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Concise Review – Invited

Linking mitochondria, fatty acids, and hematopoietic stem cell expansion during infection: implications for aging and metabolic diseases

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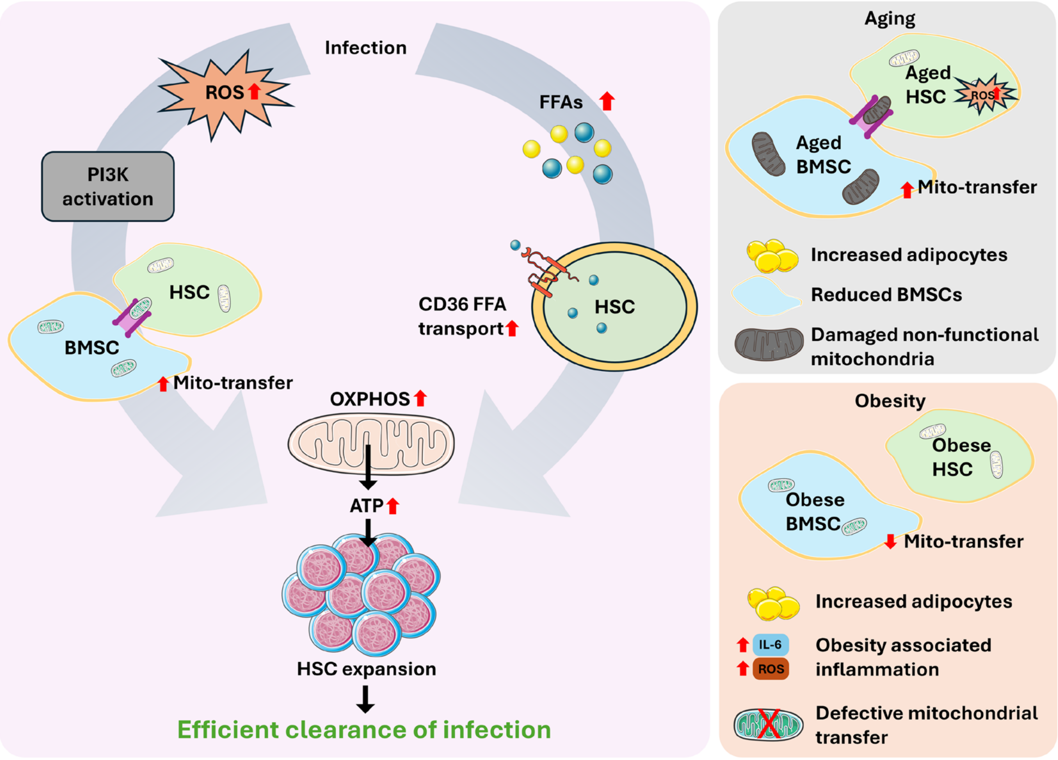
Abstract

In steady state, hematopoietic stem cells (HSCs) reside quiescently in their hypoxic niche with minimal mitochondrial activity, maintaining characteristically low levels of reactive oxygen species (ROS) and instead favoring glycolysis to meet their low energy requirements. However, stress, such as acute infection, triggers a state of emergency hematopoiesis during which HSCs expand more rapidly to produce up to 10-fold more downstream differentiated immune cells. To cope with this demand, HSCs increase their energy production by switching from low ATP-yielding glycolysis to high ATP-yielding mitochondrial oxidative phosphorylation. It is this metabolic switch that enables rapid HSC expansion and differentiation into downstream progeny to increase the immune cell pool and effectively clear the infection. This metabolic switch relies on the sufficient availability of healthy mitochondria as well as fuel in the form of free fatty acids to drive the necessary production of cellular components. This concise review aims to focus on how HSCs increase their mitochondrial content and fuel ATP production via fatty acid oxidation and the impact of HSC dysfunction during aging and other metabolic diseases.

Key words: acute myelogenous leukemia; adult hematopoietic stem cells; bone marrow; stem cell expansion; adipose.

Graphical abstract



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Significance statement

This review aims to focus on how the metabolic changes occur within the bone marrow microenvironment in response to stress and the impact of hematopoietic stem cell dysfunction during aging and other metabolic diseases.

