IJAE
Vol. 116, n. 1 (Supplement): 199, 2011
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Non coding RNAs: reprogramming of miRNAs network in cancer and highly specific transcribed ultraconserved regions in human normal tissues and pluripotent stem cells

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We studied miRNA profiles in over 4000 human samples, corresponding to 50 normal tissues and 51 cancer types. The complexity of our database enabled us to perform a detailed analysis of microRNA (miRNA) activities. We inferred genetic networks from miRNA expression in normal tissues and cancer. We also built, for the first time, specialized miRNA networks for solid tumors and leukemias. Non-malignant tissues and cancer networks displayed a change in hubs, the most connected miRNAs. Cancer networks appeared as built from disjointed subnetworks, as opposed to normal tissues. A comparison of these nets allowed us to identify key miRNA cliques in cancer. By combining differential expression, genetic networks, and DNA copy number alterations, we confirmed, or discovered, miRNAs with comprehensive roles in cancer. Finally, we experimentally validated the miRNA network with acute lymphocytic leukemia originated in Mir155 transgenic mice. Most of miRNAs deregulated in these transgenic mice were located close to hsa-miR-155 in the cancer network. We used a similar database of healthy and pathologic tissues for the study of ultraconserved sequences (UCRs). There are 481 UCRs longer than 200 bases in the genomes of human, mouse and rat. These are DNA sequences absolutely conserved, showing 100% identity with no insertions or deletions. We tested the expression of UCRs in 618 normal samples from 50 different tissues. This database enabled us to perform a detailed analysis of coordinated T-UCRs activities. Only a portion of the T-UCRs tested is expressed. T-UCRs signature can correctly separate the different cell types and we also identified UCRs with differential regulation in human embryonic stem cells, induced pluripotent stem cells and the differentiation series (trophoblast, embryonic bodies, at 7 days and 14 days, definitive endoderm and spontaneous differentiated monolayer). These cell types were characterized by different level of UCR expression in a specific manner and has been characterized T-UCRs differentially transcribed during developmental stage.

Keywords: miRNA, T-UCR, solid tumor, leukemia, human pluripotent stem cells