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The Possible Crosstalk of MOB2 With NDR1/2 Kinases in Cell Cycle and DNA Damage Signaling

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Abstract

This article is the authors' opinion of the roles of the signal transducer Mps one binder 2 (MOB2) in the control of cell cycle progression and the DNA Damage Response (DDR). We recently found that endogenous MOB2 is required to prevent the accumulation of endogenous DNA damage in order to prevent the undesired, and possibly detrimental, activation of cell cycle checkpoints. In this regard, it is noteworthy that MOB2 has been linked biochemically to the regulation of the NDR1/2 (aka STK38/STK38L) protein kinases, which themselves have functions at different steps of the cell cycle. Therefore, we are speculating in this article about the possible connections of MOB2 with NDR1/2 kinases in cell cycle and DDR Signaling.

Keywords

Cell cycle progression; DNA damage signaling; mps one binder; Nuclear Dbf2-related kinase; Serine/threonine protein kinase 38; Phosphorylation; Protein-protein interaction

Introduction

The family of Mps one binder proteins (MOBs) is highly conserved in eukaryotes [1]. MOBs represent signal transducers in essential intracellular Signaling pathways through their regulatory interactions with serine/threonine protein kinases of the NDR/LATS family [1–3]. In budding and fission yeast, Mob1p and Mob2p are crucial for mitotic exit and cell morphogenesis as regulators of the yeast NDR/LATS kinases Dbf2p, Cbk1p, Sid2p and Orb6p, respectively [4–6]. In *Drosophila*, three different MOB proteins are expressed by independent genes, with dMOB1 (aka Mats) functioning as a core component of the Hippo tumor suppressor pathway as regulator of the fly LATS kinase Warts [7–9]. *Drosophila* MOB2 (dMOB2) contributes to neuromuscular junction and photoreceptor morphology [10,11] and the biological function(s) of dMOB3 is currently unknown, although all three dMOBs can genetically interact with the fly NDR kinase Tricorned [12]. Mammalian

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Competing Interest

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genomes contain at least six different MOB genes termed MOB1A, MOB1B, MOB2, MOB3A, MOB3B and MOB3C [1]. MOB1A/B likewise to dMOB1 functions as a regulator of LATS kinases in mammalian Hippo signaling [1,2], although current evidence proposes that the interaction of MOB1 with NDR kinases is likely to also play a role in Hippo signaling [3].

In contrast to MOB1, MOB2 interacts specifically with NDR, but not with LATS kinases in mammalian cells [13–15]. MOB3A/B/C neither form a complex with NDR nor LATS kinases, but instead associate with the pro-apoptotic kinase MST1 (aka STK4) [16]. Taken together, throughout the eukaryotic kingdom MOBs can play diverse roles as regulators of members of the NDR/LATS kinase family and apparently also other protein kinases in specific settings. In this article we will focus on discussing recent discoveries regarding roles of endogenous MOB2 in cell cycle progression and the DNA damage response (DDR) in the context NDR kinase signaling. Up to recently [17], mammalian NDR kinases were the only reported binding partners of MOB2 [1,15]. More precisely, biochemical experiments showed that MOB2 competes with MOB1 for NDR binding, with the MOB1/NDR complex corresponding to increased NDR kinase activity and the MOB2/NDR complex being associated with diminished NDR activity [15]. In other words, MOB2 binding to NDR can block the activation of NDR kinases. However, the biological significance of MOB2/NDR complex formation is currently unknown. Actually, no clearly defined physiologically relevant functions of endogenous MOB2 were known until recently. Therefore, we set out to understand important cell biological roles of endogenous MOB2. Intriguingly, a genome wide screen for novel putative DDR factors identified MOB2 (also termed HCCA2 and hMOB3 [1]) as one of many potential candidates [18]. Considering that the DDR is essential to maintain genome stability and functions as a barrier for ageing and tumorigenesis [19], we investigated whether MOB2 is indeed a DDR protein. Intriguingly, we initially found that MOB2 knockdown, but not MOB2 overexpression, caused a cell proliferation defect associated with a G1/S cell cycle arrest in untransformed human cells [17].