Hematopoisis

Hematopoiesis is the process by which all blood cells are formed. At the center of hematopoiesis are approximately 10 000 long-term hematopoietic stem cells (HSCs), one of the most characterized adult stem cells.[1] Hematopoietic stem cells make up around 0.001% of all bone marrow cells, but are responsible for indirectly producing over 500 billion blood cells daily.[2] Hematopoiesis is tightly regulated, with the surrounding microenvironment of highly organized nonhematopoietic cells including stromal cells, endothelial cells, and adipocytes forming a crucial part of HSC regulation and maintenance.[3] Distinct subpopulations of stromal cells release cytokines and chemokines to support HSCs and play a key role in determining HSC fate and functionality. For a more detailed review which includes the epigenetic regulation of HSCs, see Kasbekar et al.[4]

Mitochondrial function of the HSC

Mitochondria are central to cellular metabolism, producing ATP via oxidative phosphorylation (OXPHOS). They dynamically adjust in morphology and number to match energy demands, undergoing fission and fusion through Drp1 and GTPases to maintain function and integrity.[5,6] Mitochondrial mass—regulated by the balance between biogenesis and mitophagy—determines a cell's metabolic capacity.[7] While increased mitochondrial mass enhances ATP output, it also elevates reactive oxygen species (ROS) levels, which, if excessive, can trigger apoptosis.[8] Thus, cells tightly regulate mitochondrial number to meet energy needs while limiting ROS production.

Quiescent HSCs were historically thought to have low mitochondrial mass and reduced respiration compared to lineage-committed progenitors.[9-11] However, recent studies show comparable mitochondrial content in quiescent and cycling HSCs.[7] This discrepancy likely stems from HSCs actively excluding mitochondrial dyes like MitoTracker Green via xenobiotic efflux pumps. More accurate quantification can be achieved by measuring mitochondrial DNA (mtDNA): nuclear DNA ratios via PCR or using efflux pump inhibitors with MitoTracker probes.

Despite similar mitochondrial content between HSCs and progenitors, HSCs exhibit significantly lower respiratory capacity, as measured by oxygen consumption rate (OCR).[7] Mitochondrial membrane potential (MMP), measured by dyes like tetramethylrhodamine ethyl ester (TMRE), is also lower in HSCs compared to differentiated progenitors, correlating with enhanced regenerative capacity in vivo, suggesting a hallmark of primitive stem cell states.[10,11] This reduced mitochondrial activity in quiescent HSCs is maintained by limited lysosomal activity, restricting glucose uptake and promoting the degradation of damaged mitochondria, reducing ROS and preserving stem cell function and genomic integrity.[11]

Mitochondrial dynamics, including fission mediated by Drp1, support long-term HSC regenerative capacity, while fusion, regulated by mitofusin 2 and the transcription factor Prdm16, balances these dynamics.[10,12,13] Thus, mitochondrial activity in HSCs is tightly controlled to minimize ROS generation and protect stem cell integrity.

Mitochondrial function is also linked to glycolysis in HSCs. In the hypoxic bone marrow niche, HSCs rely on anaerobic glycolysis, with hypoxia-inducible factor (HIF)-1α stabilizing under low oxygen conditions to promote glycolytic enzyme expression and suppress mitochondrial ATP production.[9,14] Deletion of the glycolytic enzyme Pgam1 reduces HSC numbers, underscoring the importance of glycolysis for HSC maintenance.[15] Hypoxia-inducible factor-1α also induces multiple Pdks including Pdk1, 2, and 4, which inhibit pyruvate dehydrogenase, enhancing glycolysis while reducing mitochondrial ATP production. The Pdk family is crucial for HSC engraftment after transplantation, linking metabolic control to regenerative capacity.[16,17] However, no direct in vivo evidence confirms a link between HIF-1α and Pdk1, indicating the complexity of HSC metabolic regulation.[16]

HSC metabolism: glycolysis vs OXPHOS

Although quiescent HSCs are often described as predominantly glycolytic, recent studies reveal a more complex metabolic profile that includes a critical role for mitochondrial OXPHOS. Deletion of PTPMT1, a key mitochondrial phosphatase, impairs mitochondrial function by reducing OCR without affecting mitochondrial mass, resulting in blocked differentiation and hematopoietic failure.[18] This challenges the view that HSCs rely solely on glycolysis.

