106]
TPEN/zinc-depleted medium + 1α 25-dihydroxyvitamin D3 (1,25D3) monocyte differentiator	In vitro	HL-60 (pro-myelocytic) cell line	Decrease in intracellular free zinc and reduced ZIP transporter expression; increased expression of monocyte markers CD11b and CD14; TNF secretion, phagocytosis, oxidative burst were augmented by differentiation in low zinc conditions	[107,133]
Genetic ZIP-4 mutation; nonfunctional intestinal zinc importer	In vivo; humans and mice	Langerhans MΦ	Severe zinc deficiency; profound loss of skin-resident macrophages; severe dysregulation of function in NK cells, granulocytes, monocytes, and macrophages	[110]
Reduced intracellular free zinc	In vitro	Neutrophils	Low zinc availability prevents NETosis induction; S100A9 ^{−/−} neutrophils (non-functional calprotectin) more readily promoted NETosis	[134–136]
ZnSO ₄ supplemented cell culture (30 min)	In vitro	U937 leukemic pro-monocytes	Zinc alters membrane fluidity; reduced surface expression of GM-CSFR; Suppression of GM-CSF/GM-CSFR mediated STAT5 phosphorylation	[118]
ZnSO ₄ supplemented cell culture (30 min)	In vitro	Human PMBCs	Zinc decreased GM-CSFR on monocytes; increased GM-CSFR on neutrophils. Subsequent GM-CSF treatment reduced free zinc in neutrophils by 15%	[134]

Interestingly, systemic inflammatory conditions similar to those previously described in this review have been observed to alter the differentiation of neutrophil-committed

precursors towards monocytic lineage [135,136] (Table 1). While the broad comparison of in vitro TPEN-supplemented, in vitro zinc-exhausted, and in vivo systemic inflammatory conditions is imperfect, all of these models result in a similar polarization of precursor cells towards monocytic lineage commitment, underscoring the crucial role of zinc bioavailability in the modulation of this process. In contrast to enhancing the inflammatory response in monocytes and their precursors, TPEN-mediated zinc chelation appears to impair a variety of functions in human-blood-derived neutrophil granulocytes, including chemotaxis, phagocytosis, oxidative burst, degranulation, and LPS-induced pro-inflammatory cytokine secretion [133]. Multiple studies have reported that reducing the intracellular concentrations of free divalent cations, including zinc, actively prevents the induction of NETosis [137,138]. This is further substantiated by the findings that neutrophils deficient in the S100A9 protein, which forms the zinc-chelating heterodimeric protein calprotectin, were able to induce NETosis more readily [139]. This enhanced NETosis function and increased quantity of NETs, presumably due to sufficient access to zinc, enhances the macrophage phagocytosis of bacteria [139]. These studies underscore the differential responses by neutrophils and monocytes in response to pathogenic challenge, linked through the changing zinc environment in the host.

Zinc as a modulator of GM-CSF receptor signaling and myeloid cell function: Granulocyte-macrophage colony stimulating factor (GM-CSF) has long been established as a crucial regulator of functionality and proliferation of neutrophils, granulocytes and monocytes [140–142]. GM-CSF is produced by multiple cell types, and its receptors (abbreviated as GM-CSFR) are similarly expressed by a wide variety of cells, with the pathway inducing a variety of pleiotropic effects including upregulation of specific genes related to inflammation, survival, differentiation and cell proliferation [143]. Crucially, zinc signaling has been observed to play a key role in modulating the regulatory capabilities of GM-CSF-dependent cell differentiation and proliferation.

For example, zinc treatment of U937 leukemic pro-monocyte cells prior to their GM-CSF exposure significantly reduced the surface expression of GM-CSFR and suppressed GM-CSF/GM-CSFR-mediated STAT5 phosphorylation [118]. Similarly, a 30 min zinc treatment of human peripheral blood mononuclear cells (PBMCs) resulted in decreased surface expression of GM-CSFR on monocytes, but increased expression in neutrophils and lymphocytes [134]. When these PBMCs were incubated with GM-CSF, intracellular free zinc levels in neutrophils were significantly reduced by 15%, but a similar reduction was not observed in monocytes or lymphocytes [134]. Taken together, it appears that zinc decreases GM-CSFR and therefore STAT5 phosphorylation in monocytes—the precursor cells which may become macrophages. In inflammatory conditions, GM-CSF was able to modulate zinc transporter expression and functionality in macrophages infected with the intracellular pathogen *Histoplasma capsulatum* [119]. Vignesh et al. showed that GM-CSF supplementation activated intracellularly infected macrophages and significantly increased the total cellular concentration of zinc, with an approximately 60-fold increase in expression of the zinc importer ZIP2 as well as more modest 2- and 4-fold increases for zinc exporters ZnT-7 and ZnT-4, respectively [119]. Ultimately, GM-CSF was found to drive zinc mobilization through STAT5 and STAT3-mediated zinc sequestration, and resulted in enhanced oxidative burst capabilities which could be reversed upon zinc supplementation [119]. Taken together, zinc, GM-CSF, and pathogenic inflammation act in concert to dictate STAT5 phosphorylation in the monocyte/macrophage cell lineage. The precise mechanistic interplay between zinc and GM-CSF and the extent of zinc's impact on the GM-CSFR pathway remain unclear. Further investigation of the greater effect of zinc on the GM-CSFR pathway through the zinc-modulating abilities of monocyte/macrophages may reveal novel interactions between neutrophils and monocytes at both the systemic and

local levels. Overall, it is clear that inflammation leads to intracellular and extracellular zinc mobilization in the host through a panel of zinc transporters. Fundamental insights into zinc mobilization pathways and the discovery of new factors underpinning the process can be leveraged for therapeutic benefit against infections.

1.3. Zinc Mobilization and Neutrophils in TB Pathogenesis

Historically, macrophages have dominated conceptual frameworks of TB pathogenesis, viewed both as the primary intracellular niche for Mtb and as the structural core of granulomatous lesions [144]. However, accumulating evidence has fundamentally reshaped this macrophage-centric paradigm by revealing a central and often underappreciated role for neutrophils. As the most abundant leukocytes in human circulation and a cornerstone of the innate immune system, neutrophils mount an immediate response to microbial invasion at infection sites through an arsenal of antimicrobial mechanisms—including phagocytosis, reactive oxygen species (ROS) production, protease and antimicrobial peptide release, and the formation of NETs [145,146]. In many bacterial infections, such as those caused by *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Escherichia coli*, neutrophils are indispensable for pathogen clearance, and their absence results in overwhelming disease [147,148]. In TB, however, this paradigm does not readily apply. Although neutrophils are rapidly recruited to Mtb-infected lungs and frequently dominate blood transcriptional signatures [149,150], bronchoalveolar lavage samples, and histopathological sections of TB lesions [151], their antimicrobial activity rarely has a sterilizing effect on Mtb. Instead, excessive neutrophil accumulation and activation are consistently associated with lung tissue destruction, heightened inflammation, and bacterial dissemination [152–154]. These observations place neutrophils at the core of a central paradox in TB immunology: cells that contribute to early host defense can become potent drivers of immunopathology during persistent infection. Beyond direct antimicrobial activity, neutrophils also shape the inflammatory milieu through extensive interactions with macrophages and adaptive immune cells with profound influence on tissue pathology. Thus, the contribution of neutrophils to TB pathogenesis is multifaceted.

In the context of this review, we will limit our discussion on the emerging role of neutrophils in zinc sequestration as a component of nutritional immunity during TB pathogenesis. Neutrophils play a central role in this process through the release of metal-binding proteins and specialized granule components, with the previously introduced heterodimeric protein calprotectin at the forefront [111,120,121]. Owing to the sheer quantity of circulating neutrophils in the blood [123], and the abundant reservoir of calprotectin which again makes up half of the neutrophil cytosolic protein [122], nutritional immunity can be observed to be a highly conserved tool which is effective against a variety of pathogens. However, Mtb has evolved sophisticated mechanisms to withstand nutrient deprivation while exploiting hostile inflammatory environments.

Crucially, neutrophils contain a highly organized system of cytoplasmic granules and vesicles generated sequentially during granulopoiesis which are released in a tightly regulated hierarchy upon activation [155]. This organization enables rapid antimicrobial responses while minimizing collateral tissue damage under homeostatic conditions. In TB, however, sustained neutrophil recruitment and activation disrupt this balance, leading to excessive granule release that drives lung tissue destruction, extracellular matrix degradation, and cavitary disease [156]. Highly expressed calprotectin is also associated with secondary and gelatinase granules, and is released extracellularly during neutrophil activation, degranulation, NET formation, and cell death. Elevated calprotectin levels have been detected in TB patient sputum and plasma and correlate with neutrophil-driven

inflammation, lung pathology, and disease severity, underscoring its dual role in host defense and immunopathology.

Neutrophil-driven nutritional immunity against pathogens: As previously mentioned, nutritional immunity is a fundamental host defense strategy that limits pathogen access to essential nutrients, particularly transition metals such as iron, zinc, and manganese [112,157]. Because these metals serve as critical cofactors for microbial enzymes involved in metabolism, replication, and antioxidant defense, their sequestration can profoundly restrict pathogen growth.

While this review has focused extensively on zinc, iron sequestration is the best-characterized arm of nutritional immunity [158,159]. Neutrophil-derived lactoferrin binds iron with exceptionally high affinity, imposing iron starvation on invading microbes and limiting bacterial proliferation. In parallel, neutrophils secrete lipocalin-2 (also known as NGAL), which binds catecholate-type bacterial siderophores such as enterobactin, preventing pathogens from reclaiming iron through their own scavenging systems [160,161]. Together, lactoferrin and lipocalin-2 represent complementary mechanisms that restrict extracellular and siderophore-mediated iron acquisition.

