

Abstract

Centrioles are cylindrical microtubule-based structures, embedded in a proteinaceous matrix called pericentriolar material (PCM). Together, this structure is referred as the centrosome. In animal cells, the centrosomes play a crucial role in cellular functions such as cell division and motility. Abnormalities in centrosome-associated proteins have been linked to human diseases, including cancer and neurodevelopmental disorders. Mutations in the core centriole protein, Centrosomal P4.1-associated protein (CPAP), have been associated with primary microcephaly (MCPH6), a disorder characterized by reduced brain size and cognitive disability. This study focuses on understanding the impact of CPAP mutations on centrosome and spindle organization in primary microcephaly. Specifically, it investigates the effects of two MCPH-associated mutations, E1235V and D1196N, in the CPAP G-box domain. The study reveals that E1235V causes increased centriole length, while D1196N leads to an increase in centriole number. Interestingly, E1235V does not localize at the centriole, whereas D1196N maintains its centriolar localization despite reduced interaction with the upstream centriole protein, STIL, similar to E1235V. This suggests the involvement of an alternate route involving the proximal parent centriole protein, CEP152. Moreover, we demonstrate that centriole abnormalities result in multipolar spindle formation and decreased cell viability. These findings shed light on the importance of regions within CPAP outside the direct microtubule-interacting domains in influencing centriole organization, providing valuable insights into the molecular mechanisms underlying primary microcephaly.

The second part of the thesis work explores the development of novel chemical scaffolds for chemotherapeutics. The cell division machinery, comprised of centrosomes and microtubules, is crucially regulated during the cell cycle. Dysregulation of these structures can lead to human diseases, including cancer. Paclitaxel, a microtubule-targeting anticancer drug, has clinical approval but faces challenges due to the development of resistance in many cancer types. Hence, there is a need to identify new chemical scaffolds for designing effective anticancer drugs. In this study, a novel S-aryl dithiocarbamate chemical scaffold is identified as a potent anticancer compound with promising pharmacophore properties. The lead compound exhibits an IC_{50} of $<0.5 \mu M$ in lung and cervical cancer cells. It stabilizes

microtubules, resulting in p53-p21-dependent cell cycle arrest in the G₂/M stage and cellular apoptosis. Interestingly, the lead compound shows comparable docking parameters to paclitaxel in the taxol-binding pocket of β -tubulin. These findings present a promising alternative scaffold that can be further modified to enhance efficacy and potency as an anticancer drug.