

**Thesis Title:** Deciphering HMGB1: Across a spectrum of DNA and nucleosome dynamics

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### **Abstract**

HMGB1 is most abundant nonhistone nuclear protein that has been thoroughly studied for its functions beyond the nucleus, especially in the cytoplasm, where it serves as an autophagy mediator, and in the extracellular matrix, where it operates as an inflammatory molecule. Nonetheless, the complete range of its roles within the nucleus is still not well comprehended. This *in vitro* research sought to address this gap by examining the binding properties of HMGB1 with different types of DNAs, nucleosomes, and chromatin. The research discovered that HMGB1 shows varying binding affinities, displaying a particularly high affinity for modified DNA structures like triplex and bulge DNA. This implies that HMGB1 might be important in detecting and reacting to DNA damage or structural irregularities. Moreover, the study emphasized that HMGB1 binding disrupts nucleosome remodelling by the CHD7 chromatin remodeller, indicating that HMGB1 could impact chromatin accessibility and remodelling activities, potentially influencing transcriptional regulation. The research also showed that HMGB1 attaches to the linker DNA between nucleosomes, possibly affecting chromatin structure and function. These results offer fresh perspectives on the diverse functions of HMGB1, potentially going beyond its established roles in inflammation and autophagy to encompass significant contributions to gene expression, viral replication, and genetic disorders like CHARGE syndrome, where alterations in the CHD7 gene disrupt normal chromatin remodelling. This research consequently paves the way

for investigating HMGB1's functions in the nucleus, possibly resulting in innovative treatment strategies for disorders associated with chromatin dysregulation.