Zinc and manganese limitation constitutes another critical component of neutrophil-driven nutritional immunity and is mediated primarily by calprotectin [162]. Calprotectin binds zinc and manganese with high affinity, thereby depriving pathogens of metals required for key enzymatic processes, including superoxide dismutase-mediated antioxidant defenses [157]. By withholding these metals, calprotectin weakens microbial resistance to oxidative stress and enhances susceptibility to neutrophil-derived ROS.

These mechanisms are broadly relevant across infectious diseases. Iron restriction mediated by lactoferrin and lipocalin-2 limits the growth of *Escherichia coli* and *Klebsiella pneumoniae*, while calprotectin-dependent zinc and manganese sequestration is essential for controlling *Staphylococcus aureus* infections [132,148]. Fungal pathogens such as *Candida albicans* and *Aspergillus fumigatus* are similarly constrained by metal limitation, underscoring the versatility of neutrophil-driven nutritional immunity across diverse microbial classes.

Nutritional immunity in TB is both compelling and complex. Mtb is highly adapted to the host environment and has evolved robust strategies to resist nutrient deprivation, often limiting the effectiveness of neutrophil-mediated restriction. Iron sequestration exemplifies this challenge. Although neutrophil-derived lactoferrin reduces extracellular iron availability, Mtb produces high-affinity siderophores, including mycobactin and carboxymycobactin, which enable iron acquisition even under severely restrictive conditions. Moreover, cell death within TB lesions can release iron-containing molecules such as heme and ferritin, paradoxically replenish local nutrient pools and support bacterial metabolism within necrotic granulomas. In contrast, zinc and manganese withholding by calprotectin may represent a more formidable barrier to Mtb survival. These metals are essential for Mtb enzymes involved in oxidative stress resistance and central metabolism, and their sequestration within granulomas can impair bacterial fitness. However, Mtb can counteract this pressure by upregulating high-affinity metal transport systems such as MntH, as well as by remodeling ribosomal function to reduce metal dependence [66]. Ribosome hibernation and the subsequent slow-replicating state in Mtb under severe zinc starvation, as shown in vitro [25], highlights an ongoing evolutionary arms race between host nutritional immunity and bacterial adaptation. The ability of Mtb to persist under such oppressive conditions only to later emerge from dormancy confers great advantage to survivability.

Nutritional immunity mediated through NETs adds further complexity to TB pathogenesis. NETs are decorated with granule-derived proteins, including calprotectin and lactoferrin, embedding metal sequestration directly within extracellular antimicrobial structures [163–165]. While NET-associated calprotectin may restrict mycobacterial growth

locally, excessive NET formation in TB has been strongly linked to lung tissue damage, extracellular matrix degradation, and cavitory pathology [126]. Thus, NET-driven nutritional immunity may impose antimicrobial pressure at the cost of exacerbated immunopathology.

Beyond direct metal sequestration, neutrophil-driven metabolic effects indirectly shape TB outcomes. Arginase-1 released from tertiary granules depletes local L-arginine levels, limiting nitric oxide production by macrophages—a critical antimicrobial mechanism against *Mtb* [166]. Consequently, while neutrophils restrict certain nutrients required by *Mtb*, they may simultaneously suppress complementary host defenses, tipping the balance toward disease progression rather than bacterial clearance.

Overall, neutrophils occupy a uniquely ambivalent position in TB immunity. Equipped with an extensive granule arsenal, they contribute to antimicrobial defense and nutritional immunity, yet *Mtb* has evolved strategies to resist, evade, or exploit these mechanisms. Nutritional immunity exemplifies this tug-of-war: while lactoferrin, lipocalin-2, and calprotectin impose metal starvation, *Mtb* counters these pressures through siderophore production, metal transport systems, and metabolic adaptation. Further, neutrophil death can inadvertently replenish nutrient reservoirs.

A deeper understanding of how neutrophil nutritional immunity operates within TB lesions is therefore critical. Dissecting the balance between protective nutrient restriction and pathological inflammation may reveal new therapeutic opportunities. Strategies that enhance beneficial aspects of neutrophil nutritional immunity while limiting tissue damage could serve as valuable adjuncts to antibiotic therapy, offering fresh avenues to combat this persistent global threat.

2. Concluding Remarks

Zinc is a crucial resource for bacteria and is necessary for metabolic activity. The sequestration of zinc from pathogens by the host's innate immune response could be a powerful defense mechanism to restrict invading pathogens. However, the adaptation of *Mtb* to low-zinc environments could not only counter this host pressure, but also result in increased antibiotic tolerance or persistence (Figure 1), thereby posing significant challenges during TB chemotherapy.

Crucially, calprotectin, GM-CSF, and inflammation-mediated zinc transporter upregulation on hepatocytes appear to modulate zinc availability both locally and systemically, affecting both host and pathogen. The direct chelation and uptake of free zinc from the extracellular space to impose a zinc-deficient environment for the pathogen could also directly affect signaling in hematopoietic and inflammatory pathways. As neutrophils regulate zinc availability in the tissue microenvironment and are also affected by zinc, a deeper understanding of neutrophil-dependent nutritional immunity and its impact on TB pathogenesis may reveal new therapeutic opportunities.

Due to system-wide tight regulation of zinc homeostasis in the host, direct intrapulmonary zinc supplementation into localized sites of infection may induce therapeutic benefit when utilized in conjunction with conventional targeted therapies such as antibiotics. Such supplementation may subvert the ability of *Mtb* to persist in lungs. Ultimately, strategies that enhance the beneficial aspects of neutrophil-mediated nutritional immunity while limiting tissue damage could serve as valuable adjuncts to antibiotic and/or nutritional therapy, offering fresh avenues to combat this persistent global threat.

