Modeling Snyder-Robinson Syndrome in multipotent stromal cells reveals impaired mitochondrial function as a potential cause for deficient osteogenesis.

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Public Summary:
Patients with Snyder-Robinson Syndrome (SRS) exhibit deficient Spermidine Synthase (SMS) gene expression, which causes neurodevelopmental defects and osteoporosis, often leading to extremely fragile bones. To determine the underlying mechanism for impaired bone formation, we modelled the disease by silencing SMS in human bone marrow - derived multipotent stromal cells (MSCs) derived from healthy donors. We found that silencing SMS in MSCs led to reduced cell proliferation and deficient bone formation in vitro, as evidenced by reduced mineralization and decreased bone sialoprotein expression. Furthermore, transplantation of MSCs in osteoconductive scaffolds into immune deficient mice shows that silencing SMS also reduces ectopic bone formation in vivo. Tag-Seq Gene Expression Profiling shows that deficient SMS expression causes strong transcriptome changes, especially in genes related to cell proliferation and metabolic functions. Similarly, metabolome analysis by mass spectrometry, shows that silencing SMS strongly impacts glucose metabolism. This was consistent with observations using electron microscopy, where SMS deficient MSCs show high levels of mitochondrial fusion. In line with these findings, SMS deficiency causes a reduction in glucose consumption and increase in lactate secretion. Our data also suggests that SMS deficiency affects iron metabolism in the cells, which we hypothesize is linked to deficient mitochondrial function. Altogether, our studies suggest that SMS deficiency causes strong transcriptomic and metabolic changes in MSCs, which are likely associated with the observed impaired osteogenesis both in vitro and in vivo.

Scientific Abstract:
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