By profiling an array of cell cycle markers we discovered that MOB2-depleted cells displayed a significant activation of the p53 and p21/Cip1 cell cycle regulators, which was functionally relevant, since co-knockdown of p53 or p21 together with MOB2 did not result in the activation of the G1/S cell cycle checkpoint, consequently restoring cell proliferation [17]. Once we had established that MOB2 knockdown causes the activation of a p53/p21-dependent G1/S cell cycle checkpoint, we wondered how this activation occurred. Considering that endogenous MOB2 is potentially linked to the DDR [18] and that activation of the p53/p21 pathway can occur upon activation of DDR signaling [20–22], we studied the levels of DDR Signaling and endogenous DNA damage in MOB2-depleted cells [17]. These investigations revealed that MOB2 knockdown causes the accumulation of DNA damage, and consequently activation of the DDR kinases ATM and CHK2, in the absence of exogenously induced DNA damage. Next, we aimed to consolidate these findings by studying the response of MOB2 knockdown cells to exogenously induced DNA damage. This showed that endogenous MOB2 is needed to promote cell survival and G1/S cell cycle arrest upon exposure to DNA damaging agents such as ionizing radiation (IR) or the topoisomerase II poison doxorubicin [17]. Moreover, we discovered that MOB2 is required to support IR-induced DDR Signaling through the DDR kinase ATM.

Collectively, these observations uncovered endogenous MOB2 as a novel DDR factor that plays a role in DDR Signaling, cell survival and cell cycle checkpoints upon exposure to DNA damage. However, we still had not understood how MOB2 may function as DDR protein on a molecular level. In this regard, using a yeast two-hybrid screen we had identified RAD50 as a novel binding partner of MOB2 [17], which potentially was important, since RAD50 is a central component of the essential MRE11-RAD50-NBS1 (MRN) DNA damage sensor complex, which in turn is crucial for the sequestering/activation of the DDR kinase ATM at DNA lesions [23–25]. Therefore, we examined this potential interaction in more detail, revealing that MOB2/RAD50 complex formation can be detected using exogenous and endogenous proteins [17]. Moreover, we found that MOB2 supports the recruitment of MRN and activated ATM to DNA damaged chromatin, suggesting that MOB2-depleted cells display a defective DDR due to impaired functionality of the MRN [17]. However, although we could map the binding sites of MOB2 on RAD50 to two functionally relevant domains of RAD50 [17], we did not succeed in identifying MOB2 variants carrying single point mutations that block MOB2/RAD50 complex formation [Gomez V and Hergovich A, unpublished observation], which would have enabled us to investigate the functional significance of the MOB2/RAD50 interaction in more detail. Therefore, our study [17] could not conclusively establish that the interaction of MOB2 with RAD50 is functionally essential for the roles of MOB2 in DDR Signaling, cell survival and cell cycle checkpoints upon exposure to DNA damage.

In this regard, it is noteworthy that in the genome wide screen performed by Elledge et al. [18] the knockdown of MRN components did not result in DDR defects (as judged by sensitivity to mitomycin C and a defective G2/M DNA damage checkpoint) as observed in MOB2-depleted transformed human cells [18]. Thus, the link of MOB2 to the MRN does not appear to be relevant in all DDR settings, suggesting that additional mechanisms should be considered. In general, we have only begun to appreciate the cell biological functions of endogenous MOB2 in processes that are relevant to human health and disease. In particular regarding the link of MOB2 with the DDR, quite a few key questions are yet to be understood. For example, we have yet to comprehend which types of DNA damage repair mechanism(s) [26,27] is dependent on normal MOB2 levels. Maybe the expression/localization status of MOB2 has the potential to be clinically exploited for the prediction and/or prognosis of responses to DNA damaging agents (i.e. radiotherapy, DNA damaging chemotherapeutics, targeted DDR inhibition, and others). Furthermore, we have yet to obtain a clear mechanistic understanding of how MOB2 can function as a DDR protein and how MOB2 is regulated in a context-dependent manner.

Currently, we are far from grasping all these important concepts. Nevertheless, our previous [1,15] biochemical characterization of MOB2 in complex with the NDR1/2 kinases may be of help to lead some of the way. However, based on our own experiments we already speculated that MOB2 apparently functions as cell cycle/DDR regulator independently of NDR1/2 kinase Signaling [17]. More specifically, we observed that knockdown of NDR1 (aka STK38) or NDR2 (STK38L) in untransformed human cells did not trigger a p53/p21-dependent G1/S cell cycle arrest as observed in MOB2-depleted cells [17]. Overexpression of hyperactive NDR1-PIF [28] also did not cause an obvious cell cycle/proliferation defect [17]. However, we believe that further investigations are still required to completely rule out