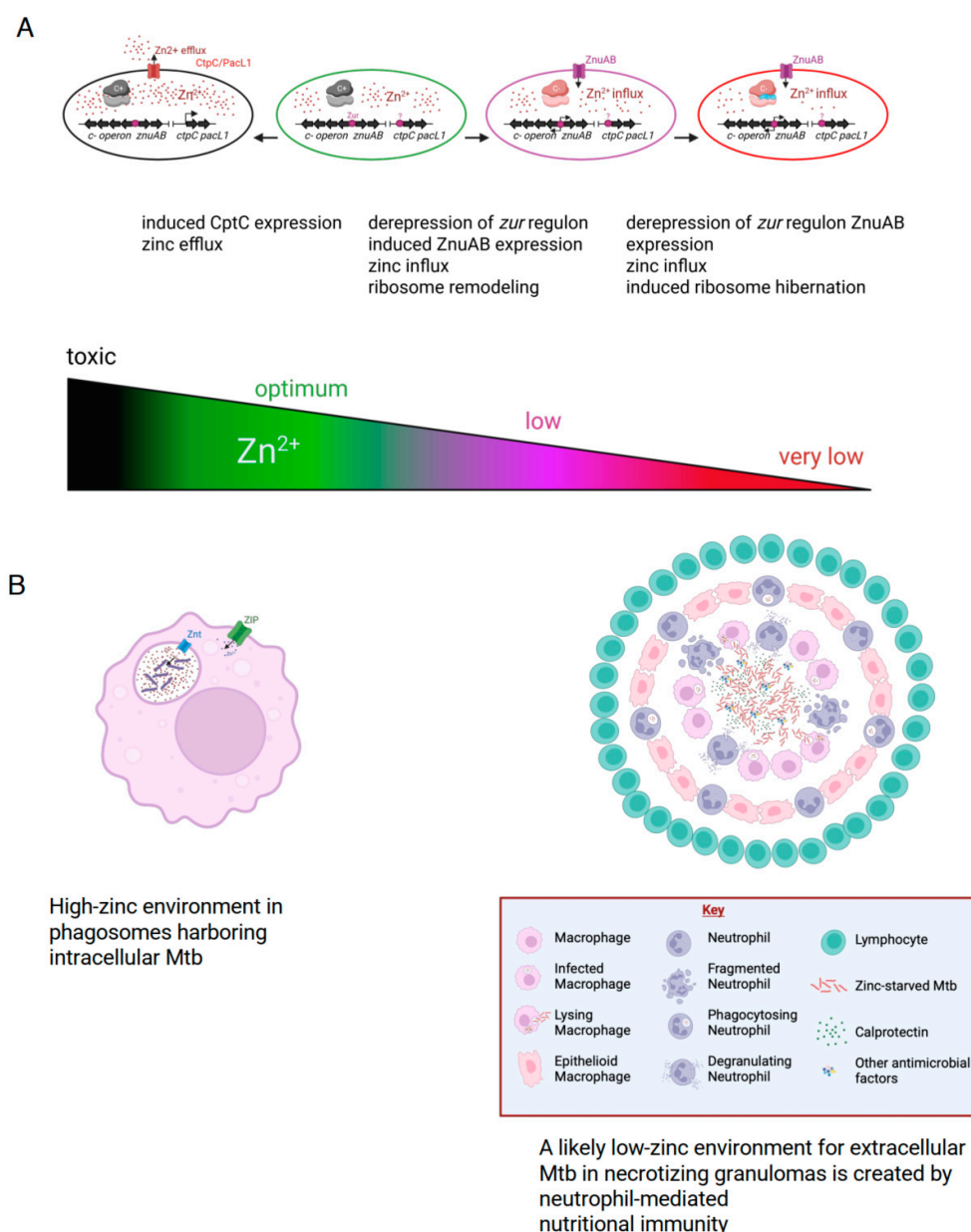


Figure 1. Zinc-driven host pathogen interaction in TB pathogenesis. (A) Adaptation of Mtb to high- and low-levels of zinc. A high zinc level, which can be potentially toxic, induces the expression of CtpC and associate chaperone PacL1. The CtpC-PacL1 likely efflux zinc out of the cytosol to mitigate toxicity (PMID: 21925112, 35961955). While a substantial free zinc is sequestered by the zinc-binding C+ ribosomal proteins in the ribosome. Under low zinc condition, derepression of Zur regulon, which includes C- protein paralog and zinc importers, ZnuAB, maintain zinc level to sustain metabolic demand. Severe zinc limitation induces hibernation of C- ribosomes by Mpy, possibly to maintain a stable pool of non-translating ribosomes while also modulating the translation frequency to align with slowed metabolism. (B) Depiction of the high- and low-zinc environments for Mtb in the host. The high-zinc environment in the phagosomal compartments harboring intracellular Mtb is likely produced by the zinc-mobilizing activities of ZIP and Znt transporters across the plasma membrane and phagosomal membrane, respectively (PMID: 21925112). The low-zinc condition is likely presented to the extracellular Mtb bacilli in necrotizing granulomas through neutrophil-dependent nutritional immunity, in which the release of zinc chelating factors like calprotectin released by degranulating neutrophils sequester free zinc from the bacilli. The figure was created using Biorender licensed to A: Corro, J. (2026) <https://BioRender.com/lky83r8>, accessed on 5 February 2026, B: Corro, J. (2026) <https://BioRender.com/107yi0d>, accessed on 5 February 2026.

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References

1. World Health Organization. *Global Tuberculosis Report 2025*; World Health Organization: Geneva, Switzerland, 2025.
2. World Health Organization. *Global Tuberculosis Report 2024*; World Health Organization: Geneva, Switzerland, 2024.
3. Pai, M.; Behr, M.A.; Dowdy, D.; Dheda, K.; Divangahi, M.; Boehme, C.C.; Ginsberg, A.; Swaminathan, S.; Spigelman, M.; Getahun, H.; et al. Tuberculosis. *Nat. Rev. Dis. Prim.* **2016**, *2*, 16076. [[CrossRef](#)] [[PubMed](#)]
4. Sotgiu, G.; Centis, R.; D'ambrosio, L.; Migliori, G.B. Tuberculosis treatment and drug regimens. *Cold Spring Harb. Perspect. Med.* **2015**, *5*, a017822. [[CrossRef](#)] [[PubMed](#)]
5. Jindani, A.; Doré, C.J.; Mitchison, D.A. Bactericidal and Sterilizing Activities of Antituberculosis Drugs during the First 14 Days. *Am. J. Respir. Crit. Care Med.* **2003**, *167*, 1348–1354. [[CrossRef](#)] [[PubMed](#)]
6. Lee, H.Y.; Chae, K.O.; Lee, C.H.; Choi, S.M.; Lee, J.; Park, Y.S.; Lee, S.-M.; Yoo, C.-G.; Kim, Y.W.; Han, S.K.; et al. Culture Conversion Rate at 2 Months of Treatment According to Diagnostic Methods among Patients with Culture-Positive Pulmonary Tuberculosis. *PLoS ONE* **2014**, *9*, e103768. [[CrossRef](#)] [[PubMed](#)]
7. Blumberg, H.M.; Burman, W.J.; E Chaisson, R.; Daley, C.L.; Etkind, S.C.; Friedman, L.N.; Fujiwara, P.; Grzemska, M.; Hopewell, P.C.; Iseman, M.D.; et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of Tuberculosis. *Am. J. Respir. Crit. Care Med.* **2003**, *167*, 603–662. [[CrossRef](#)] [[PubMed](#)]
8. Wallis, R.S.; Patil, S.; Cheon, S.H.; Edmonds, K.; Phillips, M.; Perkins, M.D.; Joloba, M.; Namale, A.; Johnson, J.L.; Teixeira, L.; et al. Drug tolerance in *Mycobacterium tuberculosis*. *Antimicrob. Agents Chemother.* **1999**, *43*, 2600–2606. [[CrossRef](#)] [[PubMed](#)]
9. Gold, B.; Nathan, C. Targeting Phenotypically Tolerant *Mycobacterium tuberculosis*. *Microbiol. Spectr.* **2017**, *5*, 317–360. [[CrossRef](#)] [[PubMed](#)]
10. Vandal, O.H.; Pierini, L.M.; Schnappinger, D.; Nathan, C.F.; Ehrt, S. A membrane protein preserves intrabacterial pH in intraphagosomal *Mycobacterium tuberculosis*. *Nat. Med.* **2008**, *14*, 849–854. [[CrossRef](#)] [[PubMed](#)]
11. Woolhiser, L.; Tamayo, M.H.; Wang, B.; Gruppo, V.; Belisle, J.T.; Lenaerts, A.J.; Basaraba, R.J.; Orme, I.M. In Vivo Adaptation of the Wayne Model of Latent Tuberculosis. *Infect. Immun.* **2007**, *75*, 2621–2625. [[CrossRef](#)] [[PubMed](#)]
12. Wayne, L.G.; Hayes, L.G. An in vitro model for sequential study of shutdown of *Mycobacterium tuberculosis* through two stages of nonreplicating persistence. *Infect. Immun.* **1996**, *64*, 2062–2069. [[CrossRef](#)] [[PubMed](#)]
13. Huynh, K.K.; Grinstein, S. Regulation of Vacuolar pH and Its Modulation by Some Microbial Species. *Microbiol. Mol. Biol. Rev.* **2007**, *71*, 452–462. [[CrossRef](#)] [[PubMed](#)]
14. Ohkuma, S.; Poole, B. Fluorescence probe measurement of the intralysosomal pH in living cells and the perturbation of pH by various agents. *Proc. Natl. Acad. Sci. USA* **1978**, *75*, 3327–3331. [[CrossRef](#)] [[PubMed](#)]
15. Baker, J.J.; Johnson, B.K.; Abramovitch, R.B. Slow growth of *Mycobacterium tuberculosis* at acidic pH is regulated by *phoPR* and host-associated carbon sources. *Mol. Microbiol.* **2014**, *94*, 56–69. [[CrossRef](#)] [[PubMed](#)]
16. Gouzy, A.; Healy, C.; Black, K.A.; Rhee, K.Y.; Ehrt, S. Growth of *Mycobacterium tuberculosis* at acidic pH depends on lipid assimilation and is accompanied by reduced GAPDH activity. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2024571118. [[CrossRef](#)] [[PubMed](#)]
17. Kumar, A.; Toledo, J.C.; Patel, R.P.; Lancaster, J.R.; Steyn, A.J.C. *Mycobacterium tuberculosis* DosS is a redox sensor and DosT is a hypoxia sensor. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 11568–11573. [[CrossRef](#)] [[PubMed](#)]

