Institut Européen de Chimie et Biologie

I E C B

Structural studies of Bcl-x alternative splicing: Role of RNA structure, G-quadruplexes, and splicing factors.

Cyril DOMINGUEZ
University of Leicester, UK

The Bcl-x gene produces two alternative isoforms that have antagonist functions: Bcl-x_L is anti-apoptotic, while Bcl-x_S is pro-apoptotic (3). In many cancer cells, the anti-apoptotic Bcl-x_L isoform is upregulated. Our research aims at better understanding the regulation of Bcl-x alternative splicing and deriving small molecules that shift splicing towards the pro-apoptotic isoform.
We have previously suggested that the splicing factor hnRNP F/H could regulate Bcl-x splicing by competing with G-quadruplex formation. We have now solved the 2D structure of a region of the Bcl-x pre-mRNA, characterized the presence of two G-quadruplexes, and identified one small G-quadruplex binding molecules that regulate the alternative splicing of Bcl-x towards the pro-apoptotic isoform.
The splicing factor Sam68 belongs to the STAR family of proteins involved in many cellular processes such as signal transduction, post-transcriptional gene regulation, tumorigenesis and viral metabolism. Sam68 and the closely related protein TSTAR contain a STAR domain responsible for RNA binding, as well as several motifs that are targeted for post-translational modifications following signaling pathways. We have solved the structure of T-STAR and Sam68 STAR domains in complex with RNA, and propose a model whereby these proteins regulate alternative splicing by looping out regions of the pre-mRNA.

Institut Européen de Chimie et Biologie
2, rue Robert Escarpit - 33607 Pessac, France
Tél. : +33(0)5 40 00 30 38 - Fax. : +33(0)5 40 00 22 15
www.iecb.u-bordeaux.fr