that NDR1/2 Signaling is not linked to cell cycle/DDR processes through MOB2, since different reports have recently linked the NDR1/2 kinases to cell cycle and DDR signaling [3]. In addition, compensatory mechanisms may occur upon selective NDR1 or NDR2 manipulations. In mammals, the NDR1/2 protein kinases have been linked to cell biological processes such as cell cycle progression, the DDR, apoptosis, stress signaling and autophagy, with important roles in embryogenesis, immunology and neurobiology [3]. As mentioned above, in particular the connections of NDR1/2 with the cell cycle and DDR are intriguing with respect to MOB2 (Figure 1). On the one hand, NDR1/2 are linked to the regulation of G1/S cell cycle progression by controlling protein levels of c-myc and p21/Cip1 [29–32]. The role of NDR1/2 in the G1/S cell cycle progression is further supported by cyclin D1 [33] and can have a role in opposing a TGF β -mediated cell cycle arrest [34]. Furthermore, NDR1 has important functions in mitosis [35–38]. Thus, various tissue culture cell experiments support the notion that NDR1/2 can play diverse roles in the regulation of cell cycle progression. On the other hand, NDR1 has been linked to different aspects of the DDR. NDR1-depleted transformed human cells have increased sensitivity to IR [39]. NDR1 possibly has a function in nucleotide excision repair, a specific type of DNA damage repair [40]. In addition, NDR1 potentially is involved in the DNA damage induced G2/M cell cycle checkpoint by phosphorylating the CDC25A phosphatase [41], although this phosphorylation of CDC25A is also mediated by the DDR kinase CHK1 [42], hence warranting future investigations into this possible link of NDR1 and the DNA damage induced G2/M cell cycle checkpoint. Taken together, current evidence suggests that the NDR1/2 kinase pathway is linked to the regulation of certain aspects of cell cycle progression and signal transduction in response to DNA damage (Figure 1).

Nevertheless, in spite of the involvement of NDR1/2 in the cell cycle and DDR [3] in a similar fashion as observed for MOB2 [17,18], it is currently unknown whether the MOB2 and NDR1/2 pathways are functionally connected, as suggested by our recent biochemical evidence [15]. In this regard, we can envision different scenarios. Based on our biochemical understanding [15], MOB2 may act upstream of NDR1/2 by functioning as inhibitor of MOB1-mediated NDR1/2 signaling. However, simply based on our current lack of evidence, we should not exclude the possibility that NDR1/2 may play a role upstream of MOB2, in which case it would be very informative to understand the involvement of the NDR1/2 kinase activity, in addition to the regulation of MOB2 by NDR1/2 (or vice versa) through direct protein-protein interactions. In this regard, experimenters should also keep in mind that single NDR1 or NDR2 knockdown compared to co-depletion of NDR1 and NDR2 may result in different phenotypes due to possible compensatory mechanisms [43]. More specifically, we found that single NDR1 or NDR2 knockout mice are viable and fertile due to compensatory tissue specific up regulation of NDR2 or NDR1, respectively [43,44]. In contrast, NDR1/2 double-knockout mice die before birth around embryonic day E10 [43]. These findings collectively suggest that NDR1 and NDR2 can compensate for each other in a context- and tissue-specific fashion [43,44]. In case MOB2 functions negatively upstream of NDR1/2 in DDR signaling, one would expect that MOB2 knockdown or hyperactivation of NDR1/2 result in similar phenotypes, which does not seem to be the case [17]. If NDR1/2 were to act upstream of MOB2 in DDR Signaling, one would predict that positive regulators of NDR1/2, such as MOB1 [1], may also contribute to the DDR. Interestingly, this seems to

be the case, since MOB1A or MOB1B knockdown appears to be sufficient to cause spontaneous DNA double-strand break formation in human cells [45], proposing that the regulation of NDR1/2 by MOB1 might also play a role in the DDR. However, whether NDR1/2 can function upstream of MOB2 in cell cycle and/or DDR signaling is yet to be established experimentally. The possible involvement of MOB1 in NDR1/2-MOB2 signaling is also of purely speculative nature at the moment, in particular when considering that MOB1 can associate with different kinases of the Hippo core cassette such as LATS1/2 and MST1/2 [1,3]. In this context, we also would like to emphasize the fact that currently the molecular (structural) regulation of NDR1/2 kinases by MOB1 vs. MOB2 is incompletely understood. Possibly, MOB2 is part of positive and/or negative feedback loops that serve to amplify and/or dampen cell cycle and/or DDR Signaling, respectively. Certainly, these speculative points illustrate the need for more intensified experimental efforts to understand MOB2 as a novel DDR protein on the structural, molecular, cellular and organismal level in the context of human biology in health and disease.

