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Editorial

U5 snRNP Role in Cancer

Abdul Rahman Asif*

Department of Clinical Chemistry/Central Laboratory, Georg-August-University, Gottingen, Germany

EDITORIAL NOTE

Pre-mRNA splicing is performed by the spliceosome, a dynamic macromolecular complex consisting of five small uridine-rich ribonucleoprotein complexes are U1, U2, U4, U5, and U6 snRNPs and numerous auxiliary splicing factors. A plethora of human disorders are caused by genetic variants affecting the function and/or expression of splicing factors, including the core snRNP proteins. Alternatives in the genes encoding proteins of the U5 snRNP cause two distinct and tissue-specific human disease phenotypes variants in PRPF6, PRPF8, and SNRP200 are connected with retinitis pigmentosa, while variants in EFTUD2 and TXNL4A cause the craniofacial disorders mandibulofacial dysostosis Guion-Almeida type and Burn-McKeown syndrome, respectively. Additionally, recurrent somatic mutations or changes in the expression levels of a number of U5 snRNP proteins (PRPF6, PRPF8, EFTUD2, DDX23, and SNRNP40) have been associated with human cancers. How and why variants in ubiquitously expressed spliceosome proteins required for pre-mRNA splicing in all human cells result in tissue-restricted disease phenotypes is not clear. Moreover, why variants in different, yet interacting, proteins making up the same core spliceosome snRNP result in completely distinct disease consequences RP, craniofacial defects or cancer is unclear. In this review, we define the roles of different U5 snRNP proteins in RP, craniofacial disorders and cancer, including how disease-associated genetic variants affect pre-mRNA splicing and the proposed disease mechanisms. We then propose potential hypotheses for how U5 snRNP variants cause tissue specificity subsequent in the restricted and distinct human disorders.

U5 snRNP and human disease. In particular, the tissue-specific and distinct phenotypic consequences of genetic variants in different, but interacting, proteins of the same spliceosomal complex-RP and craniofacial disorders-remains arguably the biggest enigma in this field. Also, the association of certain U5 snRNP proteins with cancer, including proteins also linked to RP or craniofacial defects, introduces an additional layer of complexity as mutations in and/or altered expression levels of the same protein can have very different phenotypic outcomes. RP and the craniofacial disorders MFDGA and BMKS, much evidence from disease modelling supports the mis-splicing of distinct subsets of genes which may be involved in retinal function or craniofacial growth, respectively. It may be that at least some of these mis-spliced genes are mainly or only expressed in the retina or NCCs and are vitally significant in development of that tissue, meaning these tissues are the more sensitive to mutation in the U5 snRNP and most affected phenotypically. The pathways affected by the mis-splicing events may also have a greater role in the development of certain tissues than others. Retina-specific mis-spliced transcripts have not yet been identified in PRPF6, PRPF8, and SNRNP200-associated RP, though data from PRPF31-defective RP patient retinal pigment epithelium (RPE) and retinal organoids has recognized retinal-specific mis-splicing events, molecular and cellular penalties of variants in the U5 snRNP proteins and how they relate to human disease and cancer, further research is required to understand the tissue specificity of these disorders, the distinct phenotypes rising from variants in interacting proteins of the same spliceosome complex, and the pleiotropic phenotypes arising from dissimilar changes in the same U5 snRNP factor.

Correspondence to: Abdul Rahman Asif, Department of Clinical Chemistry/Central Laboratory, Georg-August-University, Gottingen, Germany, E-mail: abdhulasif@gmail.com

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