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Epigenetic regulation of calcium-sensing receptor and its impact in colorectal tumorigenesis

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Numerous studies have associated intake of sufficient amounts of calcium with reduced risk of colorectal cancer (CRC). The antiproliferative and prodifferentiating effects of calcium in colonocytes are suggested to be mediated, at least in part, by the extracellular calcium-sensing receptor (CaSR). Expression of the CaSR in CRC is downregulated. We investigated whether loss of the CaSR expression in CRC is caused by DNA hypermethylation, imbalance of transcriptionally permissive/repressive histone alterations, and aberrancies in microRNA expression.

RNA expression of the CaSR in 65 colorectal tumors and their adjacent mucosae from the same patients, and colon tumor cell lines was measured by real time qRT-PCR. The CaSR protein levels were determined by immunofluorescence. Methylation levels of the CaSR promoter were assessed by pyro- and bisulfite-sequencing. Chromatin immunoprecipitation was employed to determine the abundance of the histone marks H3K4me2 and H3K9ac bound to the CaSR promoter. Microarray study identified 22 differentially expressed microRNAs that potentially target the CaSR. These results were validated by performing gain- and loss-of-function studies in various CRC lines with the top microRNA candidates: miR-9, miR-27a, miR-135b, and miR-146b.

Silencing of the CaSR expression in colorectal cancer is dependent on various epigenetic layers, including CaSR promoter 2 hypermethylation and H3K9 deacetylation. Additionally, we demonstrated that overexpression of miR-135b-5p and miR-146b-5p is associated with the loss of CaSR expression in colorectal tumors. Regulation of CaSR expression by epigenetic mechanisms is of crucial importance, providing a platform for developing new and better approaches for colorectal treatment.

Biography

Irfete S Fetahu received her PhD at the Medical University of Vienna (Austria) under the supervision of Prof. Enikő Kallay as a Marie Curie Early Stage Researcher. During this time she was the recipient of several national and international awards, including fellowships from the European Association for Cancer Research and the Federation of European Biochemical Societies. She was a board member of the Young Scientist Association of the Medical University of Vienna. Following her PhD graduation, she started her postdoctoral fellowship at the Harvard Medical School (USA), where she is currently working in uncovering the aberrancies in the epigenomes of Alzheimer's disease and melanoma. She is also a board member of the Harvard Medical Postdoc Association.

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