Identification and Characterization of Host Proteins that Regulate Human LINE-1 Retrotransposition

Tomoichiro Miyoshi

Graduate school of Biostudies, Kyoto University

Long INterspersed Element-1 (LINE-1 or L1) retrotransposons comprise about 17% of the human genome. L1 mobility (*i.e.*, retrotransposition) continues to generate intra- and inter-individual genetic diversity, where it can also pose a threat to genome integrity, as exemplified by L1-mediated gene disruption or chromosomal deletion. L1s encode two proteins, ORF1p and ORF2p; ORF1p is an RNA-binding protein and ORF2p is the catalytic component that possesses endonuclease (EN) and reverse transcriptase (RT) activities. Biochemical activities associated with both ORF1p and ORF2p are required for efficient L1 retrotransposition; however, the identification of cellular proteins that facilitate retrotransposition requires elucidation.

Here, we immunoprecipitated the ORF2p complex in human cells, followed by tandem mass spectrometry, which led to the identification of cellular proteins that interact with ORF2p. Although L1 ORF2p is expressed at low levels and is difficult to detect in the nucleus, we were able to identify ORF2p-interacting host proteins involved in nuclear functions such as chromatin binding, DNA replication, and DNA repair. Intriguingly, we identified DNA repair proteins that associate with wild-type ORF2p, but not with endonuclease-deficient ORF2p mutants, suggesting that some DNA repair proteins recognize the endonucleolytic nick created by ORF2p during retrotransposition. In sum, while previous reports have suggested a negative regulatory role for host proteins to limit damage from L1 retrotransposition, our data suggest that L1s take advantage of some host DNA repair proteins to facilitate efficient retrotransposition.