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Revealing microRNAs in malignant progression of oligodendrogliomas

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MicroRNAs (miRNAs, miRs) are short non-coding regulatory RNA molecules found ubiquitously in living beings. Recently, miRNAs have also been implicated in oncogenesis, acting as tumor suppressors or oncogenes. Hitherto, the role of miRNAs in CNS tumors has been intensively investigated in glioblastomas and medulloblastomas, but there are few data regarding the role of miRNAs in oligodendrogliomas. We performed a systematic evaluation of miRNAs and mRNAs expressions in a series of oligodendrogliomas of different grades of malignancy to determine miRNAs and putative target genes that are differentially expressed in grade III oligodendrogliomas. Total RNA was extract from 14 cases of bona fide grade II and III oligodendrogliomas naïve of treatment (7 cases per grade) after tumor microdissection. For each case, the expression of miRNAs (100ng) and mRNAs (200ng) was evaluated using microarray-based expression profiling platforms (723 transcripts and 41,000 genes, respectively). Samples of temporal white matter from patients operated for epilepsy were used as controls (n = 15). The study was approved by Ethical Committee. Fifteen and 20 miRNAs were significantly over- and underexpressed in anaplastic oligodendrogliomas, respectively. However, after matching with the expressions of putative target-mRNAs disclosed by microarray, we were able to validate 8 out of 10 miRNAs by RT-qPCR (assays in duplicate). Among the hypo-expressed miRNAs, we found some miRs that were previously described in cell differentiation of embryonic stem cells (miR27a, miR-30a/PDGFA and miR24/HDAC2) as well as miR193a-3p and miR30c/RARB. Conversely, among the hyper-expressed miRNAs, we validated the microarray data of miR301/BCL-2 and miR378/FGF2, and PPP4R4 and CD44. Nonetheless, we were able to identify and validate some oncogenic miRNAs and putative target-mRNAs that can be operating in malignant progression of oligodendrogliomas. The biological roles of these miRNAs are being addressed through functional assays in primary cell lines of gliomas.

Oxidative stress-induced tRNA modifications and cancer cell adaptive responses

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In this presentation I will introduce tRNA modifications and describe their dynamic nature. Also, I will describe the role that tRNA methyltransferases (Trms) play in cell stress responses, elaborating on Trm9 (human Alkbh8) activity and oxidative-stress responses linked to selenocysteine protein expression. Next, I will present an innovative hypothesis that up-regulated Trm activity can promote cancer cell adaptive responses. The adaptive responses proposed are: cell survival under inherently high oxidative stress conditions, and enhanced dNTP production to facilitate a rapidly dividing cell population. Support for this hypothesis will be provided from the literature and our own observations in ovarian and bladder cancer cell lines. Last, I will discuss the future prospect of using the Alkbh8 → tRNA modification –I ROS pathway as a platform for developing drugs that might be used to enhance ROS-inducing chemotherapies.

Biography

Lauren Endres has been studying cancer cell signaling pathways for more than 15 years. These studies have been published in numerous top-ranking cancer and molecular biology journals. In 2010, she was awarded an NRSA Fellowship from the NIEHS to study the role of a tRNA methyltransferase (Alkbh8) in DNA damage response signaling. Her current studies on RNA epigenetic signals related to cancer development stem from this research project. She has been a member of the RNA Society since 2013, and has acted as a peer-reviewer for *PLOS ONE, WIREs RNA, The Journal of Biological Chemistry, Cancer Research and Clinical Cancer Research*.