18. Via, L.E.; Lin, P.L.; Ray, S.M.; Carrillo, J.; Allen, S.S.; Eum, S.Y.; Taylor, K.; Klein, E.; Manjunatha, U.; Gonzales, J.; et al. Tuberculous Granulomas Are Hypoxic in Guinea Pigs, Rabbits, and Nonhuman Primates. *Infect. Immun.* **2008**, *76*, 2333–2340. [[CrossRef](#)] [[PubMed](#)]
19. Levitte, S.; Adams, K.N.; Berg, R.D.; Cosma, C.L.; Urdahl, K.B.; Ramakrishnan, L. Mycobacterial Acid Tolerance Enables Phagolysosomal Survival and Establishment of Tuberculous Infection In Vivo. *Cell Host Microbe* **2016**, *20*, 250–258. [[CrossRef](#)] [[PubMed](#)]
20. Welin, A.; Raffetseder, J.; Eklund, D.; Stendahl, O.; Lerm, M. Importance of Phagosomal Functionality for Growth Restriction of Mycobacterium tuberculosis in Primary Human Macrophages. *J. Innate Immun.* **2011**, *3*, 508–518. [[CrossRef](#)] [[PubMed](#)]
21. Dow, A.; Burger, A.; Marcantonio, E.; Pristic, S. Multi-Omics Profiling Specifies Involvement of Alternative Ribosomal Proteins in Response to Zinc Limitation in Mycobacterium smegmatis. *Front. Microbiol.* **2022**, *13*, 811774. [[CrossRef](#)] [[PubMed](#)]
22. Dow, A.; Pristic, S. Alternative ribosomal proteins are required for growth and morphogenesis of Mycobacterium smegmatis under zinc limiting conditions. *PLoS ONE* **2018**, *13*, e0196300. [[CrossRef](#)] [[PubMed](#)]
23. Dow, A.; Sule, P.; O'donnell, T.J.; Burger, A.; Mattila, J.T.; Antonio, B.; Vergara, K.; Marcantonio, E.; Adams, L.G.; James, N.; et al. Zinc limitation triggers anticipatory adaptations in Mycobacterium tuberculosis. *PLoS Pathog.* **2021**, *17*, e1009570. [[CrossRef](#)] [[PubMed](#)]
24. Pristic, S.; Hwang, H.; Dow, A.; Barnaby, O.; Pan, T.S.; Lonzanida, J.A.; Chazin, W.J.; Steen, H.; Husson, R.N. Zinc regulates a switch between primary and alternative S18 ribosomal proteins in Mycobacterium tuberculosis. *Mol. Microbiol.* **2015**, *97*, 263–280. [[CrossRef](#)] [[PubMed](#)]
25. Li, Y.; Sharma, M.R.; Koripella, R.K.; Yang, Y.; Kaushal, P.S.; Lin, Q.; Wade, J.T.; Gray, T.A.; Derbyshire, K.M.; Agrawal, R.K.; et al. Zinc depletion induces ribosome hibernation in mycobacteria. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 8191–8196. [[CrossRef](#)] [[PubMed](#)]
26. Li, Y.; Corro, J.H.; Palmer, C.D.; Ojha, A.K. Progression from remodeling to hibernation of ribosomes in zinc-starved mycobacteria. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 19528–19537. [[CrossRef](#)] [[PubMed](#)]
27. Li, Y.; Sharma, M.R.; Koripella, R.K.; Banavali, N.K.; Agrawal, R.K.; Ojha, A.K. Ribosome hibernation: A new molecular framework for targeting nonreplicating persisters of mycobacteria. *Microbiology* **2021**, *167*, 001035. [[CrossRef](#)] [[PubMed](#)]
28. Li, Y.; Koripella, R.K.; Sharma, M.R.; Lee, R.E.; Agrawal, R.K.; Ojha, A.K. Replacement of S14 Protein in Ribosomes of Zinc-Starved Mycobacteria Reduces Spectinomycin Sensitivity. *Antimicrob. Agents Chemother.* **2021**, *65*, 10–1128. [[CrossRef](#)] [[PubMed](#)]
29. Prossliner, T.; Winther, K.S.; Sørensen, M.A.; Gerdes, K. Ribosome Hibernation. *Annu. Rev. Genet.* **2018**, *52*, 321–348. [[CrossRef](#)] [[PubMed](#)]
30. Lai, R.P.J.; Cortes, T.; Marais, S.; Rockwood, N.; Burke, M.L.; Garza-Garcia, A.; Horswell, S.; Sesay, A.K.; O'garra, A.; Young, D.B.; et al. Transcriptomic Characterization of Tuberculous Sputum Reveals a Host Warburg Effect and Microbial Cholesterol Catabolism. *mBio* **2021**, *12*, e0176621. [[CrossRef](#)] [[PubMed](#)]
31. Xia, P.; Lian, S.; Wu, Y.; Yan, L.; Quan, G.; Zhu, G. Zinc is an important inter-kingdom signal between the host and microbe. *Veter. Res.* **2021**, *52*, 39. [[CrossRef](#)]
32. Capdevila, D.A.; Wang, J.; Giedroc, D.P. Bacterial Strategies to Maintain Zinc Metallostasis at the Host-Pathogen Interface. *J. Biol. Chem.* **2016**, *291*, 20858–20868. [[CrossRef](#)] [[PubMed](#)]
33. Cuajungco, M.P.; Ramirez, M.S.; Tolmasky, M.E. Zinc: Multidimensional Effects on Living Organisms. *Biomedicines* **2021**, *9*, 208. [[CrossRef](#)] [[PubMed](#)]
34. Mikhaylina, A.; Ksibe, A.Z.; Scanlan, D.J.; Blindauer, C.A. Bacterial zinc uptake regulator proteins and their regulons. *Biochem. Soc. Trans.* **2018**, *46*, 983–1001. [[CrossRef](#)] [[PubMed](#)]
35. Hussain, S.; Khan, M.; Sheikh, T.M.M.; Mumtaz, M.Z.; Chohan, T.A.; Shamim, S.; Liu, Y. Zinc Essentiality, Toxicity, and Its Bacterial Bioremediation: A Comprehensive Insight. *Front. Microbiol.* **2022**, *13*, 900740. [[CrossRef](#)] [[PubMed](#)]
36. Cerasi, M.; Ammendola, S.; Battistoni, A. Competition for zinc binding in the host-pathogen interaction. *Front. Cell. Infect. Microbiol.* **2013**, *3*, 108. [[CrossRef](#)] [[PubMed](#)]
37. Martin, J.E.; Edmonds, K.A.; Bruce, K.E.; Campanello, G.C.; Eijkelkamp, B.A.; Brazel, E.B.; McDevitt, C.A.; Winkler, M.E.; Giedroc, D.P. The zinc efflux activator SczA protects *Streptococcus pneumoniae* serotype 2 D39 from intracellular zinc toxicity. *Mol. Microbiol.* **2017**, *104*, 636–651. [[CrossRef](#)] [[PubMed](#)]
38. Kloosterman, T.G.; Van Der Kooi-Pol, M.M.; Bijlsma, J.J.E.; Kuipers, O.P. The novel transcriptional regulator SczA mediates protection against Zn²⁺ stress by activation of the Zn²⁺-resistance gene czcD in *Streptococcus pneumoniae*. *Mol. Microbiol.* **2007**, *65*, 1049–1063. [[CrossRef](#)] [[PubMed](#)]
39. Hantke, K. Bacterial zinc uptake and regulators. *Curr. Opin. Microbiol.* **2005**, *8*, 196–202. [[CrossRef](#)] [[PubMed](#)]
40. Ducret, V.; Gonzalez, D.; Perron, K. Zinc homeostasis in Pseudomonas. *Biometals* **2022**, *36*, 729–744. [[CrossRef](#)] [[PubMed](#)]
41. Blindauer, C.A. Advances in the molecular understanding of biological zinc transport. *Chem. Commun.* **2015**, *51*, 4544–4563. [[CrossRef](#)] [[PubMed](#)]

42. Schulz, V.; Galea, D.; Schleuder, G.; Strohmeyer, P.; Große, C.; Herzberg, M.; Nies, D.H. The efflux system CdfX exports zinc that cannot be transported by ZntA in *Cupriavidus metallidurans*. *J. Bacteriol.* **2024**, *206*, e0029924. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Choi, S.; Bird, A.J. Zinc'ing sensibly: Controlling zinc homeostasis at the transcriptional level. *Metallomics* **2014**, *6*, 1198–1215. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Goethe, E.; Laarmann, K.; Lühns, J.; Jarek, M.; Meens, J.; Lewin, A.; Goethe, R. Critical Role of Zur and SmtB in Zinc Homeostasis of *Mycobacterium smegmatis*. *Msystems* **2020**, *5*, 10–1128. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Brocklehurst, K.R.; Hobman, J.L.; Lawley, B.; Blank, L.; Marshall, S.J.; Brown, N.L.; Morby, A.P. ZntR is a Zn(II)-responsive MerR-like transcriptional regulator of *zntA* in *Escherichia coli*. *Mol. Microbiol.* **1999**, *31*, 893–902. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Saha, R.P.; Samanta, S.; Patra, S.; Sarkar, D.; Saha, A.; Singh, M.K. Metal homeostasis in bacteria: The role of ArsR–SmtB family of transcriptional repressors in combating varying metal concentrations in the environment. *Biometals* **2017**, *30*, 459–503. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Sanson, M.; Makthal, N.; Flores, A.R.; Olsen, R.J.; Musser, J.M.; Kumaraswami, M. Adhesin competence repressor (AdcR) from *Streptococcus pyogenes* controls adaptive responses to zinc limitation and contributes to virulence. *Nucleic Acids Res.* **2014**, *43*, 418–432. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Khan, S.; Brocklehurst, K.R.; Jones, G.W.; Morby, A.P. The functional analysis of directed amino-acid alterations in ZntR from *Escherichia coli*. *Biochem. Biophys. Res. Commun.* **2002**, *299*, 438–445. [\[CrossRef\]](#) [\[PubMed\]](#)
49. Shin, J.-H.; Oh, S.-Y.; Kim, S.-J.; Roe, J.-H. The Zinc-Responsive Regulator Zur Controls a Zinc Uptake System and Some Ribosomal Proteins in *Streptomyces coelicolor*A3(2). *J. Bacteriol.* **2007**, *189*, 4070–4077. [\[CrossRef\]](#) [\[PubMed\]](#)
50. Nuonming, P.; Khemthong, S.; Sukchawalit, R.; Mongkolsuk, S. Identification of Zur boxes and determination of their roles in the differential regulation of the Zur regulon in *Agrobacterium tumefaciens* C58. *Appl. Microbiol. Biotechnol.* **2020**, *104*, 2109–2123. [\[CrossRef\]](#) [\[PubMed\]](#)
51. Choi, Y.; Koh, J.; Cha, S.-S.; Roe, J.-H. Activation of zinc uptake regulator by zinc binding to three regulatory sites. *Nucleic Acids Res.* **2024**, *52*, 4185–4197. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Makthal, N.; Kumaraswami, M. Zinc'ing it out: Zinc homeostasis mechanisms and their impact on the pathogenesis of human pathogen group A streptococcus. *Metallomics* **2017**, *9*, 1693–1702. [\[CrossRef\]](#) [\[PubMed\]](#)
53. Ma, H.; Wang, M.; Yao, Y.; Zhang, S.; Wang, M.; Zhu, D.; Jia, R.; Chen, S.; Zhao, X.; Yang, Q.; et al. ZntR is a critical regulator for zinc homeostasis and involved in pathogenicity in *Riemerella anatipestifer*. *Microbiol. Spectr.* **2025**, *13*, e0317824. [\[CrossRef\]](#) [\[PubMed\]](#)
54. Outten, C.E.; O'Halloran, T.V. Femtomolar Sensitivity of Metalloregulatory Proteins Controlling Zinc Homeostasis. *Science* **2001**, *292*, 2488–2492. [\[CrossRef\]](#) [\[PubMed\]](#)
55. Hantke, K. Bacterial zinc transporters and regulators. In *Zinc Biochemistry, Physiology, and Homeostasis*; Maret, W., Ed.; Springer Science + Business Media: Dordrecht, The Netherlands, 2001; pp. 53–63.
56. Patzer, S.I.; Hantke, K. The ZnuABC high-affinity zinc uptake system and its regulator Zur in *Escherichia coli*. *Mol. Microbiol.* **1998**, *28*, 1199–1210. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Botella, H.; Peyron, P.; Levillain, F.; Poincloux, R.; Poquet, Y.; Brandli, I.; Wang, C.; Tailleux, L.; Tilleul, S.; Charrière, G.M.; et al. Mycobacterial P1-Type ATPases Mediate Resistance to Zinc Poisoning in Human Macrophages. *Cell Host Microbe* **2011**, *10*, 248–259. [\[CrossRef\]](#) [\[PubMed\]](#)
58. Boudehen, Y.-M.; Faucher, M.; Maréchal, X.; Miras, R.; Rech, J.; Rombouts, Y.; Sénèque, O.; Wallat, M.; Demange, P.; Bouet, J.-Y.; et al. Mycobacterial resistance to zinc poisoning requires assembly of P-ATPase-containing membrane metal efflux platforms. *Nat. Commun.* **2022**, *13*, 4731. [\[CrossRef\]](#) [\[PubMed\]](#)
59. Ganguly, T.; Peterson, A.M.; Kajfasz, J.K.; Abranches, J.; Lemos, J.A. Zinc import mediated by AdcABC is critical for colonization of the dental biofilm by *Streptococcus mutans* in an animal model. *Mol. Oral Microbiol.* **2021**, *36*, 214–224. [\[CrossRef\]](#) [\[PubMed\]](#)
60. Lam, L.N.; Brunson, D.N.; Molina, J.J.; Flores-Mireles, A.L.; Lemos, J.A. The AdcACB/AdcAII system is essential for zinc homeostasis and an important contributor of *Enterococcus faecalis* virulence. *Virulence* **2022**, *13*, 592–608. [\[CrossRef\]](#) [\[PubMed\]](#)
61. Peng, E.D.; Lyman, L.R.; Schmitt, M.P. Identification and characterization of zinc importers in *Corynebacterium diphtheriae*. *J. Bacteriol.* **2024**, *206*, e0012424. [\[CrossRef\]](#) [\[PubMed\]](#)
62. Santos, R.E.R.S.; Júnior, W.P.d.S.; Harrison, S.; Skaar, E.P.; Chazin, W.J.; Neto, J.F.d.S. The Zinc Transporter ZnuABC Is Critical for the Virulence of *Chromobacterium violaceum* and Contributes to Diverse Zinc-Dependent Physiological Processes. *Infect. Immun.* **2021**, *89*, e0031121. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Ammendola, S.; Pasquali, P.; Pistoia, C.; Petrucci, P.; Petrarca, P.; Rotilio, G.; Battistoni, A. High-Affinity Zn²⁺ Uptake System ZnuABC Is Required for Bacterial Zinc Homeostasis in Intracellular Environments and Contributes to the Virulence of *Salmonella enterica*. *Infect. Immun.* **2007**, *75*, 5867–5876. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Goethe, E.; Gieseke, A.; Laarmann, K.; Lühns, J.; Goethe, R. Identification and Characterization of *Mycobacterium smegmatis* and *Mycobacterium avium* subsp. *paratuberculosis* Zinc Transporters. *J. Bacteriol.* **2021**, *203*, 10–1128. [\[CrossRef\]](#) [\[PubMed\]](#)