Oxidative phosphorylation depends on NADH and $FADH_2$ produced in the TCA cycle from acetyl-CoA.[19] While glucose contributes to acetyl-CoA production, fatty acids are a major source during metabolic stress.[20] Free fatty acids (FFAs), from dietary or endogenous sources, undergo fatty acid oxidation (FAO) in mitochondria and peroxisomes to generate acetyl-CoA.[21] ACLY, which converts citrate to acetyl-CoA, also regulates HSC metabolism, lower ACLY activity is linked to greater stemness and self-renewal.[22] These findings suggest HSCs rely on both glycolytic and mitochondrial pathways for metabolic adaptability and function.

Bone marrow adipocytes are a key source of FFAs, influencing HSCs both metabolically and via paracrine signals. Lipolysis releases FFAs and glycerol into the marrow, providing substrates for FAO in HSCs.[21] However, their role is context-dependent.[23] Reduced adiposity, whether genetically (A-ZIP/F-1 mice) or via peroxisome proliferator-activated receptor (PPAR)γ antagonism, improves HSC engraftment posttransplant.[24] Conversely, adipocytes also secrete supportive cytokines like stem cell factor (SCF); adipocyte-specific SCF deletion impairs HSC regeneration.[24]

Fatty acid oxidation is important in HSC maintenance and long-term function. Its inhibition with etomoxir (a CPT1A inhibitor) causes HSC exhaustion and hematopoietic failure.[25] PPARδ, a FAO regulator expressed in HSCs, enhances HSC maintenance; its effect is abolished when FAO is blocked.[26,27]

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Yet, FAO's necessity may vary with context: deletion of long-chain FAO enzymes in healthy mice did not affect HSC maintenance, suggesting metabolic flexibility, such as glutamine compensation.[28] Thus, while FAO supports HSC function during stress, it may not be essential under homeostasis.

Role of mitochondria in the HSC response to infection

Recent studies have highlighted a key role for mitochondria in the HSC response to infection. Using MitoTracker dyes (in combination with efflux inhibitors) and mtDNA quantification via RT-PCR, it has been shown that mitochondrial mass increases in HSCs following infectious challenge.[29] This increase has been observed in multiple infection models, including *Salmonella typhimurium* and lipopolysaccharide (LPS), an endotoxin derived from *Escherichia coli*. Notably, this mitochondrial expansion correlates with enhanced HSC regenerative capacity,[30] suggesting a direct link between mitochondrial dynamics and functional adaptation of HSCs during immune stress.

While some studies have specifically demonstrated this phenomenon within the HSC compartment,[29] the response is not unique to HSCs. In fact, mitochondrial biogenesis in response to stress appears to be a conserved feature across various cell types. For example, macrophages exhibit increased mitochondrial mass following LPS exposure,[31] and epithelial cells in the human lung similarly respond to oxidative stress by expanding their mitochondrial content.[32]

This phenomenon also extends to pathological contexts. Malignant cells, including those from acute myeloid leukemia (AML), have been shown to upregulate mitochondrial biogenesis to support elevated bioenergetic demands. Acute myeloid leukemia cells display increased mitochondrial mass, which contributes to their metabolic flexibility and survival advantage.[33,34] Collectively, these findings underscore the importance of mitochondrial adaptability in cellular stress responses. For HSCs, the ability to expand mitochondrial content may serve as a crucial mechanism for meeting the heightened energy requirements during infection and promoting effective regenerative responses.

Mitochondrial transfer in HSC

Studies show that increasing mitochondrial mass can benefit HSCs during stress.[35] However, increasing mitochondrial number via mitochondrial biogenesis takes time and alternative faster methods for cells to increase their mitochondrial content have been explored. Functional mitochondrial transfer, first described by Spees et al., allows cells to quickly alter their mitochondrial mass, bypassing the need for mitochondrial biogenesis or mitophagy. Mitochondrial transfer occurs via 3 main methods: (1) release of either free mitochondria (from platelets) or mitochondria packaged into extracellular vesicles from donor cells which recipient cells then endocytose; (2) transfer of mitochondria through directly through cell–cell contact via gap junctions; and (3) transfer through tunneling nanotubules.[36,37]

While later sustained increases in mitochondrial mass may be explained by increased mitochondrial biogenesis, some papers have reported an initial increase in mitochondrial mass that precedes any upregulation of mitochondrial biogenesis genes. For example, Mistry et al. demonstrated that following LPS treatment, mice had increased HSC mitochondrial content within 2 h, but mitochondrial biogenesis did not occur until much later.[29] In vivo transplant models support this, showing that nearby bone marrow stromal cells (BMSCs) transfer their mitochondria to HSCs in response to LPS, leading to reduced mitochondrial mass in BMSCs.[29]

