The differentiation of mesenchymal stem cells to osteoblasts is one of the critical steps of bone formation. Osterix (Osx) is an osteoblast-specific transcriptional factor required for bone formation and osteoblast differentiation, which has been shown to interact with other factors to control the expression of osteoblast-specific genes. A novel JmjC domain containing protein NO66 has been identified in the regulation network of Osx, which plays an important role in osteoblast differentiation through interaction with Osx. Here we report the crystal structure of NO66, showing it exists as a functional tetramer form. A hinge domain links N-terminal JmjC domain and C-terminal wHTH domain of NO66 and is essential for its tetrameric assembly. The oligomerization interface of NO66 provides the binding site for Osx, which interacts with a conserved fragment of Osx. Further work demonstrates that the hinge domain-dependent oligomerization is essential for NO66 to interact with Osx and controls Osx-dependent gene expression. Our finding reveals that homo-oligomerization of JmjC domain containing proteins plays a critical role in interaction with regulatory factors and may have significant physiological roles.

Keywords: NO66, Osx, osteoblast differentiation