65. Shin, J.-H.; Jung, H.J.; An, Y.J.; Cho, Y.-B.; Cha, S.-S.; Roe, J.-H. Graded expression of zinc-responsive genes through two regulatory zinc-binding sites in *Zur*. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 5045–5050. [[CrossRef](#)] [[PubMed](#)]
66. Maciag, A.; Dainese, E.; Rodriguez, G.M.; Milano, A.; Provvedi, R.; Pasca, M.R.; Smith, I.; Palù, G.; Riccardi, G.; Manganello, R. Global Analysis of the *Mycobacterium tuberculosis* *Zur* (FurB) Regulon. *J. Bacteriol.* **2007**, *189*, 730–740. [[CrossRef](#)] [[PubMed](#)]
67. Kandari, D.; Joshi, H.; Bhatnagar, R. *Zur*: Zinc-Sensing Transcriptional Regulator in a Diverse Set of Bacterial Species. *Pathogens* **2021**, *10*, 344. [[CrossRef](#)] [[PubMed](#)]
68. Gabriel, S.E.; Helmann, J.D. Contributions of *Zur*-Controlled Ribosomal Proteins to Growth under Zinc Starvation Conditions. *J. Bacteriol.* **2009**, *191*, 6116–6122. [[CrossRef](#)] [[PubMed](#)]
69. Rasmussen, R.A.; Wang, S.; Camarillo, J.M.; Sosnowski, V.; Cho, B.-K.; Goo, Y.A.; Lucks, J.B.; O'halloran, T.V. *Zur* and zinc increase expression of *E. coli* ribosomal protein L31 through RNA-mediated repression of the repressor L31p. *Nucleic Acids Res.* **2022**, *50*, 12739–12753. [[CrossRef](#)] [[PubMed](#)]
70. Lucarelli, D.; Russo, S.; Garman, E.; Milano, A.; Meyer-Klaucke, W.; Pohl, E. Crystal Structure and Function of the Zinc Uptake Regulator FurB from *Mycobacterium tuberculosis*. *J. Biol. Chem.* **2007**, *282*, 9914–9922. [[CrossRef](#)] [[PubMed](#)]
71. Sachla, A.J.; Helmann, J.D. A bacterial checkpoint protein for ribosome assembly moonlights as an essential metabolite-proofreading enzyme. *Nat. Commun.* **2019**, *10*, 1526. [[CrossRef](#)] [[PubMed](#)]
72. Makarova, K.S.; Ponomarev, V.; Koonin, E.V. Two C or not two C: Recurrent disruption of Zn-ribbons, gene duplication, lineage-specific gene loss, and horizontal gene transfer in evolution of bacterial ribosomal proteins. *Genome Biol.* **2001**, *2*, research0033-1. [[CrossRef](#)] [[PubMed](#)]
73. Chen, K.; Roberts, E.; Luthey-Schulten, Z. Horizontal gene transfer of zinc and non-zinc forms of bacterial ribosomal protein S4. *BMC Evol. Biol.* **2009**, *9*, 179. [[CrossRef](#)] [[PubMed](#)]
74. Owen, G.A.; Pascoe, B.; Kallifidas, D.; Paget, M.S.B. Zinc-Responsive Regulation of Alternative Ribosomal Protein Genes in *Streptomyces coelicolor* Involves *Zur* and σ^R . *J. Bacteriol.* **2007**, *189*, 4078–4086. [[CrossRef](#)] [[PubMed](#)]
75. Shin, J.-H.; Helmann, J.D. Molecular logic of the *Zur*-regulated zinc deprivation response in *Bacillus subtilis*. *Nat. Commun.* **2016**, *7*, 12612. [[CrossRef](#)] [[PubMed](#)]
76. Natori, Y.; Nanamiya, H.; Akanuma, G.; Kosono, S.; Kudo, T.; Ochi, K.; Kawamura, F. A fail-safe system for the ribosome under zinc-limiting conditions in *Bacillus subtilis*. *Mol. Microbiol.* **2006**, *63*, 294–307. [[CrossRef](#)] [[PubMed](#)]
77. Chen, Y.-X.; Xu, Z.-Y.; Ge, X.; Sanyal, S.; Lu, Z.J.; Javid, B. Selective translation by alternative bacterial ribosomes. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 19487–19496. [[CrossRef](#)] [[PubMed](#)]
78. Keren, I.; Minami, S.; Rubin, E.; Lewis, K. Characterization and Transcriptome Analysis of *Mycobacterium tuberculosis* Persisters. *MBio* **2011**, *2*, 10–1128. [[CrossRef](#)] [[PubMed](#)]
79. Yoshida, H.; Wada, A.; Shimada, T.; Maki, Y.; Ishihama, A. Coordinated Regulation of Rsd and RMF for Simultaneous Hibernation of Transcription Apparatus and Translation Machinery in Stationary-Phase *Escherichia coli*. *Front. Genet.* **2019**, *10*, 1153. [[CrossRef](#)] [[PubMed](#)]
80. Ekemezie, C.L.; Melnikov, S.V. Hibernating ribosomes as drug targets? *Front. Microbiol.* **2024**, *15*, 1436579. [[CrossRef](#)] [[PubMed](#)]
81. Akiyama, T.; Williamson, K.S.; Schaefer, R.; Pratt, S.; Chang, C.B.; Franklin, M.J. Resuscitation of *Pseudomonas aeruginosa* from dormancy requires hibernation promoting factor (PA4463) for ribosome preservation. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 3204–3209. [[CrossRef](#)] [[PubMed](#)]
82. Basu, A.; Yap, M.N.F. Ribosome hibernation factor promotes Staphylococcal survival and differentially represses translation. *Nucleic Acids Res.* **2016**, *44*, 4881–4893. [[CrossRef](#)] [[PubMed](#)]
83. Franken, L.E.; Oostergetel, G.T.; Pijning, T.; Puri, P.; Arkhipova, V.; Boekema, E.J.; Poolman, B.; Guskov, A. A general mechanism of ribosome dimerization revealed by single-particle cryo-electron microscopy. *Nat. Commun.* **2017**, *8*, 722. [[CrossRef](#)] [[PubMed](#)]
84. Gohara, D.W.; Yap, M.-N.F. Survival of the drowsiest: The hibernating 100S ribosome in bacterial stress management. *Curr. Genet.* **2017**, *64*, 753–760. [[CrossRef](#)] [[PubMed](#)]
85. Helena-Bueno, K.; Rybak, M.Y.; Ekemezie, C.L.; Sullivan, R.; Brown, C.R.; Dingwall, C.; Baslé, A.; Schneider, C.; Connolly, J.P.R.; Blaza, J.N.; et al. A new family of bacterial ribosome hibernation factors. *Nature* **2024**, *626*, 1125–1132. [[CrossRef](#)] [[PubMed](#)]
86. Kato, T.; Yoshida, H.; Miyata, T.; Maki, Y.; Wada, A.; Namba, K. Structure of the 100S Ribosome in the Hibernation Stage Revealed by Electron Cryomicroscopy. *Structure* **2010**, *18*, 719–724. [[CrossRef](#)] [[PubMed](#)]
87. Kline, B.C.; McKay, S.L.; Tang, W.W.; Portnoy, D.A. The *Listeria monocytogenes* Hibernation-Promoting Factor Is Required for the Formation of 100S Ribosomes, Optimal Fitness, and Pathogenesis. *J. Bacteriol.* **2014**, *197*, 581–591. [[CrossRef](#)] [[PubMed](#)]
88. McKay, S.L.; Portnoy, D.A. Ribosome Hibernation Facilitates Tolerance of Stationary-Phase Bacteria to Aminoglycosides. *Antimicrob. Agents Chemother.* **2015**, *59*, 6992–6999. [[CrossRef](#)] [[PubMed](#)]
89. Polikanov, Y.S.; Blaha, G.M.; Steitz, T.A. How Hibernation Factors RMF, HPF, and YfiA Turn off Protein Synthesis. *Science* **2012**, *336*, 915–918. [[CrossRef](#)] [[PubMed](#)]
90. Ueta, M.; Wada, C.; Wada, A. Formation of 100S ribosomes in *Staphylococcus aureus* by the hibernation promoting factor homolog SaHPF. *Genes Cells* **2009**, *15*, 43–58. [[CrossRef](#)] [[PubMed](#)]

