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Lipid-cell cycle nexus

SREBP regulates microRNAs targeting Fbxw7

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The 2 major cellular lipid species, sterols and fatty acids, have many roles in physiology. Not only are they essential structural components of eukaryotic cell membranes, but they are also used as sources for cellular energy, serve as precursors for biosynthesis of key cellular macromolecules, are strategically used as post-translational modifications of many proteins, and function as signaling molecules for a wide variety of cellular tasks. Lipid availability is tightly associated with cell growth and cell cycle progression; therefore, regulatory mechanisms have evolved to balance lipid levels with their diverse cellular roles. Because of their intimate association with cellular growth, it is not surprising that small perturbations in the regulatory pathways that modulate lipid levels contribute to the development and progression of a myriad of metabolic diseases. Thus, organisms have evolved sensitive regulatory mechanisms that operate at the transcriptional and post-transcriptional levels to maintain lipid homeostasis. A key transcriptional pathway for regulating lipid metabolism that is conserved throughout the eukarya is mediated by the sterol regulatory element-binding proteins (SREBPs).[1] In mammals there are 3 SREBP proteins expressed from 2 unlinked structural genes. The individual SREBP isoforms are regulated by different cellular cues, and all 3 have evolved to mediate slightly different roles in lipid metabolism. Selective SREBP knockout studies, combined with unbiased genome-wide analyses have also provided evidence of a broader role for SREBPs in physiology and metabolism.[1]

SREBPs are synthesized with 2 closely spaced hydrophobic helices in the middle of the coding sequence that anchor the transcription factor precursor in a hairpin configuration in the ER membrane.[1,2] This extra-nuclear, inactive SREBP forms a complex with another ER membrane protein called SREBP cleavage activating protein (SCAP). When cholesterol levels are replete, SCAP interacts with cholesterol in the ER membrane, and in this form SCAP also binds to the ER retention factor Insig. In contrast, as sterol levels decline, the SCAP–cholesterol interaction is dis-favored, SCAP undergoes a conformational change and dissociates from Insig. This dissociation unmasks a small peptide signal within SCAP containing the sequence MELADL, which interacts with Sec24 of the COPII trafficking system. COP II escorts the SCAP–SREBP complex to the Golgi apparatus, where 2 proteases cleave the precursor SREBP, releasing the N-terminal portion, which represents the mature SREBP transcription factor. The soluble SREBP rapidly enters the nucleus and activates expression of SREBP target genes. Nuclear SREBP levels are regulated through an ubiquitin-dependent degradation pathway utilizing Fbxw7 as the requisite ubiquitin–E3 ligase-targeting factor. In addition to low-sterol conditions, it is likely that additional cellular cues alter the SCAP–SREBP itinerary to modulate SREBP activity.

The precision and sensitivity of the SCAP–SREBP trafficking process requires a dynamic interplay between all of the interacting components, and changes in their relative concentrations can tip the balance and significantly alter the final levels of nuclear SREBPs. In a new study, we revealed that expression of a conserved microRNA (miR) island from mouse chromosome 6 is directly activated by SREBP-2.[2] A single primary RNA transcript from this region is processed to yield 3 separate mature miRs: miR-96, miR-182, and miR-183. The mature 22–24 nucleotide miRs are incorporated into the RISC complex, which is then targeted to specific mRNAs by base-pair complementarity between the miRs and their target mRNAs, resulting in reduced expression of the corresponding protein. We showed that miR-96 targets the Insig2 and miR-182 targets Fbxw7. Since both of these proteins negatively influence the level of nuclear SREBPs, their inhibition by these miR siblings constitutes a feedback pathway to regulate SREBP activity. Because the 2 miRs are encoded by the same primary transcript that is regulated by SREBP-2, this system has the hallmark features of bacterial operons that are involved in regulating prokaryotic metabolism.[2]

Fbxw7 not only targets nuclear SREBPs for proteasomal degradation, but it also targets several oncogenic and cell cycle-regulatory proteins for degradation.[3] Interestingly, miR-182 is overexpressed in several cancer models, where it may influence oncogene activity along with modulating SREBP function.[4] In fact, SREBPs activate key genes of cell cycle regulation,[5,6] and SREBPs are associated with the elevated rates of lipid synthesis required for growth of tumor cells in vitro and in tumor models in vivo.[7]

Another microRNA, miR-33, is produced from an intron of the SREBP-2 gene, and because SREBP-2 gene expression is auto-regulated, miR-33 is

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another SREBP-responsive micro-RNA.[8] Interestingly, Fernandez-Hernando and colleagues reported that miR-33 inhibits the expression of the CDK6 and cyclin D1, thereby reducing cell proliferation and cell cycle progression.[5] Taken together with the results from our new study, these observations portend a more intricate connection between SREBPs, cell cycle regulation, and tumor metabolism.

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