Title:	Role of Mutually eXclusive Exons (MXEs) in the functional shift of isoforms: A case study of human Pyruvate Kinase M (PKM)
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Abstract:	The process of alternative splicing (AS) is known to account for a major source of human proteome diversity. Among various known types of AS events, Mutually eXclusive Exon (MXE) splicing results in isoforms having one (or more) out of two (or more) exons mutually eliminated in a coordinated manner. MXE events are known to generate highly diverse function protein variants from the same gene. These splicing events can lead to proteins with similar length and scaffold but highly specific functions. It has been of great interest to understand how change(s) in region(s) of a protein can significantly alter the function of protein. In order to gain insights into structural changes in isoforms generated from MXEs events, we considered human Pyruvate Kinase M (PKM) as a model system because tertiary structures are known for both isoforms (PKM1 and PKM2). It is known that PKM1 is a constitute enzyme and PKM2 shows allostery on binding various effectors. In the present study, we have systematically analyzed the origin of allosteric behavior in monomeric structures by extensive analyses of structural features of both PKM1 and PKM2. Our analyses showed that differences in the inherent dynamics of loop, which is a region encoded by the mutually exclusive exons, in PKM1 and PKM2 could affect oligomerization as well as affect allosteric transitions. The analyses of allosteric paths suggest that FBP-mediated allostery is greatly enhanced in PKM2 whereas in PKM1 the path has low significance.
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