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Oxidative stress-induced S100B accumulation in myoblasts converts myoblasts into brown preadipocytes via an NF-κB/YY1/MIR-133 axis and NF-κB/YY1/BMP7 axis

Ileana Giambanco - Giulio Morozzi - Sara Beccafico - Ilaria Bellezza - Roberta Bianchi - Cataldo Arcuri [1] - Alba Minelli [1] - Rosario Donato

Università degli Studi di Perugia, Dipartimento di Medicina Sperimentale, Perugia, Italia

Muscles of sarcopenic people show hypotrophic myofibers and infiltration with adipose and, at later stages, fibrotic tissue. The origin of infiltrating adipocytes resides in fibro-adipogenic precursors, nonmyogenic mesenchymal progenitor cells, and satellite cells, the adult stem cells of skeletal muscles. Myoblasts and brown adipocytes share a common Myf5+ progenitor cell, and cell fate decision depends on levels of BMP7, a TGF-β family member; high BMP7 levels cause Myf5+ progenitor cells to differentiate in brown adipocytes. When expressed at relatively high levels as observed in myoblasts from sarcopenic humans, intracellular S100B, a Ca2+-binding protein of the EF-hand type (1), exerts anti-myogenic effects that are reversed by S100B knockdown (2,3). We show that ROS-activated NF-κB induces accumulation of S100B that causes myoblasts to convert into brown preadipocytes via 1) an NF-κB/YY1 axis that negatively regulates the promyogenic and anti-brown adipogenic miR-133 with consequent accumulation of the pro-brown adipogenic transcription factor, PRDM16, and 2) an NF-κB/YY1/BMP7 axis with resultant BMP7 autocrine activity. Also, culturing L6C8 (S100b-overexpressing) myoblasts (2) in adipocyte differentiation medium causes NF-κB-dependent upregulation of S100B expression, which precedes and is required for lipid droplet formation. Lastly, S100B knockdown in myoblast-derived brown adipocytes reconvert them into fusion competent myoblasts. Thus, S100B is a major molecular determinant of cell fate decision of proliferating myoblasts; while modulating myoblast differentiation (2,3), at high levels S100B promotes myoblast-brown adipocyte transition, which might have pathophysiological implications in sarcopenia.

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References

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Myoblast; brown adipocyte; chronic oxidative conditions; S100B; sarcopenia.