91. Yoshida, H.; Wada, A. The 100S ribosome: Ribosomal hibernation induced by stress: 100S ribosome. *Wiley Interdiscip. Rev. RNA* **2014**, *5*, 723–732. [[CrossRef](#)] [[PubMed](#)]
92. Majumdar, S.; Li, Y.; Manjari, S.R.; Gamper, H.B.; Hou, Y.M.; Banavali, N.K.; Ojha, A.K.; Agrawal, R.K. A Novel Actinobacteria-Specific Ribosome Hibernation Factor in *Mycobacterium tuberculosis*. *BioRxiv* **2024**. [[CrossRef](#)]
93. Ziemski, M.; Leodolter, J.; Taylor, G.; Kerschenmeyer, A.; Weber-Ban, E. Genome-wide interaction screen for *Mycobacterium tuberculosis* ClpCP protease reveals toxin–antitoxin systems as a major substrate class. *FEBS J.* **2020**, *288*, 99–114. [[CrossRef](#)] [[PubMed](#)]
94. Marsee, J.D.; Ridings, A.; Yu, T.; Miller, J.M. *Mycobacterium tuberculosis* ClpC1 N-Terminal Domain Is Dispensable for Adaptor Protein-Dependent Allosteric Regulation. *Int. J. Mol. Sci.* **2018**, *19*, 3651. [[CrossRef](#)] [[PubMed](#)]
95. Andreini, C.; Banci, L.; Bertini, I.; Rosato, A. Counting the zinc-proteins encoded in the human genome. *J. Proteome Res.* **2006**, *5*, 196–201. [[CrossRef](#)] [[PubMed](#)]
96. Andreini, C.; Bertini, I.; Rosato, A. Metalloproteomes: A bioinformatic approach. *Acc. Chem. Res.* **2009**, *42*, 1471–1479. [[CrossRef](#)] [[PubMed](#)]
97. Roohani, N.; Hurrell, R.; Kelishadi, R.; Schulin, R. Zinc and its importance for human health: An integrative review. *J. Res. Med. Sci.* **2013**, *18*, 144–157. [[PubMed](#)]
98. Luan, R.; Ding, D.; Xue, Q.; Li, H.; Wang, Y.; Yang, J. Protective role of zinc in the pathogenesis of respiratory diseases. *Eur. J. Clin. Nutr.* **2022**, *77*, 427–435. [[CrossRef](#)] [[PubMed](#)]
99. Palmer, L.D.; Traina, K.C.; Juttukonda, L.J.; Lonergan, Z.R.; Bansah, D.A.; Ren, X.; Geary, J.H.; Pinelli, C.; Boyd, K.L.; Yang, T.S.; et al. Dietary zinc deficiency promotes *Acinetobacter baumannii* lung infection via IL-13 in mice. *Nat. Microbiol.* **2024**, *9*, 3196–3209. [[CrossRef](#)] [[PubMed](#)]
100. Stiles, L.I.; Ferrao, K.; Mehta, K.J. Role of zinc in health and disease. *Clin. Exp. Med.* **2025**, *24*, 38.
101. Wessels, I.; Maywald, M.; Rink, L. Zinc as a Gatekeeper of Immune Function. *Nutrients* **2017**, *9*, 1286. [[CrossRef](#)] [[PubMed](#)]
102. Bin, B.-H.; Seo, J.; Kim, S.T. Function, Structure, and Transport Aspects of ZIP and ZnT Zinc Transporters in Immune Cells. *J. Immunol. Res.* **2018**, *2018*, 9365747. [[CrossRef](#)] [[PubMed](#)]
103. Kitamura, H.; Morikawa, H.; Kamon, H.; Iguchi, M.; Hojyo, S.; Fukada, T.; Yamashita, S.; Kaisho, T.; Akira, S.; Murakami, M.; et al. Toll-like receptor-mediated regulation of zinc homeostasis influences dendritic cell function. *Nat. Immunol.* **2006**, *7*, 971–977. [[CrossRef](#)] [[PubMed](#)]
104. Yu, M.; Lee, W.; Tomar, D.; Pryshchep, S.; Czesnikiewicz-Guzik, M.; Lamar, D.L.; Li, G.; Singh, K.; Tian, L.; Weyand, C.M.; et al. Regulation of T cell receptor signaling by activation-induced zinc influx. *J. Exp. Med.* **2011**, *208*, 775–785. [[CrossRef](#)] [[PubMed](#)]
105. Kaltenberg, J.; Plum, L.M.; Ober-Blöbaum, J.L.; Hönscheid, A.; Rink, L.; Haase, H. Zinc signals promote IL-2-dependent proliferation of T cells. *Eur. J. Immunol.* **2010**, *40*, 1496–1503. [[CrossRef](#)] [[PubMed](#)]
106. Haase, H.; Ober-Blöbaum, J.L.; Engelhardt, G.; Hebel, S.; Heit, A.; Heine, H.; Rink, L. Zinc signals are essential for lipopolysaccharide-induced signal transduction in monocytes. *J. Immunol.* **2008**, *181*, 6491–6502. [[CrossRef](#)] [[PubMed](#)]
107. Dubben, S.; Hönscheid, A.; Winkler, K.; Rink, L.; Haase, H. Cellular zinc homeostasis is a regulator in monocyte differentiation of HL-60 cells by 1 α ,25-dihydroxyvitamin D₃. *J. Leukoc. Biol.* **2010**, *87*, 833–844. [[CrossRef](#)] [[PubMed](#)]
108. Nishida, K.; Uchida, R. Regulatory Mechanism of Mast Cell Activation by Zinc Signaling. *Yakugaku Zasshi J. Pharm. Soc. Jpn.* **2017**, *137*, 495–501. [[CrossRef](#)]
109. Aydemir, T.B.; Liuzzi, J.P.; McClellan, S.; Cousins, R.J. Zinc transporter ZIP8 (SLC39A8) and zinc influence IFN- γ expression in activated human T cells. *J. Leukoc. Biol.* **2009**, *86*, 337–348. [[CrossRef](#)] [[PubMed](#)]
110. Kawamura, T.; Ogawa, Y.; Nakamura, Y.; Nakamizo, S.; Ohta, Y.; Nakano, H.; Kabashima, K.; Katayama, I.; Koizumi, S.; Kodama, T.; et al. Severe dermatitis with loss of epidermal Langerhans cells in human and mouse zinc deficiency. *J. Clin. Investig.* **2012**, *122*, 722–732. [[CrossRef](#)] [[PubMed](#)]
111. Kehl-Fie, T.E.; Chitayat, S.; Hood, M.I.; Damo, S.; Restrepo, N.; Garcia, C.; Munro, K.A.; Chazin, W.J.; Skaar, E.P. Nutrient metal sequestration by calprotectin inhibits bacterial superoxide defense, enhancing neutrophil killing of *Staphylococcus aureus*. *Cell Host Microbe* **2011**, *10*, 158–164. [[CrossRef](#)] [[PubMed](#)]
112. Hood, M.I.; Skaar, E.P. Nutritional immunity: Transition metals at the pathogen–host interface. *Nat. Rev. Microbiol.* **2012**, *10*, 525–537. [[CrossRef](#)] [[PubMed](#)]
113. Tanaka, T.; Narazaki, M.; Kishimoto, T. IL-6 in Inflammation, Immunity, and Disease. *Cold Spring Harb. Perspect. Biol.* **2014**, *6*, a016295. [[CrossRef](#)] [[PubMed](#)]
114. Liuzzi, J.P.; Lichten, L.A.; Rivera, S.; Blanchard, R.K.; Aydemir, T.B.; Knutson, M.D.; Ganz, T.; Cousins, R.J. Interleukin-6 regulates the zinc transporter Zip14 in liver and contributes to the hypozincemia of the acute-phase response. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 6843–6848. [[CrossRef](#)] [[PubMed](#)]
115. Aydemir, T.B.; Chang, S.-M.; Guthrie, G.J.; Maki, A.B.; Ryu, M.-S.; Karabiyik, A.; Cousins, R.J. Zinc Transporter ZIP14 Functions in Hepatic Zinc, Iron and Glucose Homeostasis during the Innate Immune Response (Endotoxemia). *PLoS ONE* **2012**, *7*, e48679. [[CrossRef](#)] [[PubMed](#)]

