Succinyl-coenzyme A: a key metabolite and succinyl group donor in erythropoiesis

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Red blood cells, the most abundant cell type in the body, are primarily responsible for delivering oxygen to tissues. With a lifespan of 120 days, red blood cells account for 65% of the cell turnover per day in the human body, i.e. a turnover/production of ~$0.2x10^{12}$ cells per day.[1] Like all hematopoietic cells in our organism, erythroid cells arise from the hematopoietic stem cell compartment. After commitment to the erythroid lineage, hematopoietic progenitors will generate burst-forming unit-erythroid cells, which will further develop into colony-forming unit-erythroid, pro-erythroblasts, and erythroblasts, to eventually undergo terminal erythroid differentiation. Lineage commitment coincides with the expression of key molecules such as GATA-1 and EPOR[2] and relies on the accumulation of essential metabolites e.g., succinyl-coenzyme A (CoA) and glycine metabolites.[3] More recently, post-translational modifications, such as methylation, acetylation, phosphorylation and ubiquitination, were shown to remodel the proteome during erythroid differentiation.[4-6]

The mature red blood cell possesses one of the simplest cellular proteomes, with hemoglobin comprising an impressive ~98% of its soluble protein content.[7] However, to reach this stage, red blood cells must first accumulate the essential metabolites for heme synthesis, including succinyl-CoA and glycine, and any disturbance might compromise erythropoiesis. For instance, succinyl-CoA deficiency in *IDH1*-mutant hematopoietic cells disrupts heme biosynthesis, impairing erythroid differentiation at the late erythroblast stage.[8] In myelodysplastic neoplasms, aberrant splicing of the CoA synthase (COASY) transcript in *SF3B1*-mutant clones results in reduced levels of CoA and its by-product, succinyl-CoA. This disruption plays a critical role in contributing to ineffective erythropoiesis. Strikingly, supplementation with exogenous succinyl-CoA can partially restore erythropoiesis in cells from patients with *SF3B1* mutations, highlighting a potential therapeutic avenue.[9]

In addition to its key role as a metabolite, succinyl-CoA provides the succinyl group for protein succinylation. Indeed, lysine succinylation (Ksu) has recently emerged as a protein modification that regulates diverse biological processes. For instance, succinate-CoA ligase (*SUCLG1*) reduces succinyl-CoA levels to restrict mitochondrial RNA polymerase (*POLRMT*) succinylation, and consequently mitochondrial DNA transcription, mitochondrial biogenesis, and leukemia cell proliferation are maintained.[10]

In their manuscript published in this issue of *Haematologica*, Hu *et al*. address the critical question of the role of protein succinylation during erythropoiesis.[11] The authors show that succinyl-CoA is highly abundant in primary human cells undergoing erythroid differentiation, and that its increase is paralleled by a rise in the abundance of nuclear and cytoplasmic succinylated proteins, whereas other post-translational modifications remain largely unchanged.

To investigate the role of protein succinylation in erythroid differentiation, the authors either knocked down succinyltransferase lysine acetyltransferase 2A (*KAT2A*) or overexpressed desuccinylase sirtuin 5 (*SIRT5*) in human hematopoietic stem and progenitor cells. Both approaches resulted in impaired erythroid differentiation *in vitro*. Likewise, *SIRT5* overexpression *in vivo* led to significant decreases of red blood cell count and hemoglobin levels, while no changes were observed in the white blood cell count.

Then, using the HUDEP2 erythroid cell line derived from human umbilical cord blood $CD34^+$ cells, Hu *et al*. performed in-depth proteome and succinylome analyses and catalogued 3,562 succinylated sites across 939 distinct proteins. Noteworthily, the majority of succinylated proteins were shared between the early and late stages of erythroid differentiation, reflecting alterations of succinylation rather than *de novo* modifications.

Approximately 60% of the succinylated proteins had two or more succinylation sites, with those containing over ten

sites being enriched in pathways associated with respiratory electron transport and ATP synthesis. Proteins with more than two succinylation (Ksu) sites displayed heightened succinylation at the late stage of erythroid differentiation and were almost uniformly distributed across key subcellular compartments, including the nucleus, cytoplasm, and mitochondria.

Histone 3 (H3) and cytochrome C (CYCS) were among the top ten most succinylated proteins, with both showing extensive modification. H3 succinylation at lysine 79 (K79) is KAT2A-dependent and increased steadily during erythropoiesis to reach a plateau around days 7-9 of differentiation. CUT&TAG analysis of H3K79 succinylation (H3K79Ksu) revealed an enrichment in genes associated with chromatin remodeling. CYCS, which exhibited the most pronounced succinylation changes in mitochondria, plays a key role in maintaining cell integrity during erythroid differentiation. Targeted mutagenesis of succinylation sites K28 and K40 on CYCS disrupted erythroid differentiation, increased apoptosis, inhibited cell proliferation, and reduced mitochondrial membrane potential.

In conclusion, Hu and colleagues provide novel data and resources relating to the distribution and role of protein succinylation during erythropoiesis, identifying 939 highly succinylated proteins involved in erythroid development processes such as mitochondrial metabolism, heme synthesis and chromatin remodeling. Their findings also raise intriguing questions regarding the balance between succinyl-CoA as a metabolic intermediate and as a donor for succinylation. Among the 939 catalogued proteins, how do the succinyl groups alter protein structure, activity, stability and protein-protein interactions? These effects underscore the potential regulatory roles of succinylation in erythropoiesis and highlight the need for further investigation into its mechanistic impact on protein function.

Disclosures

No conflicts of interest to disclose.

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