This is further supported by in vitro studies, where bone marrow-derived macrophages treated with LPS for under 6 h showed no increase in mitochondrial mass or biogenesis.[38] Mitochondrial mass only increased after 12 h of LPS exposure,[31,39] and this was blocked by ethidium bromide pretreatment, which inhibits mtDNA replication and transcription.[31] These findings consistently show that LPS-induced mitochondrial biogenesis does not occur within the first 6 h in vitro. In contrast, in vivo studies demonstrate early increases in mitochondrial mass, likely due to microenvironmental contributions such as mitochondrial transfer. This supports the idea that initial mitochondrial expansion in HSCs is driven by transfer rather than biogenesis.

ROS-driven mitochondrial transfer in HSCs during infection

Up to 90% of ROS are generated within mitochondria. Under normal, low-stress conditions, only a small fraction of the oxygen consumed by mitochondria is converted into ROS.[40] In HSCs, restriction of mitochondrial metabolism helps maintain low ROS levels, preserving quiescence and stemness by preventing premature differentiation and lineage commitment.[41] However, in response to physiological stress, such as infection, ROS levels increase sharply, contributing to a proinflammatory environment.[42]

An ROS surge activates the PI3K pathway, promoting mitochondrial transfer from BMSCs to HSCs via CX43-mediated gap junctions (Figure 1).[29] This was demonstrated by the inhibition of transfer using the ROS scavenger NAC, or by pharmacological blockade of PI3K or CX43.[43] The PI3K–CX43 axis has been further validated in other studies.[43] Beyond transfer, PI3K also mediates HSC activation via interleukin (IL)-1β and drives emergency granulopoiesis through ROS signaling.[42,44] Supporting its broader role, ROS has been shown to increase mitochondrial mass and mtDNA in nonhematopoietic cells, such as fibroblasts treated with BSO (a known inducer of ROS).[32,45] These findings highlight ROS–PI3K signaling as a key regulator of mitochondrial expansion in HSCs during stress responses like infection.

Fatty acid oxidation and emergency hematopoiesis

The ability to rapidly transfer mitochondria to HSCs likely ensures swift engagement of OXPHOS to meet the elevated energy demands associated with HSC activation and proliferation during emergency hematopoiesis. This energy is thought to be derived in large part from FFAs, as circulating FFA levels have been shown to rise dramatically during infection in both animal models and human studies.[46-48] The proinflammatory state created as part of the innate response to stresses such as infection is created by the rapid release of multiple proinflammatory cytokines, most notably IL-6 and potentially IL-1β.[44,49] IL-6 has been shown to stimulate lipolysis in both preclinical models as well as in humans, regulating downstream FAO-related genes such as PPARgamma coactivator 1 alpha,[50,51] providing a direct link between IL-6 and FAO. Furthermore, high levels of circulating IL-6 are consistently found in a wide range of infections which correlates with increased FFAs.[52]

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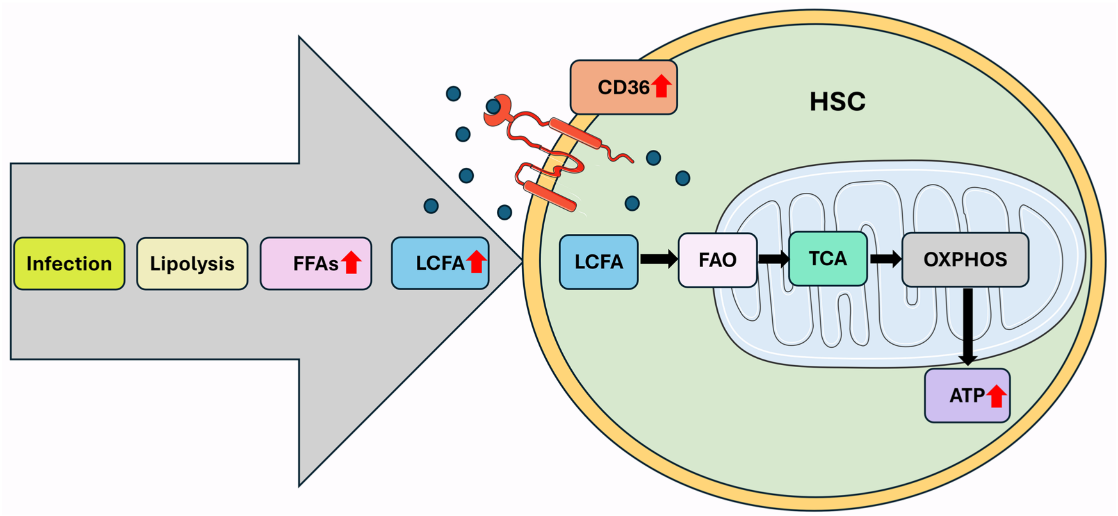

