Title: Phosphorylation-mediated disassembly of Ctbp2 tetramer impedes epigenetic silencing of pluripotency in mouse embryonic stem cells

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Abstract

Cells need to overcome both intrinsic and extrinsic threats. Although pluripotency is associated with damage responses, how stem cells respond to DNA damage remains controversial. Here, we elucidate that DNA damage activates Chk2, leading to the phosphorylation of serine 164 on C-terminal binding protein 2 (Ctbp2). The phosphorylation of Ctbp2 induces the disruption of Ctbp2 tetramer, weakening interactions with zinc finger proteins, leading to the dissociation of phosphorylated Ctbp2 from chromatin. This transition to a monomeric state results in the separation of histone deacetylase 1 from Ctbp2, consequently slowing the rate of H3K27 deacetylation. In contrast to the nucleosome remodeling and deacetylase complex, phosphorylated Ctbp2 increased binding affinity to polycomb repressive complex 2, interacting through the N-terminal domain of Suz12. Through this domain, Ctbp2 competes with Jarid2, inhibiting the function of polycomb repressive complex 2. Thus, the phosphorylation of Ctbp2 under stress conditions represents a precise mechanism aimed at preserving stemness traits by inhibiting permanent transcriptional shutdown.