Title: Mob1 Localization and Function during Mitosis

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Summary:
Maintenance of chromosomal ploidy during cell division requires a precise coordination of chromosome segregation and cytokinesis such that the contractile ring does not assemble before all replicated sister chromatids are correctly attached to the mitotic spindle and the spindle assembly checkpoint is satisfied. In budding and fission yeast, this process is facilitated by a signaling cascade termed the Mitotic Exit Network/Septation Initiation Network that coordinates mitotic exit and cytokinesis, is based at the spindle pole bodies, and plays an active role in initiating constriction of the actin ring. To date, few functional homologues have been characterized in animal cells, but in the case of the terminal components (Mob1 and Dbf2/Sid2), there have been expansions in both gene families. And while tumor suppressor functions have been ascribed to the mammalian and *Drosophila* orthologs of Mob1 and Dbf2/Sid2 during G1/S, little is known about how these molecules participate in mitosis and cytokinesis in animal cells. Preliminary studies of Mob1 isoforms in cultured human cells indicate that the localization dynamics mirror that observed in yeast, with Mob1 enriched at the kinetochores and spindle poles early in mitosis, and the spindle midzone and midbody during cytokinesis.

Moreover, we have determined that Mob1 and the chromosomal passenger complex are mutually dependent on each other kinetochore localization early in mitosis. Lastly, we identified Large Tumor Suppressor 2 (Lats2) as a Mob1A-specific binding protein and possible functional homolog of the Dbf2/Sid2 kinase. Using these preliminary studies as a foundation, this research combines molecular, biochemical and live cell analyses to test the hypothesis that Mob1 proteins perform roles in regulating in maintaining chromosomal ploidy during both mitosis and interphase.

The lines of experimentation that form the Specific Aims will:

- Determine the molecular determinants of Mob1 localization to the kinetochore
- Dissect how Mob1 affects Aurora B function at the kinetochore
- Assess the Involvement of Mob1 In the Lats2-p53 response to cytoskeletal disruption.

These studies will shed novel insights into a gene family that in animal cells appears to act as a negative regulator of cell proliferation (and whose loss of function is associated with tumor formation), yet is essential for completing cell division in yeast. It is anticipated that these studies will help us reconcile how Mob1 is capable of participating in both of these very different but absolutely critical features of cell cycle regulation.