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Editorial
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MOB Co-activators Associate with NDR/LATS Kinases to Function in DNA Damage Response Signaling and Hippo Pathways

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Editorial

Signal transduction cascades link biological reactions with environmental changes, and regulation of the cascades are sophisticated, so various protein kinases are one of the largest superfamilies transcripted by human genome. AGC kinases are a big family of protein kinases playing diverse and crucial roles in cellular activities, such as cell circle and oncogenesis. NDR (nuclear Dbf2-related) kinases and LATS (large tumor suppressor) kinases are important members of AGC kinases family, and are highly conserved from yeast to human beings. Human cells express four related NDR kinases, NDR1, NDR2, LATS1 and LATS2. In *Saccharomyces cerevisiae*, Dbf2p, Cbk1p, Sid2p and Orb6p are identified as NDR kinases, while in *Drosophila melanogaster*, Trc and Warts kinases are homologs of human NDR1/2 and LATS1/2 respectively [1].

MOB (Mps one binder) proteins are highly conserved in eukaryotes. They perform as signal transducers in intracellular signalling pathways through interactions with NDR/LATS kinases. In budding yeast, MOB1 and MOB2 was found playing central roles in the mitotic exit network (MEN) and cell morphogenesis. In mammals, at least six different MOB proteins are encoded by independent genes, including MOB1A, MOB1B, MOB2, MOB3A, MOB3B and MOB3C. MOB1A/B interacts with NDR/LATS kinases to function in mammalian Hippo signalling, while MOB2 interacts specifically with NDR1/2 kinases to function in DNA damage response and cell circle checkpoint. Both MOB1 and MOB2 can interact with NDR, and their combinations are competitive, with MOB1 upregulating NDR activity and MOB2 downregulating NDR activity [2].

Hippo signalling pathway is an ancient and highly conserved protein kinase signalling system controlling basic cellular bioactivities, including cell proliferation, survival and morphogenesis. In these systems, MST/hippo kinases together with MOB coactivators activate AGC kinases NDR/LATS, controlling cell fate and tissue architecture. NDR/LATS kinase-MOB coactivator modules are in the core position of all known hippo pathways [3,4].

DNA damage response (DDR) is activated by a cascade of protein kinases that regulate DNA repair in both transcriptional and posttranslational levels. DDR signaling will persist until DNA repair process is completed, during which time cell circle will arrest. According to a large scale screening for DDR factors performed by Stephen J. Elledge in 2011, MOB2 functions as a DDR protein and MOB2 knockdown can cause a cell proliferation defect related to G1/S cell circle arrest [5].

Recently Alexander Hergovich performed series biochemistry experiments showing that MOB2 can prevent the accumulation of endogenous DNA damage and a subsequent p53/p21-dependent G1/S cell cycle arrest, while this regulation seems independent of NDR kinases. They also screened for binding partners of MOB2, and they revealed that MOB2 can interact with RAD50 to facilitate the recruitment of MRN (MRE11-RAD50-NBS1) DNA damage sensor complex and activated DDR kinase ATM (Ataxia telangiectasia mutated) to the damaged chromatin. According to them, MOB2 is required for *ATM-NBS1-SMC1* signalling in DDR, and MOB2 deletion triggers a DNA damage-*ATM-CHK2-p53-p21* cascade, which will cause G1/S cell cycle arrest due to accumulated unrepaired DNA damage. Interestingly, NDR kinases can also function in DDR cascade and cell cycle arrest while these two factors seem to function independently in contrast to their tight connections in hippo signalling pathways [1].

Detailed structure analyses of MOB proteins were performed by several groups around the world [6-8]. Crystal structure of MOB1 has shown that MOB1 binds to NDR/LATS kinases through conserved residues. A stretch of conserved hydrophobic and positively charged residues in the N-terminal of the catalytic domain of NDR/LATS kinases is required for the association with MOB1 protein. Many kinds of MOB-NDR/LATS kinase complexes are central to hippo signalling pathways, and these enzymes have a primarily similar structure, with the variable regions achieving functional diversity, and the catalytic core performing kinase activities. Very recently, Eric L. Weiss solved the structure of Cbk1-MOB2 complex, which is the first structure of NDR/LATS kinase-MOB complex, showing the binding of MOB coactivator can allosterically regulate the conformation of NDR/LATS kinase, indicating an activation mechanism unique to NDR/LATS kinases [4]. Further efforts are still needed to show the clear mechanism of how MOB2 and NDR/LATS kinases function in DDR signalling and cell cycle checkpoint.

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