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ADULT RENAL STEM/PROGENITOR CELLS EXPRESS LONG NON-CODING RNAS INVOLVED IN WNT AND THE BMP SIGNALING PATHWAY

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INTRODUCTION AND AIMS: Adult renal stem/progenitor cells (ARPCs) are a very promising population cells that has been recently identified in the human kidney and have a great potential in view of developing future treatments for both acute and chronic renal injury. However, to fully exploit such potential it is necessary to study the conditions that regulate the stem cell behavior. Recently, long noncoding RNAs (lncRNAs) have emerged as an important class of regulators of gene expression. lncRNAs have several distinctive features that confer unique regulatory functions, including cell- and tissue-specific expression and the capacity to transduce higher-order spatial information. Several lncRNAs regulate specific somatic tissue stem cell renewal or differentiation, while others promote a differentiation program. Their functions are often facilitated by protein partners that impart the ability to activate or repress gene expression or posttranscriptionally regulate other RNAs. Moreover, in the last years, the study of the regulation of miRNA networks revealed an additional mechanism through which lncRNAs exert control. Indeed, multiple lncRNAs have been shown to act as competing endogenous RNAs, where the lncRNAs are proposed to bind to and compete miRNAs away from cognate mRNA targets. The aim of the study was to evaluate the basal expression profile of lncRNA expressed specifically in ARPCs.
METHODS: lncRNA expression profile was obtained from ARPCs and renal proximal tubular cells (RPTECs) by Agilent SurePrint G3 Human Gene Expression Microarrays providing comprehensive coverage of genes and transcripts using the latest annotation databases. Genespring and R software were used for the analysis. lncRNA expression was validated by Real-time PCR.
RESULTS: We compared lncRNA expression between ARPCs and RPTECs: 45 lncRNA were differently modulated in ARPCs vs RPTECs (Fold change 1.5; FDR <0.05). In particular, we found 13 lncRNA upregulated and 32 lncRNA downregulated. Classification analysis showed that most of lncRNA modulated in ARPCs interfere with WNT signaling pathway, immune cell activation, and G-protein signaling pathway. Moreover, the overrepresentation test showed their involvement in calcium-mediated signaling, cell cycle and protein glycosylation processes ($p<0.005$). Among most significantly modulated lincRNA lncRNA LINC00966 and LINC00263 were downregulated (FC -2.5 and -3, respectively) and LINC00336 was upregulated (FC 4.5). LINC00966 encodes within its sequence the microRNA 124-2, targeting the homeobox transcription factor Dlx5 that acts as an immediate early BMP-responsive transcriptional activator. LINC00263 could be involved in the expression of genes regulating cytostructure, cell activation and membrane signaling. Moreover, we identified an highly upregulated lncRNA, LINC00336, that has been shown positively correlated with the survival in renal cancer.
CONCLUSIONS: ARPCs express specific lncRNAs that could explain the activation of WNT and the BMP signaling pathway during a renal damage. Our findings suggest that lncRNA may represent a novel therapeutic target in acute and chronic renal injury.