

**MLL/WDR5 complex recruits centriolar satellite protein Cep72 to regulate
microtubule nucleation and spindle formation**

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Background: The centrosome acts as the primary microtubule-organizing center (MTOC) and is essential for proper spindle assembly and chromosome segregation during mitosis. Abnormalities in centrosome structure or function often cause mitotic errors and developmental issues. The mixed-lineage leukemia protein (MLL, also called KMT2A) is a histone H3K4 methyltransferase mainly known for its role in regulating transcription through chromatin remodeling and gene activation. However, clinical evidence shows that mutations or haploinsufficiency of MLL lead to Wiedemann–Steiner syndrome (WSS), a neurodevelopmental disorder marked by facial dysmorphism and growth delay, implying that MLL might have functions beyond transcriptional regulation. Despite this, it remains unclear whether MLL has a non-transcriptional role at the centrosome.

Objective: To determine whether MLL, together with its interacting partner WDR5, regulates centrosome-associated processes independent of its chromatin-modifying activity. Specifically, the research investigated how the MLL/WDR5 complex influences the localization and function of the centriolar satellite protein Cep72, which is known to participate in microtubule nucleation and spindle organization.

Results: Through a series of biochemical and cell biological experiments, this study demonstrated that MLL localizes to the pericentriolar material (PCM) and forms a functional complex with WDR5. Loss of MLL or WDR5 led to a marked reduction in Cep72 accumulation at the centrosome and resulted in disorganized microtubule arrays, abnormal spindle morphology, and chromosome misalignment during mitosis. Microtubule regrowth assays confirmed that the MLL/WDR5 complex is required for efficient microtubule nucleation, while rescue experiments showed that overexpression of Cep72 restored proper spindle organization. These findings indicate that MLL/WDR5 regulates centrosome integrity and microtubule organization independently of the histone methyltransferase activity of MLL, revealing a noncanonical cytoplasmic function for MLL.

Conclusion: Overall, this study reveals an unrecognized, non-transcriptional role of the MLL/WDR5 complex in maintaining centrosome integrity. By recruiting and stabilizing Cep72 at the centrosome, MLL ensures proper microtubule nucleation and spindle formation. These findings broaden the understanding of the cellular functions of MLL beyond gene regulation and provide mechanistic insight into how MLL mutations may contribute to mitotic and developmental abnormalities associated with WSS.