Figure 1. Mitochondrial transfer from BMSCs to HSCs in response to infection. Infection increases ROS within the cell, subsequently activating the PI3K pathway and mediating an increase in CX43 gap junctions. Increased gap junctions facilitate mitochondrial transfer from BMSCs to HSCs. Abbreviations: BMSCs, bone marrow stromal cells; HSCs, hematopoietic stem cells; ROS, reactive oxygen species.

Importantly, pharmacological inhibition of IL-6 in healthy human subjects led to reduced circulating FFA levels without affecting glucose metabolism, lipolysis, or FAO.[53] In contrast, giving healthy human participants recombinant IL-6 caused a significant increase in systemic FFAs and FAO; however, glucose remained unaffected.[54] Mouse models demonstrate similar findings, showing that IL-6 significantly increases in models of stress including infection and fasting, which correlated with increased serum FFAs.[46,49,55] These increases were reversed in IL-6 knockout mice or following treatment with IL-6 neutralizing antibodies.[46,55]

In HSCs, levels of intracellular lipids were elevated, which correlated with increased FAO and subsequent OXPHOS in models of both *S. typhimurium* and LPS.[46] However, while it is evident that FFAs become readily available during infection, the precise cellular and molecular mechanisms governing their uptake and utilization by HSCs remain unclear and warrant further investigation.

Mechanisms of cellular uptake of FFA

Multiple membrane-associated proteins facilitate the cellular uptake of lipids, including FFAs. Key among these are CD36, fatty acid-binding proteins, CD206, and fatty acid transport proteins (also known as solute carrier family 27).[56-58] These proteins function together to mediate the uptake and intracellular trafficking of fatty acids, particularly long-chain fatty acids (LCFAs). CD36 plays a central role in this process. It binds LCFAs via its extracellular domain and undergoes a conformational change that enables translocation of fatty acids across the lipid bilayer.[59,60] CD36 is expressed in a variety of tissues and cell types, including HSCs, underscoring its role in fatty acid uptake during both homeostasis and hematopoietic stress.[61]

Importantly, HSC expression of CD36 is significantly upregulated in response to infection, facilitating enhanced FFA uptake during emergency hematopoiesis.[46] Genetic deletion or pharmacological inhibition of CD36 impairs this process, resulting in reduced FFA uptake, impaired HSC proliferation, diminished regenerative capacity, and a failure to expand in response to infection.[46,61] Moreover, loss of CD36 directly reduces FAO rates,[62] linking CD36 not only to lipid uptake but also to downstream mitochondrial metabolism and ATP production. These findings collectively highlight CD36 as a crucial regulator of FFA uptake and subsequent metabolic reprogramming in HSCs during hematopoietic stress responses (Figure 2).

Although not yet fully elucidated, CD36 expression is thought to be regulated by several mechanisms, including transcriptional factors linked to FAO, such as the PPAR family—key mediators of the cellular response to infection and metabolic stress.[63] Activation of PPARs has been shown to induce CD36 expression in various cell types,[64,65] suggesting that lipid signaling and FFA availability may themselves contribute to a positive feedback loop that enhances CD36-mediated uptake during infection.

Once in the cytosol, FFAs are activated to fatty acyl-CoA and converted by CPT1A into fatty acyl-carnitine—a rate-limiting step in mitochondrial FAO.[66,67] This enables β-oxidation, producing acetyl-CoA and ATP.[66] CPT1A is essential for HSC quiescence; its deletion leads to loss of stemness and impaired function.[46] CPT1A knockdown also blocks HSC expansion after LPS, confirming FAO's role in emergency haematopoiesis.[46] CPT1A expression correlates with CD36 upregulation, suggesting a coordinated axis of FFA uptake and oxidation.[68]

Implications and consequences of impaired HSC expansion

Disruption of key metabolic processes such as CD36-mediated fatty acid uptake or ROS-driven mitochondrial transfer critically impairs HSC proliferation and expansion during infection. Inadequate expansion delays the initiation of effective immune responses, increasing susceptibility to systemic infection and markedly elevating the risk of morbidity and mortality. These consequences are particularly profound in vulnerable populations, including the elderly, immunocompromised individuals, and patients with metabolic comorbidities such as obesity, where baseline hematopoietic function and metabolic flexibility may already be compromised. A deeper understanding of these pathways offers important therapeutic potential for enhancing immune competence in at-risk groups.

