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UBIQUITYLATION

Mediation by degradation

> SCF^{FBXW7} can interact with and ubiquitylate MED13 and MED13L when these proteins are associated with the core Mediator complex

The tumour suppressor protein FBXW7 is the substrate recognition component of the SKP–cullin–F-box (SCF) ubiquitin ligase. FBXW7 binds threonine- or serine-phosphorylated proteins, including many oncoproteins, in the context of a conserved phosphodegron sequence, resulting in their ubiquitylation and proteasome-mediated degradation. Bruce Clurman and colleagues have found that FBXW7 interacts with components of the Mediator complex and so it might be involved in regulating gene transcription.

The authors used affinity purification and mass spectrometry to identify new FBXW7 substrates. Only proteins that bound wild-type FBXW7 and not FBXW7 in which the substrate binding site was mutated were analysed in detail. Of the 72 proteins identified, 26 belonged to the Mediator complex that links transcription factors to the basal transcription machinery, such as RNA polymerase II. Several of the proteins bound by FBXW7 belong to the so-called cyclin-dependent protein kinase 8 (CDK8) module, a four-subunit protein complex that contains CDK8 and is involved in regulating Mediator function. Further analyses revealed that FBXW7 directly interacts with MED13 and MED13L. MED13 is required to link the CDK8 module to the Mediator core complex, and MED13L is thought to have a similar function. The authors found that FBXW7 interacts with a phosphodegron sequence on MED13 and MED13L and that this interaction in the presence of a functional SCF^{FBXW7} ligase results in the ubiquitylation and degradation of these proteins.

What effect does this have on CDK8–Mediator function? Co-immunoprecipitation experiments showed that loss of FBXW7 increased the levels of MED13 and MED13L, as well as other CDK8 module proteins that were associated with the Mediator core complex. The authors also found that SCF^{FBXW7} can interact with and ubiquitylate MED13 and MED13L when these proteins are associated with the core Mediator complex. Thus, the authors concluded that FBXW7 functions to regulate the interaction of the CDK8 module with Mediator by promoting the dissociation of these complexes through the degradation of MED13.

These findings expand the potential impact of FBXW7 loss during tumorigenesis — in addition to FBXW7 loss increasing the stability of specific proteins, such as MYC and cyclin E, FBXW7 loss might also have a broader effect through the alteration of genome-wide transcriptional events. Moreover, CDK8 is a known oncogene in colorectal cancer, so further work is needed to understand the effect that FBXW7 has on the function of this oncogene.

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