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miRNAs IN PHYSIOLOGY AND DISEASE

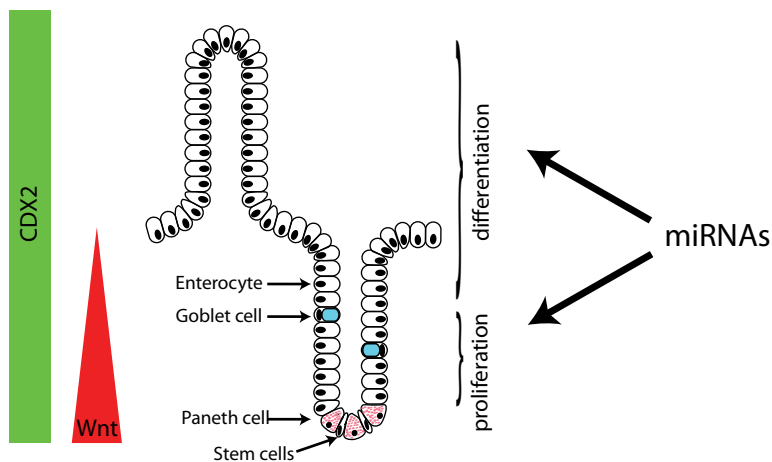
miRNAs are small non-protein-coding RNAs that can bind to mRNA transcripts of protein coding genes. Upon binding to these mRNAs, they inhibit their translation into proteins. However, each miRNA does not only recognize one target transcript, but rather numerous – in some cases several hundreds – of target transcripts. In addition, for many miRNAs, multiple different genes exist, that encode highly similar or identical mature miRNAs. The potential for combinatorial complexity and functional redundancy is therefore enormous.

We have recently started to work in the unit BCHM focusing on two main topics.

ROLE OF miRNAs IN INTESTINAL DIFFERENTIATION

The intestine is required for the digestion and absorption of essential nutrients and water. In this process, its surface epithelium is ex-

posed to one of the most toxic milieus of the whole body. It has to resist aggressive digestive juices, large pH changes, anaerobic bacteria and numerous toxic compounds. To resist this, its surface epithelium is completely renewed in less than 2 weeks. An intricate network of signaling pathways controls the proliferation and differentiation from intestinal stem cells



Intestinal architecture is maintained by the interplay of many signaling pathways.

The intestinal architecture is maintained by the interplay of numerous signaling pathways that ensure continuous renewal of intestinal surface epithelia. New cells are generated from a stem cell compartment at the base of the crypts and successively migrate up, where they are eventually shed in the lumen. We are focusing our interest on miRNAs that regulate this process.

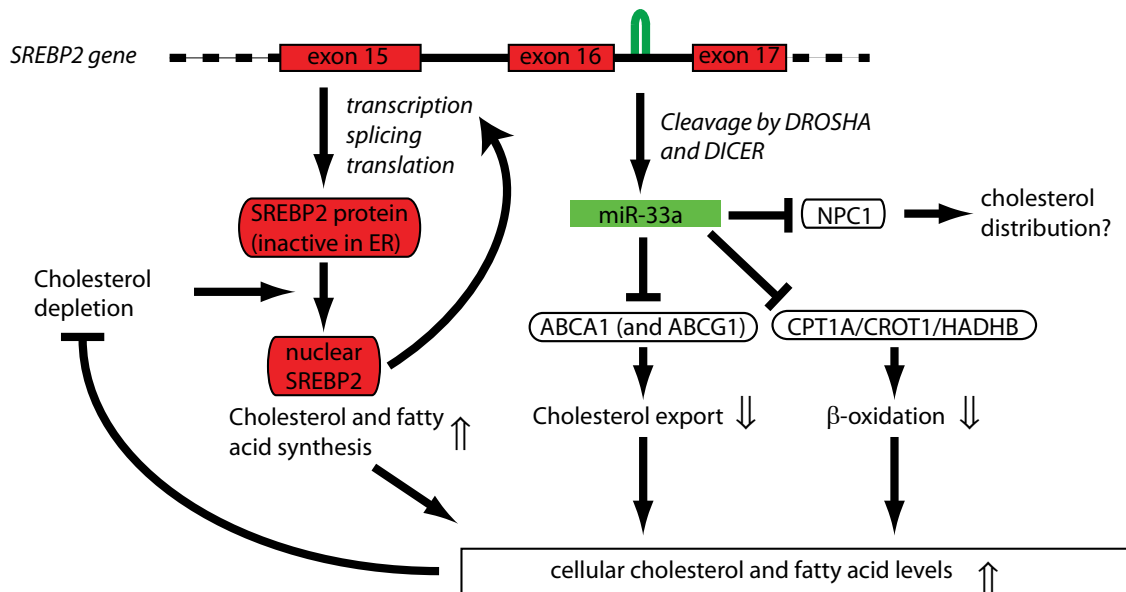
to the mature cell types. We are studying the role of miRNAs in this differentiation process and how they contribute to intestinal differentiation as well as the development of colorectal cancer.

REGULATION OF LIPID METABOLISM BY THE BIFUNCTIONAL LOCUS SREBF2-MIR33

Fatty acids, cholesterol, and their lipid derivatives play essential roles in normal cellular function and serve as structural components, signaling molecules, and/or as storage forms of energy. In multicellular organisms, cellular lipid metabolism is regulated to match the needs both of individual cells and of the entire organism.

The sterol regulatory element-binding factor-2 (SREBF2) gene is a bifunctional locus encoding SREBP-2, a well-known transcriptional regulator of genes involved in cholesterol biosynthesis, and microRNA-33a. We and others have recently shown that miR-33 can reduce the expression of several proteins involved in the cellular export of cholesterol and β -oxidation of fatty acids, thus adding an unexpected layer of complexity and fine-tuning to regulation of lipid homeostasis. In fact, work of other groups has demonstrated that this mechanism might represent a therapeutic target in the treatment of hypercholesterolemia.

We are continuing to investigate the physiological role of miR-33 in different experimental systems.



The bifunctional locus of SREBF2-miR33 regulates cholesterol and fatty acid metabolism. After processing from an intron of SREBF2, miR-33a reduces cellular cholesterol export by inhibiting expression of ABCA1 (and in the mouse ABCG1). In addition, miR-33a reduces mitochondrial fatty acid β -oxidation via inhibition of HADHB, CROT, and CPT1A to increase intracellular lipid levels. Thus the SREBF2 locus uses two distinct mechanisms to maintain lipid homeostasis: regulated transcriptional activity of SREBP-2 and translational repression by miR-33a.

SELECTED PUBLICATIONS

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