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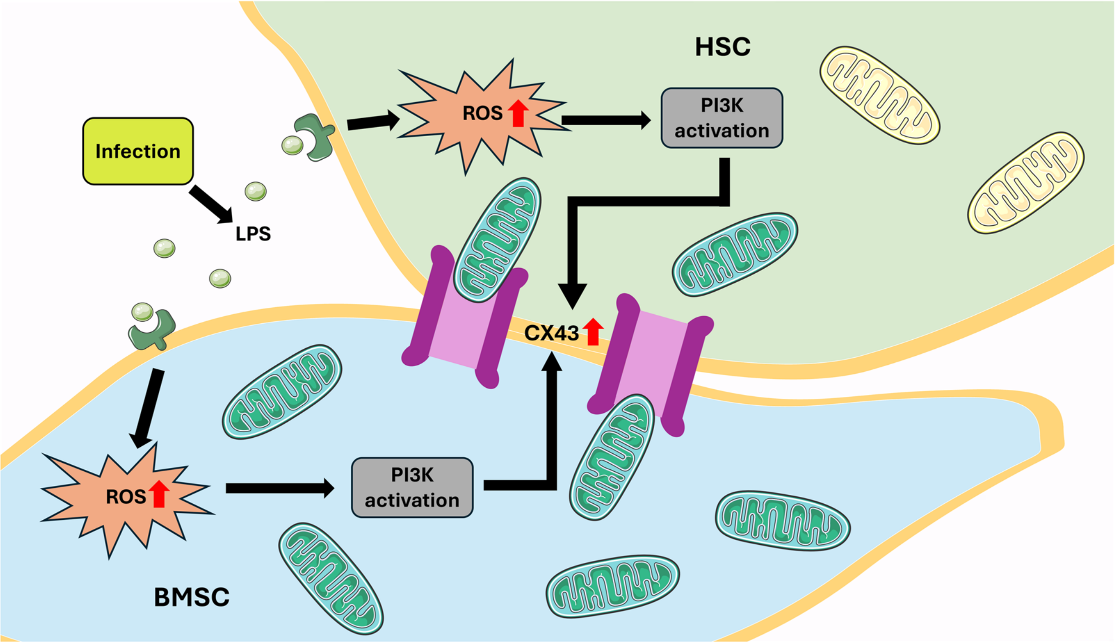

Figure 2. Infection-mediated CD36 upregulation facilitates HSC expansion. Inflammatory cytokines including IL-6 released in response to infection induce lipolysis and increase circulating FFAs. CD36 membrane expression is increased on HSCs, allowing them to take up excess LCFA to be utilized in the FAO pathway and subsequent OXPHOS. Increased ATP from OXPHOS enables HSC proliferation in response to the infection. Abbreviations: FAO, fatty acid oxidation; FFAs, free fatty acids; HSCs, hematopoietic stem cells; LCFA, long-chain fatty acid; OXPHOS, oxidative phosphorylation.

Impact of aging

Frailty, characterized by a decline in physical and cognitive function, significantly compromises immune responses and increases vulnerability to infection. The risk of infection-related hospitalization rises sharply with age and frailty, with frailty alone increasing this risk by 78%.[69,70] In England alone, more than 1 million infection-related hospital admissions occurred in a single year, with two-thirds of adult admissions involving individuals over 65 years of age.[71] As populations age across most Western countries, these numbers are expected to grow, underscoring an urgent need for targeted therapeutic strategies to improve infection resilience in the elderly.