116. Wessels, I.; Cousins, R.J. Zinc dyshomeostasis during polymicrobial sepsis in mice involves zinc transporter Zip14 and can be overcome by zinc supplementation. *Am. J. Physiol. Liver Physiol.* **2015**, *309*, G768–G778. [[CrossRef](#)] [[PubMed](#)]
117. Mayer, L.S.; Uciechowski, P.; Meyer, S.; Schwerdtle, T.; Rink, L.; Haase, H. Differential impact of zinc deficiency on phagocytosis, oxidative burst, and production of pro-inflammatory cytokines by human monocytes. *Metallomics* **2014**, *6*, 1288–1295. [[CrossRef](#)] [[PubMed](#)]
118. Aster, I.; Barth, L.-M.; Rink, L.; Wessels, I. Alterations in membrane fluidity are involved in inhibition of GM-CSF-induced signaling in myeloid cells by zinc. *J. Trace Elem. Med. Biol.* **2019**, *54*, 214–220. [[CrossRef](#)] [[PubMed](#)]
119. Vignesh, K.S.; Figueroa, J.A.L.; Porollo, A.; Caruso, J.A.; Deepe, G.S. Granulocyte Macrophage-Colony Stimulating Factor Induced Zn Sequestration Enhances Macrophage Superoxide and Limits Intracellular Pathogen Survival. *Immunity* **2013**, *39*, 697–710. [[CrossRef](#)] [[PubMed](#)]
120. Lügering, N.; Stoll, R.; Kucharzik, T.; Schmid, K.W.; Rohlmann, G.; Burmeister, G.; Sorg, C.; Domschke, W. Immunohistochemical distribution and serum levels of the Ca(2+)-binding proteins MRP8, MRP14 and their heterodimeric form MRP8/14 in Crohn's disease. *Digestion* **1995**, *56*, 406–414. [[PubMed](#)]
121. Odink, K.; Cerletti, N.; Brüggem, J.; Clerc, R.G.; Tarcsay, L.; Zwadlo, G.; Gerhards, G.; Schlegel, R.; Sorg, C. Two calcium-binding proteins in infiltrate macrophages of rheumatoid arthritis. *Nature* **1987**, *330*, 80–82. [[CrossRef](#)] [[PubMed](#)]
122. Edgeworth, J.; Gorman, M.; Bennett, R.; Freemont, P.; Hogg, N. Identification of p8,14 as a highly abundant heterodimeric calcium binding protein complex of myeloid cells. *J. Biol. Chem.* **1991**, *266*, 7706–7713. [[CrossRef](#)] [[PubMed](#)]
123. Kraus, R.F.; Gruber, M.A. Neutrophils—From Bone Marrow to First-Line Defense of the Innate Immune System. *Front. Immunol.* **2021**, *12*, 767175. [[CrossRef](#)] [[PubMed](#)]
124. Burn, G.L.; Foti, A.; Marsman, G.; Patel, D.F.; Zychlinsky, A. The Neutrophil. *Immunity* **2021**, *54*, 1377–1391. [[CrossRef](#)] [[PubMed](#)]
125. Wang, H.; Kim, S.J.; Lei, Y.; Wang, S.; Wang, H.; Huang, H.; Zhang, H.; Tsung, A. Neutrophil extracellular traps in homeostasis and disease. *Signal Transduct. Target. Ther.* **2024**, *9*, 235. [[CrossRef](#)] [[PubMed](#)]
126. Urban, C.F.; Ermert, D.; Schmid, M.; Abu-Abed, U.; Goosmann, C.; Nacken, W.; Brinkmann, V.; Jungblut, P.R.; Zychlinsky, A. Neutrophil Extracellular Traps Contain Calprotectin, a Cytosolic Protein Complex Involved in Host Defense against *Candida albicans*. *PLoS Pathog.* **2009**, *5*, e1000639. [[CrossRef](#)] [[PubMed](#)]
127. Clark, H.L.; Jhingran, A.; Sun, Y.; Vareechon, C.; Carrion, S.J.; Skaar, E.P.; Chazin, W.J.; Calera, J.A.; Hohl, T.M.; Pearlman, E. Zinc and Manganese Chelation by Neutrophil S100A8/A9 (Calprotectin) Limits Extracellular *Aspergillus fumigatus* Hyphal Growth and Corneal Infection. *J. Immunol.* **2016**, *196*, 336–344. [[CrossRef](#)] [[PubMed](#)]
128. Besold, A.N.; A Gilston, B.; Radin, J.N.; Ramsoomair, C.; Culbertson, E.M.; Li, C.X.; Cormack, B.P.; Chazin, W.J.; E Kehl-Fie, T.; Culotta, V.C. Role of Calprotectin in Withholding Zinc and Copper from *Candida albicans*. *Infect. Immun.* **2018**, *86*, 10–1128. [[CrossRef](#)] [[PubMed](#)]
129. Diaz-Ochoa, V.E.; Lam, D.; Lee, C.S.; Klaus, S.; Behnsen, J.; Liu, J.Z.; Chim, N.; Nuccio, S.P.; Rath, S.G.; Mastroianni, J.R.; et al. Salmonella Mitigates Oxidative Stress and Thrives in the Inflamed Gut by Evading Calprotectin-Mediated Manganese Sequestration. *Cell Host Microbe* **2016**, *19*, 814–825. [[CrossRef](#)] [[PubMed](#)]
130. Gläser, R.; Harder, J.; Lange, H.; Bartels, J.; Christophers, E.; Schröder, J. Antimicrobial psoriasin (S100A7) protects human skin from *Escherichia coli* infection. *Nat. Immunol.* **2005**, *6*, 57–64. [[PubMed](#)]
131. Gopal, R.; Monin, L.; Torres, D.; Slight, S.; Mehra, S.; McKenna, K.C.; Junecko, B.A.F.; Reinhart, T.A.; Kolls, J.; Báez-Saldaña, R.; et al. S100A8/A9 Proteins Mediate Neutrophilic Inflammation and Lung Pathology during Tuberculosis. *Am. J. Respir. Crit. Care Med.* **2013**, *188*, 1137–1146. [[CrossRef](#)] [[PubMed](#)]
132. Corbin, B.D.; Seeley, E.H.; Raab, A.; Feldmann, J.; Miller, M.R.; Torres, V.J.; Anderson, K.L.; Dattilo, B.M.; Dunman, P.M.; Gerads, R.; et al. Metal Chelation and Inhibition of Bacterial Growth in Tissue Abscesses. *Science* **2008**, *319*, 962–965. [[CrossRef](#)] [[PubMed](#)]
133. Hasan, R.; Rink, L.; Haase, H. Chelation of Free Zn²⁺ Impairs Chemotaxis, Phagocytosis, Oxidative Burst, Degranulation, and Cytokine Production by Neutrophil Granulocytes. *Biol. Trace Elem. Res.* **2016**, *171*, 79–88. [[PubMed](#)]
134. van der Laan, M.; Büttgenbach, A.; Wolf, J.; Rink, L.; Wessels, I. The Role of Zinc in GM-CSF-Induced Signaling in Human Polymorphonuclear Leukocytes. *Mol. Nutr. Food Res.* **2022**, *66*, e2101106. [[CrossRef](#)] [[PubMed](#)]
135. Ikeda, N.; Kubota, H.; Suzuki, R.; Morita, M.; Yoshimura, A.; Osada, Y.; Kishida, K.; Kitamura, D.; Iwata, A.; Yotsumoto, S.; et al. The early neutrophil-committed progenitors aberrantly differentiate into immunoregulatory monocytes during emergency myelopoiesis. *Cell Rep.* **2023**, *42*, 112165. [[CrossRef](#)] [[PubMed](#)]
136. Serbina, N.V.; Hohl, T.M.; Cherny, M.; Pamer, E.G. Selective Expansion of the Monocytic Lineage Directed by Bacterial Infection. *J. Immunol.* **2009**, *183*, 1900–1910. [[CrossRef](#)] [[PubMed](#)]
137. Hasan, R.; Rink, L.; Haase, H. Zinc signals in neutrophil granulocytes are required for the formation of neutrophil extracellular traps. *Innate Immun.* **2013**, *19*, 253–264. [[PubMed](#)]
138. Kuźmicka, W.; Moskalik, A.; Manda-Handzlik, A.; Demkow, U.; Wachowska, M.; Ciepiela, O. Influence of iron- and zinc-chelating agents on neutrophil extracellular trap formation. *Cent. Eur. J. Immunol.* **2021**, *46*, 135–139. [[CrossRef](#)] [[PubMed](#)]

