A proto-filament superfamily evolutionally linking centrosomal functions and double strand-break repair

Takashi Ochi
Structural studies, MRC Laboratory of Molecular Biology

Cells carry a variety of filament structures including DNA, microtubules, actin and intermediate filaments. These filaments are essential for the homeostasis of cells, and their nucleation is precisely regulated by other proteins and ligands. The XRCC4 superfamily is a group of homologous proteins that form open or closed helical-filament structures to scaffold DNA or centrosomal structures. The superfamily members including SAS-6, XRCC4, XLF and PAXX are conserved throughout eukaryotes. SAS-6 is the basis of the cartwheel structure in the pro-centriole and important for the centriole duplication in centrosomes. The protein self-assembles a 9-fold ring structure, in which two dimerisation interfaces mediate cartwheel formation: An N-terminal head and following coiled-coil domains[1,2]. The coiled-coil and low complexity regions of SAS-6 interact with other centrosomal proteins and scaffold the cartwheel structure and microtubule triples of centrosomes. A mutation in *SAS6* gene causes microcephaly indicating that the protein is important for normal human development. XRCC4, XLF and PAXX work in a major DNA double-strand break (DSB) repair pathway, non-homologous end joining (NHEJ). XRCC4 and XLF interact each other and form helical filaments in a similar way to SAS-6[3] and are proposed to support bridging DNA separated by DSBs. Mutations in those genes in human also cause developmental deficiencies. I have recently discovered that an uncharacterized protein C9orf142 is a paralog of XRCC4 and named it as PAXX[4]. It interacts with key NHEJ proteins the Ku70/80 heterodimer to promotes DSB repair and has a redundant function to XLF. Structural studies of the XRCC4-superfamily proteins show that the interfaces of their filaments are small and that their filament assembly is dynamic and perhaps easily regulated by other factors. I would like to present molecular characteristics of the XRCC4 superfamily proteins, particularly focusing on NHEJ, based on my studies and discuss a common function and evolutional aspect of the superfamily. I will then extend the discussion to my future research.

Selected references

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