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Originally from Penglai, China, I completed my BSc. in Cell Biology and Genetics from Peking University (PKU) in Beijing, China. At PKU I gained research experience in tissue culture and virus vaccine studies. I was then admitted to the Department of Biochemistry at University of Alberta to pursue my graduate studies. After finishing my rotations, I decided to begin working in Dr. MacMillan's laboratory. Under his excellent supervision I have gained skills and experience necessary for analysis of the RNA world. After I finished my PhD thesis with studies on the key protein in the pre-mRNA splicing pathway called Prp8, I was so excited about our achievements with this protein that I stayed in the same lab to continue my postdoctoral research with the same project.



More than 90% of human genes undergo a processing step called splicing, whereby noncoding introns are removed from initial transcripts and coding exons are ligated together to yield mature messenger RNA. Splicing involves two sequential transesterification reactions catalyzed by a large RNA/protein complex called the spliceosome. RNA components of the spliceosome are at least partly responsible for splicing catalysis. However, the precise architecture of the spliceosome active site and whether it includes protein components remain unknown.

Numerous genetic and biochemical analyses have placed one of the largest and most highly conserved of nuclear proteins, Prp8, at the heart of the catalytic core of the splicing machinery during spliceosome assembly and through catalysis. We provide structural and functional evidence that the RNase H domain of Prp8 undergoes a conformational change during splicing which unmask a metal-binding site required for the second step of splicing. We are able to demonstrate that a magnesium ion essential for the catalysis binds to the RNase H domain of Prp8 and a metal specificity switch which abrogates metal binding severely inhibits the second step of splicing. We also show that yeast prp8 first- and second-step alleles correspond to Prp8 mutants that favour one of the two distinct Prp8 conformations observed in the crystal structure of Prp8 RNase H domain. Together these data support the model of rearrangements within the spliceosome at the time of transition between the first and second step of splicing. Our findings also establish that Prp8 is a metalloprotein which promotes exon ligation and are consistent with the designation of the spliceosome as a ribonucleoprotein enzyme.

Splicing is essential in higher organisms with up to 50% of all human genetic diseases being attributed to abnormal splicing. Prp8 mutations have also been linked to human diseases. Ultimately, our work will lead to the elucidation of splicing mechanism as well as the development of new drugs to correct the abnormal splicing.