Aging also directly affects HSC function. Hematopoietic stem cells accumulate genetic and mitochondrial damage, contributing to reduced regenerative potential, increased myeloid skewing, and a predisposition to myeloproliferative diseases and leukemias.[35,72,73] Age-related changes in the bone marrow microenvironment, particularly the increased presence of adipocytes, contribute to chronic low-grade inflammation or inflammaging. Bone marrow adipocytes secrete proinflammatory cytokines such as IL-6, which further disrupts HSC homeostasis.[41,74]

In parallel, ROS levels increase with age, impairing mitochondrial function and disrupting the delicate balance required for HSC quiescence and activation.[9,41,74] Excessive ROS drives HSCs out of quiescence, promoting exhaustion. Recently, studies have started to identify distinct HSC populations in aged mice, for example HSCs with high or low mitochondrial mass. While aged HSCs have been shown to have increased mitochondrial mass overall compared to young, the MMP measured using TMRE was significantly lower in aged HSCs with high mitochondrial mass, indicating reduced mitochondrial fitness. The HSCs with high mitochondrial mass also relied more heavily on OXPHOS over glycolysis for ATP production.[75] Interestingly, this reduced reliance on glycolysis may be beneficial in aged HSCs, promoting metabolic resilience and enhanced cell survival,[15] and has been associated with reduced mitochondrial ROS production.[75] Despite this, inflammation impairs glycolysis in aged HSCs,[76] and combined with diminished mitochondrial fitness, contributes to reduced energy availability and regenerative failure. Pharmacological strategies aimed at restoring mitochondrial health—such as the use of MitoQC—have shown promise in reversing myeloid bias and improving HSC function in steady-state condition.[74] However, their efficacy in the context of infection remains unknown.

Recent studies demonstrate that aged mice fail to mount a robust HSC expansion response following LPS exposure, unlike their younger counterparts.[77] This failure is not due to an inability to transfer mitochondria, but rather due to the transfer of dysfunctional mitochondria from aged BMSCs. Improving mitochondrial health in BMSCs can partially restore this defect, offering a potential therapeutic avenue.[78] Compounding this, increased marrow adiposity is associated with a loss of BMSCs due to a proadipogenic shift, potentially reducing the availability of donor mitochondria during stress.

Taken together, these findings indicate that aging, particularly when accompanied by frailty, profoundly impairs the ability of the bone marrow—especially HSCs—to respond effectively to infection. Mitochondrial dysfunction emerges as a central mechanism, though the influence of aging on HSC CD36 expression and fatty acid uptake remains unexplored. Uncovering the molecular basis of this age-related dysfunction may enable the development of targeted therapies to rejuvenate HSCs and restore effective hematopoiesis during infection.

Impact of obesity

Obesity induces a chronic proinflammatory state with increased ROS and cytokine production associated with HSC and

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immune dysfunction,[79] and significantly increases the risk of developing other metabolic disorders including diabetes and heart disease.[80] This places a significant strain on health-care systems, with over 1 billion people worldwide currently classified as medically obese.[81] The regenerative capacity of HSCs, particularly in response to stress, is significantly affected by obesity increasing the risk of HSC exhaustion.[79] Obesity causes a myeloid bias, significantly increasing HSC production of proinflammatory macrophages.[82] Furthermore, obesity-associated increase in adipocyte IL-6 release drives adipose tissue immune cell infiltration particularly by macrophages, which then further release high levels of multiple inflammatory cytokines including IL-6, further increasing inflammation.[51] This demonstrates the vicious cycle of cytokine production in obesity. However, fasting-induced IL-6 production and subsequent FFA release is absent in both obese and glucose intolerant mice,[55] highlighting the complexity of the dysregulated cytokine response in obesity. Metabolic disorders such as obesity have been associated with a premature aging phenotype, including mitochondrial dysfunction and increased CD36 expression.[83] In fact, CD36$^{-/-}$ mice are more resistant to diet-induced obesity,[84] highlighting a role for CD36 in obesity.

Excessive exposure to lipids also drives increased ROS production, further affecting mitochondrial health and driving dysfunctional cytokine production.[85] Within white adipose tissue, obesity impairs the normal transfer of adipocyte mitochondrial to macrophages seen in the normal immune response. This loss was ameliorated by changing from the LCFA-rich diet to a medium chain FA-rich diet.[86] Because CD36 is specifically an LCFA transporter, this could further provide a link between LCFA uptake via CD36 and mitochondrial transfer. However, interestingly this adipocyte to macrophage mitochondrial transfer was unaffected in aged mice,[86] indicating this may be a specific finding for obesity.