139. Monteith, A.J.; Miller, J.M.; Maxwell, C.N.; Chazin, W.J.; Skaar, E.P. Neutrophil extracellular traps enhance macrophage killing of bacterial pathogens. *Sci. Adv.* **2021**, *7*, eabj2101. [[CrossRef](#)] [[PubMed](#)]
140. Castellani, S.; D'oria, S.; Diana, A.; Polizzi, A.M.; Di Gioia, S.; Mariggiò, M.A.; Guerra, L.; Favia, M.; Vinella, A.; Leonetti, G.; et al. G-CSF and GM-CSF Modify Neutrophil Functions at Concentrations found in Cystic Fibrosis. *Sci. Rep.* **2019**, *9*, 12937. [[CrossRef](#)] [[PubMed](#)]
141. Laan, M.; Prause, O.; Miyamoto, M.; Sjöstrand, M.; Hytönen, A.; Kaneko, T.; Lötvall, J.; Lindén, A. A role of GM-CSF in the accumulation of neutrophils in the airways caused by IL-17 and TNF- α . *Eur. Respir. J.* **2003**, *21*, 387–393. [[CrossRef](#)] [[PubMed](#)]
142. Bourgoin, S.; Plante, E.; Gaudry, M.; Naccache, P.H.; Borgeat, P.; E Poubelle, P. Involvement of a phospholipase D in the mechanism of action of granulocyte-macrophage colony-stimulating factor (GM-CSF): Priming of human neutrophils in vitro with GM-CSF is associated with accumulation of phosphatidic acid and diradylglycerol. *J. Exp. Med.* **1990**, *172*, 767–777. [[CrossRef](#)] [[PubMed](#)]
143. Francisco-Cruz, A.; Aguilar-Santelises, M.; Ramos-Espinosa, O.; Mata-Espinosa, D.; Marquina-Castillo, B.; Barrios-Payan, J.; Hernandez-Pando, R. Granulocyte-macrophage colony-stimulating factor: Not just another haematopoietic growth factor. *Med. Oncol.* **2014**, *31*, 774. [[PubMed](#)]
144. Lenaerts, A.; Barry, C.E., III; Dartois, V. Heterogeneity in tuberculosis pathology, microenvironments and therapeutic responses. *Immunol. Rev.* **2015**, *264*, 288–307. [[CrossRef](#)] [[PubMed](#)]
145. Dallenga, T.; Schaible, U.E. Neutrophils in tuberculosis—first line of defence or booster of disease and targets for host-directed therapy? *FEMS Pathog. Dis.* **2016**, *74*, ftw012. [[CrossRef](#)]
146. Rane, D.; Patil, T.; More, V.; Patra, S.S.; Bodhale, N.; Dandapat, J.; Sarkar, A. Neutrophils: Interplay between host defense, cellular metabolism and intracellular infection. *Cytokine* **2018**, *112*, 44–51. [[CrossRef](#)] [[PubMed](#)]
147. Segal, A.W. How Neutrophils Kill Microbes. *Annu. Rev. Immunol.* **2005**, *23*, 197–223. [[CrossRef](#)] [[PubMed](#)]
148. Urban, C.F.; Lourido, S.; Zychlinsky, A. How do microbes evade neutrophil killing? *Cell. Microbiol.* **2006**, *8*, 1687–1696. [[CrossRef](#)] [[PubMed](#)]
149. Singhania, A.; Verma, R.; Graham, C.M.; Lee, J.; Tran, T.; Richardson, M.; Lecine, P.; Leissner, P.; Berry, M.P.R.; Wilkinson, R.J.; et al. A modular transcriptional signature identifies phenotypic heterogeneity of human tuberculosis infection. *Nat. Commun.* **2018**, *9*, 2308. [[CrossRef](#)] [[PubMed](#)]
150. Berry, M.P.R.; Graham, C.M.; McNab, F.W.; Xu, Z.; Bloch, S.A.A.; Oni, T.; Wilkinson, K.A.; Banchereau, R.; Skinner, J.; Wilkinson, R.J.; et al. An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. *Nature* **2010**, *466*, 973–977. [[CrossRef](#)] [[PubMed](#)]
151. Eum, S.-Y.; Kong, J.-H.; Hong, M.-S.; Lee, Y.-J.; Kim, J.-H.; Hwang, S.-H.; Cho, S.-N.; Via, L.E.; Barry, C.E. Neutrophils Are the Predominant Infected Phagocytic Cells in the Airways of Patients With Active Pulmonary TB. *Chest* **2010**, *137*, 122–128. [[CrossRef](#)] [[PubMed](#)]
152. Sankar, P.; Mishra, B.B. Early innate cell interactions with Mycobacterium tuberculosis in protection and pathology of tuberculosis. *Front. Immunol.* **2023**, *14*, 1260859. [[CrossRef](#)] [[PubMed](#)]
153. Lovewell, R.R.; Baer, C.E.; Mishra, B.B.; Smith, C.M.; Sasseti, C.M. Granulocytes act as a niche for Mycobacterium tuberculosis growth. *Mucosal Immunol.* **2020**, *14*, 229–241. [[CrossRef](#)] [[PubMed](#)]
154. Saqib, M.; Das, S.; Nafiz, T.N.; McDonough, E.; Sankar, P.; Mishra, L.K.; Zhang, X.; Cai, Y.; Subbian, S.; Mishra, B.B. Pathogenic role for CD101-negative neutrophils in the type I interferon-mediated immunopathogenesis of tuberculosis. *Cell Rep.* **2024**, *44*, 115072. [[CrossRef](#)] [[PubMed](#)]
155. Borregaard, N.; Sørensen, O.E.; Theilgaard-Mönch, K. Neutrophil granules: A library of innate immunity proteins. *Trends Immunol.* **2007**, *28*, 340–345. [[CrossRef](#)] [[PubMed](#)]
156. Borkute, R.R.; Woelke, S.; Pei, G.; Dorhoi, A. Neutrophils in Tuberculosis: Cell Biology, Cellular Networking and Multitasking in Host Defense. *Int. J. Mol. Sci.* **2021**, *22*, 4801. [[CrossRef](#)] [[PubMed](#)]
157. E Kehl-Fie, T.; Skaar, E.P. Nutritional immunity beyond iron: A role for manganese and zinc. *Curr. Opin. Chem. Biol.* **2010**, *14*, 218–224. [[CrossRef](#)] [[PubMed](#)]
158. Weinberg, E.D. Iron withholding: A defense against infection and neoplasia. *Physiol. Rev.* **1984**, *64*, 65–102. [[CrossRef](#)] [[PubMed](#)]
159. Banerjee, S.; Farhana, A.; Ehtesham, N.Z.; Hasnain, S.E. Iron acquisition, assimilation and regulation in mycobacteria. *Infect. Genet. Evol.* **2011**, *11*, 825–838. [[CrossRef](#)] [[PubMed](#)]
160. Flo, T.H.; Smith, K.D.; Sato, S.; Rodriguez, D.J.; Holmes, M.A.; Strong, R.K.; Akira, S.; Aderem, A. Lipocalin 2 mediates an innate immune response to bacterial infection by sequestering iron. *Nature* **2004**, *432*, 917–921. [[CrossRef](#)] [[PubMed](#)]
161. Gugliani, L.; Gopal, R.; Rangel-Moreno, J.; Junecko, B.F.; Lin, Y.; Berger, T.; Mak, T.W.; Alcorn, J.F.; Randall, T.D.; Reinhart, T.A.; et al. Lipocalin 2 Regulates Inflammation during Pulmonary Mycobacterial Infections. *PLoS ONE* **2012**, *7*, e50052. [[CrossRef](#)] [[PubMed](#)]
162. Clohessy, P.A.; Golden, B.E. Calprotectin-Mediated Zinc Chelation as a Biostatic Mechanism in Host Defence. *Scand. J. Immunol.* **1995**, *42*, 551–556. [[CrossRef](#)] [[PubMed](#)]

163. Remijsen, Q.; Kuijpers, T.W.; Wirawan, E.; Lippens, S.; Vandenabeele, P.; Berghe, T.V. Dying for a cause: NETosis, mechanisms behind an antimicrobial cell death modality. *Cell Death Differ.* **2011**, *18*, 581–588. [[CrossRef](#)] [[PubMed](#)]
164. Schechter, M.C.; Buac, K.; Adekambi, T.; Cagle, S.; Celli, J.; Ray, S.M.; Mehta, C.C.; Rada, B.; Rengarajan, J. Neutrophil extracellular trap (NET) levels in human plasma are associated with active TB. *PLoS ONE* **2017**, *12*, e0182587. [[CrossRef](#)] [[PubMed](#)]
165. van der Meer, A.J.; Zeerleder, S.; Blok, D.C.; Kager, L.M.; Lede, I.O.; Rahman, W.; Afroz, R.; Ghose, A.; Visser, C.E.; Zahed, A.S.M.; et al. Neutrophil extracellular traps in patients with pulmonary tuberculosis. *Respir. Res.* **2017**, *18*, 181. [[CrossRef](#)] [[PubMed](#)]
166. Haydar, D.; Gonzalez, R.; Garvy, B.A.; Garneau-Tsodikova, S.; Chandrika, N.T.; Bocklage, T.J.; Feola, D.J. Myeloid arginase-1 controls excessive inflammation and modulates T cell responses in *Pseudomonas aeruginosa* pneumonia. *Immunobiology* **2020**, *226*, 152034. [[CrossRef](#)] [[PubMed](#)]

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