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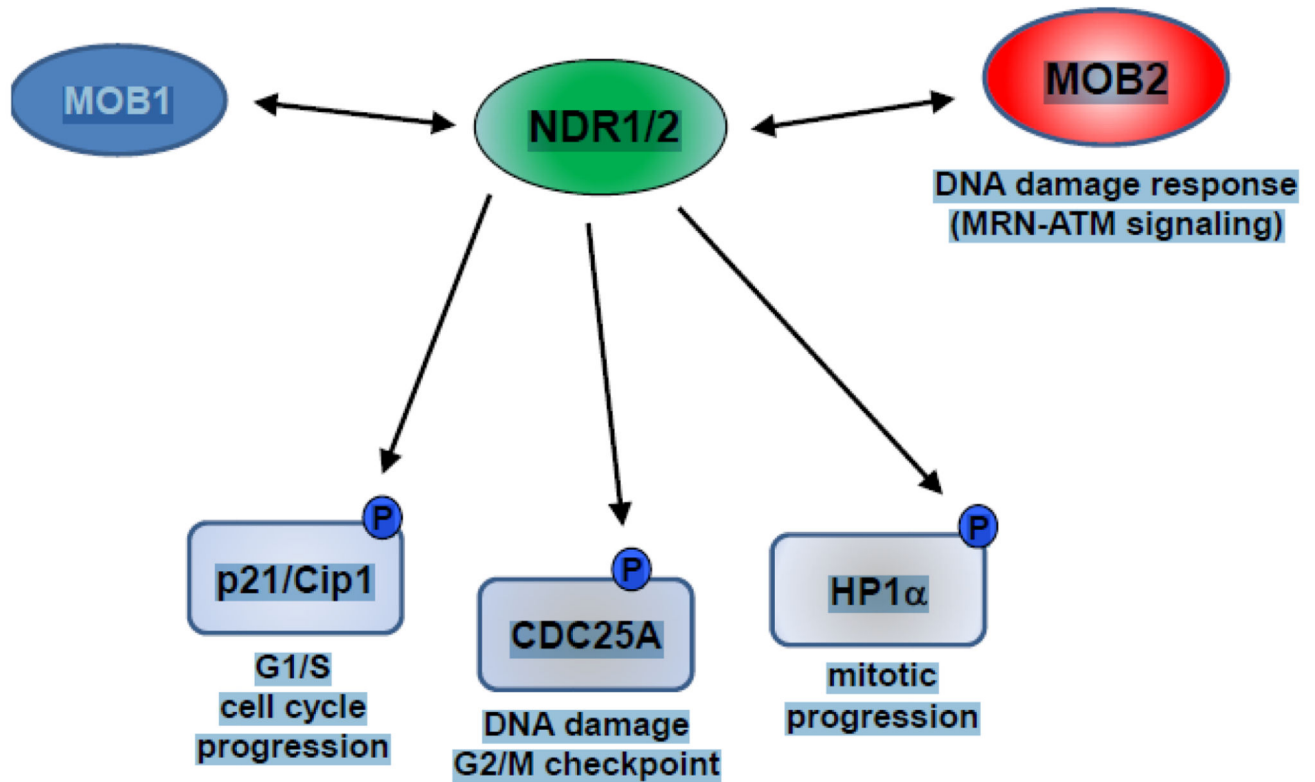


Figure 1.

Molecular processes that are possibly regulated by connected MOB2 and NDR1/2 signaling the MOB2 signal transducer acts in the DNA damage response (DDR) pathway by supporting MRN-ATM Signaling [17]. MOB2 can also interact with the NDR1/2 serine/threonine protein kinases and thereby interfere with the activation of NDR1/2 by MOB1 binding [15]. However, it is currently not known whether the associations of MOB2 (or MOB1) with NDR1/2 are functionally relevant for the regulation of NDR1/2 substrates such as the cell cycle regulator p21/Cip1, the CDC25A phosphatase, or heterochromatin protein 1 α (HP1 α , also known as CBX5), whose NDR1/2-mediated phosphorylation can play roles in G1/S cell cycle transition [30], the DNA damage G2/M cell cycle checkpoint [41], or mitotic progression [37], respectively