Exploring the role of long noncoding RNA in Retinitis Pigmentosa

Maria Zawadzka1, 2, Paola Brandi1 , Samuel Santamaria Guillen1 , Filomena Capolongo1 , Mariateresa Pizzo1 , Sandro Banfi1, 3 1Telethon Institute of Genetics and Medicine (TIGEM), Via Campi Flegrei 34, 80078, Pozzuoli, Italy, 2University of Campania "Luigi Vanvitelli", Department of Environmental, Biological and Pharmaceutical Sciences and Technologies (Distabif), Via Vivaldi 43, 81100, Naples, Italy, 3University of Campania "Luigi Vanvitelli", Department of Precision Medicine, Via Luigi De Crecchio 7, 80138, Naples, Italy

Background: Retinitis Pigmentosa (RP) is a genetically heterogeneous mendelian disorder characterized by rod photoreceptor degeneration and progressive visual impairment. The molecular mechanisms underlying photoreceptor death and disease progression are still poorly understood. In that respect, a major gap of knowledge is represented by the role of long noncoding RNAs (lncRNAs), which are known to modulate multiple biological pathways related to human disease pathogenesis. However, there is little information about their role in RP. Here, we have generated a lncRNA expression atlas in the retina across different RP mouse models using next-generation sequencing. Furthermore, we aim to identify candidates with important roles in retinal pathophysiology. Method: Transcriptomic profiling by RNA-seq was performed on the main stages of photoreceptor degeneration in Retinitis Pigmentosa mouse models (rd10, RHO-P347S, RHO-P23H). LncRNAs exhibiting significant expression changes between WT and disease models, and showing consistent deregulation across all three disease models, were selected for further analysis. To predict potential roles of these candidates, lncRNA-mRNA co-expression analysis was carried out. Functional validation of this prediction is currently being performed through loss-of-function studies in an ex vivo retinal explant model. Subsequently, transcriptomic profiling will assess global gene expression changes following lncRNA knockdown. Results: Transcriptomic analysis revealed a number of lncRNAs differentially expressed between wild type and RP retina at different disease stages. We focused on the lncRNAs that shared upregulation across all the models and identified their diverse genomic orientations and potential cis-regulated gene targets. Co-expression analysis predicted that some of the upregulated lncRNA are associated with functions related to RP pathogenesis, e.g. inflammation. Conclusion: We have identified a subset of lncRNAs that display shared dysregulation across different RP models. They represent intriguing candidates to contribute to the pathogenic mechanisms underlying photoreceptor degeneration downstream the primary genetic defect as well as potential targets for future gene-agnostic therapeutic strategies.