Targeting mitochondrial transfer

Aside from sepsis and an impaired response to infection, dysfunctional mitochondria are a prominent characteristic in a wide range of diseases from heart and lung disease to Alzheimer's and stroke, highlighting the value of using mitochondrial transfer to restore and maintain mitochondrial health. One approach to enhancing mitochondrial function involves the direct injection of healthy mitochondria. Preclinical models as well as a few clinical trials have been conducted, assessing the therapeutic potential of mitochondrial transfer to restore mitochondrial function within diseased or damaged cells.[37] Minovia Therapeutics have ongoing Phase 1 clinical trials in which participant's autologous HSCs are enriched with allogeneic placental-derived mitochondria (NCT06017869 and NCT06465160). LUCA Science has developed a novel method to isolate functional mitochondria with the idea being to store and deliver as a biopharmaceutical agent. Mitrix Bio are also working on delivering Mitlets "mitochondria encapsulated vesicles" into patients with mitochondrial diseases.[87] Together these form the backbone of potential therapeutic transfer of functional mitochondria.

There are many diseases that would benefit from either boosting mitochondrial health through mitochondrial transplantation or inhibiting mitochondrial transfer through therapeutic intervention. Many cancers have been shown to use mitochondrial transfer in vitro to enhance their metabolic output leading to increased proliferation.[34,37] Ideally understanding the mechanism by which mitochondrial transfer occurs between noncancer and cancer cells would allow for the repurposing of already developed drugs or the development of new therapeutics to target these mechanisms.

Targeting FFA availability or cellular uptake

We and others have shown that altered lipid metabolism, including elevated lipolysis and FFA availability followed by FFA uptake and FAO plays a significant role in our stem cell response to infection, as well as being hijacked by various cancer cells to enhance energy production. In the context of normal response to infection, lipolysis has been shown to be impaired in aging[88] and increased in obesity[89]; therefore, targeting the lipolytic pathways in adipose tissue or hepatic storage mechanisms could be a potential therapeutic target. This could be achieved using PPAR agonists/antagonists depending on the target organ. Various agonist and antagonists are currently used in the clinic for various conditions including fenofibrate, a PPARα agonist used to treat abnormal blood lipid levels. The development and use of PPAR modulators in health and disease is nicely reviewed by Skoczynska et al.[90]

Targeting FFA uptake and delivery into the mitochondria is potentially more appropriate for cancer treatments. This is because many cancers including hematological cancers have adapted to use FFA as an energy source.[91] Several mechanisms that control FFA uptake and metabolism are altered in cancer cells to support their survival. Both natural and synthetic compounds can block FFA uptake and metabolism with some emerging as anticancer agents. For instance, SMS121, a new inhibitor of CD36, impairs fatty acid uptake and viability of AML.[92] Furthermore, Ona Therapeutics have developed a blocking antibody for CD36 (ONA-036) with the hope targeting metastasis-initiating cells by inhibiting CD36.[93] Others have used etomoxir as a CPT1A inhibitor in clinical trials, but this has shown severe side effects[94] with more recent data showing that etomoxir having multiple targets.[95] There is a clear need and opportunity to develop therapeutics to FFA uptake and metabolism within the context of cancer.

Summary and future

In response to infection, emergency hematopoiesis rapidly expands immune cell output from a limited pool of HSCs, a process demanding high energy. This is achieved via a 2-pronged mechanism: systemic increases in ROS and IL-6 drive both mitochondrial transfer and fatty acid oxidation. Within the bone marrow, ROS activates PI3K, triggering CX43-dependent mitochondrial transfer from BMSCs to HSCs. Simultaneously, IL-6 induces systemic lipolysis, increasing circulating FFAs. Hematopoietic stem cells upregulate CD36 to import FFAs, which are then processed via CPT1A to fuel FAO and OXPHOS, supporting proliferation and differentiation.

Mitochondrial transfer and CD36-mediated FFA uptake may be more closely linked than previously thought. In macrophages, increased mitochondrial content following LPS stimulation promotes IL-6 release, while inhibiting mitochondrial biogenesis blocks both mitochondrial expansion and IL-6 expression.[31] This suggests IL-6 may act as a key integrator of mitochondrial and metabolic remodeling during immune responses.

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Understanding these tightly regulated processes in healthy HSCs provides critical insight into potential therapeutic targets. By manipulating mitochondrial transfer or FFA metabolism, we may be able to correct their dysregulation in diseases such as aging, metabolic disorders, and hematologic malignancies.

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Conflicts of interests

None declared.

Data availability

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