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Role of the variable domain in Drp1 protein assembly: a simulation study

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Dynamin-related protein 1 (Drp1), a member of the Dynamin superfamily of large GTPases, is the primary mechanoenzyme responsible for mitochondrial fission. It is composed of three main domains: a G domain that weakly binds GTP and hydrolyzes it to GDP, a coiled-coil stalk domain which is involved in self-assembly of Drp1 into into spiral-like aggregates around the circumference of a mitochondrion, and a variable domain (B domain) that is thought to modulate the self-assembly process. The B domain possesses several unique properties that suggest it is physiologically important, but its function is not well understood. In this talk, we present computer simulation studies that suggest the B domain is intrinsically disordered, in agreement with recent experimental studies. In spite of being intrinsically disordered, we also find that B domains interact specifically with each other to form dimers (and potentially higher order oligomers), thereby facilitating the Drp1 self-assembly process in an unexpected way. Moreover, we find that in the presence of a model osmolyte, trimethylamine N-oxide (TMAO), the specific intermolecular assembly of B domains is significantly enhanced. The implications of these findings for recent studies of Drp1 assembly and mitochondrial fission will be discussed.

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