# Fatty acid metabolism and its role in stem cell maintenance and differentiatio.

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## Introduction

Fatty acid metabolism plays a pivotal role in cellular energetics and biosynthesis, and its significance extends far beyond mere energy provision. In the context of stem cells—both embryonic and adult—the regulation of fatty acid metabolism has emerged as a critical determinant of cell fate, influencing whether a stem cell maintains its undifferentiated, pluripotent state or commits to a lineage-specific differentiation program. The balance between self-renewal and differentiation is tightly controlled by intrinsic metabolic cues and extrinsic signals from the microenvironment. Among these cues, lipid metabolism, especially fatty acid synthesis and oxidation, exerts profound effects on stem cell maintenance, plasticity, and specialization [1].

Stem cells are unique in their capacity for both self-renewal and differentiation. These capabilities demand tight regulation of cellular metabolism, including glucose, amino acid, and lipid pathways. Fatty acids serve multiple roles within the cell: they are fundamental building blocks of phospholipids for membrane biosynthesis, substrates for β-oxidation in mitochondria to generate ATP, and precursors for lipid-based signaling molecules that regulate gene expression and intercellular communication. The dynamic regulation of fatty acid metabolism allows stem cells to adapt to environmental conditions and intrinsic developmental cues, aligning metabolic processes with cell fate decisions [2].

In the pluripotent state, such as in embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs), fatty acid metabolism is geared toward supporting rapid proliferation and biosynthesis. These cells exhibit a high demand for lipids to form new membranes and organelles. De novo fatty acid synthesis (lipogenesis) is often upregulated in this state, driven by the activation of enzymes such as ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), and fatty acid synthase (FASN). These enzymes convert citrate from the TCA cycle into acetyl-CoA and subsequently into long-chain fatty acids. The elevated lipogenic activity provides not only structural lipids but also lipid-derived signaling molecules that maintain the transcriptional circuitry of pluripotency. For instance, specific phospholipids can interact with nuclear receptors and chromatin modifiers to reinforce the expression of genes associated with stemness [3].

Concurrently, the rate of fatty acid β-oxidation (FAO) in pluripotent stem cells is relatively low compared to differentiated cells. However, some degree of FAO activity is necessary for maintaining a poised epigenetic landscape. Intermediates generated during FAO, such as acetyl-CoA and NADH, can influence chromatin remodeling by serving as cofactors for histone acetyltransferases or modulating sirtuin activity. This interplay links metabolic flux directly with transcriptional regulation, creating a feedback loop between metabolism and gene expression [4].

In contrast, adult stem cells, including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and neural stem cells (NSCs), exhibit a more varied and often FAO-dominant metabolic phenotype in their quiescent state. Quiescence is a reversible, non-dividing state essential for preserving stem cell pools over the lifespan of an organism. In these cells, FAO serves as a metabolic strategy to efficiently generate ATP without producing excessive reactive oxygen species (ROS), which can damage cellular components and induce premature differentiation or senescence. This reliance on FAO allows quiescent stem cells to maintain their undifferentiated status and minimize oxidative stress [5].

FAO in adult stem cells is tightly regulated by pathways such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha (PPARα), which sense energy levels and lipid availability. When activated, these pathways promote the expression of carnitine palmitoyltransferase 1 (CPT1), the rate-limiting enzyme in mitochondrial fatty acid transport. Enhanced CPT1 activity facilitates the import of long-chain fatty acids into mitochondria for β-oxidation. Experimental inhibition of CPT1 has been shown to impair stem cell maintenance and promote differentiation, underscoring the functional importance of FAO in maintaining stem cell identity [6].

Upon differentiation, there is a marked metabolic shift from FAO and glycolysis toward oxidative phosphorylation and anabolic lipid synthesis, depending on the lineage. For example, during adipogenic differentiation of MSCs, there is an upregulation of lipogenesis and lipid droplet formation, reflecting the specialized function of adipocytes in lipid storage [7]. Conversely, during myogenic or osteogenic differentiation, there is increased mitochondrial biogenesis and fatty acid oxidation to meet the heightened energy demands of these lineages. This metabolic reprogramming is orchestrated by lineage-specific transcription factors such as PPARγ in adipogenesis and RUNX2 in osteogenesis, which

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also regulate key lipid metabolic enzymes. Therefore, fatty acid metabolism is not merely a background process but is actively restructured during differentiation to support the specialized function of each cell type [8].

Another important dimension of fatty acid metabolism in stem cell biology is its influence on the epigenetic landscape. Metabolites generated through fatty acid metabolism, such as acetyl-CoA, NAD+, and short-chain fatty acids, directly modulate the activity of histone-modifying enzymes. Acetyl-CoA is a key substrate for histone acetylation, a chromatin mark associated with transcriptional activation [9]. Thus, fluctuations in acetyl-CoA levels due to changes in FAO or lipogenesis can dynamically alter gene expression profiles. Similarly, NAD+ is required for the activity of sirtuins, a class of NAD+-dependent histone deacetylases that play critical roles in maintaining stem cell function and longevity. Through these metabolic-epigenetic interactions, fatty acid metabolism exerts long-lasting effects on cell identity and developmental potential.

The extracellular lipid environment, including the availability of dietary fatty acids and lipid-derived hormones, also significantly impacts stem cell behavior. Polyunsaturated fatty acids (PUFAs) such as omega-3 and omega-6 fatty acids can modulate stem cell fate through receptor-mediated signaling and incorporation into membrane phospholipids, altering membrane fluidity and signaling cascades. Lipid-derived signaling molecules such as prostaglandins and lysophosphatidic acid (LPA) have been shown to influence stem cell proliferation, migration, and differentiation through G-protein coupled receptor pathways. These findings highlight the relevance of systemic lipid metabolism and nutritional status in shaping the stem cell niche and influencing regenerative capacity [10].

## Conclusion

In summary, fatty acid metabolism is a multifaceted regulator of stem cell maintenance and differentiation. It provides energy, biosynthetic materials, and signaling molecules that collectively shape the cellular environment and influence gene expression. The dynamic balance between fatty acid synthesis and oxidation is not only a reflection of stem cell state but also a determinant of fate decisions. As research continues to elucidate the mechanisms linking lipid metabolism with stem cell function, new opportunities arise for harnessing metabolic pathways to enhance regenerative medicine and combat diseases rooted in stem cell dysfunction.

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