Structure-functional characterization of a human long non-coding RNA that controls interconnected signalling pathways

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Long non-coding RNAs (lncRNA) are key regulatory molecules, acting both in the nucleus and in the cytoplasm, and involved in crucial processes such as phase separation, membrane-less compartment formation, protein interactions, stress response or chromatin scaffolding. Hence, lncRNAs play a central role in gene expression regulation through their involvement in vital signaling pathways, where they have been identified to act as decoy, guide, or scaffold molecules. Despite their importance, the exact mechanism of how lncRNAs regulate gene expression remains poorly understood. Furthermore, while there is ample evidence that protein structure and protein-protein interactions are essential for protein function, the functional role of lncRNA structures remains largely uncharacterized.

To fill this knowledge gap, here, we propose to investigate the connections between lncRNA structure and lncRNA molecular mechanisms from a unique angle. We will focus on the structured lncRNA MEG3, which has been shown to act as a key hub of intimately interconnected signaling pathways in humans. Human MEG3 promotes p53 target gene activation and represses TGF-β pathway genes. As a result, MEG3 has recently emerged as an important lncRNA to control cell proliferation, embryonic development, and neurogenesis, and is known to act a tumor suppressor molecule.

Our previous studies allowed us to identify long-range tertiary interactions in MEG3 needed for MEG3-dependent p53 target gene activation and p53 potentiation. Here, we have now set out to characterize whether the same structural determinants also affect other signaling pathways controlled by this lncRNA. Excitingly, our preliminary results show that the same structural element involved in p53 regulation also play a role on TGF-β pathway repression, suggesting a potential interplay between the two pathways, mediated by the lncRNA MEG3.

Our study will increase our understanding of the mechanistic roles of lncRNAs in integrating various cell signaling pathways, and specifically clarify how the structure of lncRNAs allows proper regulation of gene expression. Thus, our work will open the door to potentially intervene on these recently-discovered targets with novel RNA-directed therapies for the treatment of human cancers, neurodegenerative and congenital disorders.