Emerging role of DYRK family protein kinases as regulators of protein stability in cell cycle control

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Dual-specificity tyrosine phosphorylation-regulated kinases (DYRKs) constitute an evolutionarily conserved family of protein kinases with key roles in the control of cell proliferation and differentiation. Members of the DYRK family phosphorylate many substrates, including critical regulators of the cell cycle. A recent report revealed that human DYRK2 acts as a negative regulator of G1/S transition by phosphorylating c-Jun and c-Myc, thereby inducing ubiquitination-mediated degradation. Other DYRKs also function as cell cycle regulators by modulating the turnover of their target proteins. DYRK1B can induce reversible cell arrest in a quiescent G0 state by targeting cyclin D1 for proteasomal degradation and stabilizing p27Kip1. The DYRK2 ortholog of C. elegans, MBK-2, triggers the proteasomal destruction of oocyte proteins after meiosis to allow the mitotic divisions in embryo development. This review summarizes the accumulating results that provide evidence for a general role of DYRKs in the regulation of protein stability.

DYRK Family Protein Kinases

Kinases of the DYRK family were discovered as key regulators of cell growth and differentiation in genetically tractable organisms such as budding yeast (Yak1), fission yeast (Pom1), Dictyostelium (YakA) and Drosophila (MNB).2,3 Human DYRK1A was discovered as the product of a gene localized in the Down syndrome critical region on chromosome 21.3 DYRK1A has been most extensively studied among the mammalian DYRKs, because its overexpression in trisomy 21 is believed to contribute to the neuropathological traits of Down syndrome.5,5 DYRK1A and the closely related DYRK1B (also known as MIRK) have also been characterized as negative regulators of the cell cycle that mediate cell survival and promote the switch to a quiescent state or differentiation.6-9 DYRK2 can induce apoptosis upon genotoxic stress by phosphorylating p53.10 Although members of the DYRK family are engaged in multiple and diverse regulatory processes in different experimental systems, a recurrent theme of their functions in mammalian cells as well as in yeasts, C. elegans and Dictyostelium is their role as key regulators of different checkpoints in the cell cycle.

Target Proteins of DYRKs

An increasing number of substrates and functions in signal transduction pathways is being reported for DYRKs from different organisms. Downstream effects mediated by target proteins of DYRKs include the increased activity of transcription factors, the modulation of subcellular protein distribution and the regulation of enzyme activity. Recent reviews provide an excellent overview of the biochemical properties and the currently known substrates of DYRK1A as well as the other kinases of the DYRK family.2,21 One characteristic feature of several DYRK kinases is their function as priming kinases, meaning that the phosphorylation of a given residue by a DYRK is prerequisite for the subsequent phosphorylation of a different residue by

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Abbreviations: APC, anaphase-promoting complex; DCAF, DDB1 and CUL4-associated factor; DYRK, dual-specificity tyrosine phosphorylation-regulated kinase; HIPK, homeodomain-interacting protein kinase; REST, RE1 silencing transcription factor; SCF, E3 ligase complex containing Skp, cullin and F-box protein; UPS, ubiquitin proteasome system
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Another protein kinase (GSK3 or PLK),\(^2\) here we want to call attention to another effect common to several members of the DYRK family, namely the control of protein stability. This function of DYRKs has been brought into the limelight by a new report from Taira et al.,\(^1\) who identified DYRK2 as the kinase controlling c-Jun and c-Myc degradation at the G\(_1\)/S boundary. This finding adds to accumulating evidence that members of the DYRK family from diverse organisms modulate the turnover of target proteins either by inducing degradation by the ubiquitin-proteasome system (UPS), or by stabilizing short-lived proteins.

This review summarizes the current knowledge that DYRKs function in the regulation of protein stability. Emphasis is placed on proteins involved in cell cycle control, and the scope is limited to the members of the DYRK subfamily. It should be noticed, however, that the closely related homeodomain-interacting protein kinase 2 (HIPK2) has also been reported to regulate the turnover of some target proteins. Exemplary data for HIPK2 are included in Table 1, which lists the published evidence for the regulation of protein turnover by the DYRK family.

**DYRK2 Initiates Protein Degradation via the UPS**

Two major types of E3 ubiquitin ligases cooperate to catalyze the phase-specific ubiquitination of proteins in the cell cycle, the anaphase-promoting complex (APC) multisubunit E3 ligase and the SCF form of E3 ligases. SCF E3 ligases belong to the major group of cullin-based E3 ligases, which consist of four kinds of protein subunits: an adaptor protein (Skp1 in SCF), a scaffold protein termed a cullin (CUL1 in SCF), an F-box protein (Fbw7 in SCF), and a substrate receptor (one of about 70 F-box proteins in SCF).\(^3\)

Phosphorylation-dependent protein degradation is a common mechanism for regulating protein stability in a cell cycle-dependent or stimulus-dependent manner. Kinases create phosphodegron motifs in the substrate proteins, which are then recognized by F-box proteins and ubiquitinated by E3 ligase complexes.

The recent study of Taira et al.\(^1\) reveals interesting details about the molecular mechanism by which DYRK2 regulates the turnover of c-Myc and c-Jun. Many tumor cells depend on high levels of c-Jun and c-Myc to enter S phase. Cellular levels of these onco-genic transcription factors are controlled by deregulation of the substrate proteins, which are then ubiquitinated by E3 ligase complexes.

DYRK2 has now been identified as the priming kinase for the phosphorylation of c-Jun and c-Myc by GSK3\(\beta\), meaning that phosphorylation of the substrate at the P+4 position by DYRK2 is required for substrate recognition by GSK3\(\beta\).\(^1\)

The subsequent phosphorylation of the P0 residue by GSK3\(\beta\) creates a phosphodegron required for the binding of an SCF E3 ligase complex containing the F-box protein Fbw7, eventually resulting in the polyubiquitination and ensuing proteasomal degradation of c-Jun/c-Myc (Fig. 1). DYRK2 was shown to play a key role in this chain of events, since the knockdown of DYRK2 in human cancer cells shortened the G\(_i\) phase and accelerated cell proliferation due to the escape of c-Jun and c-Myc from ubiquitination-mediated degradation.

**Roles of DYRK1A and DYRK1B in the Regulation of Protein Stability**

The first results pointing to a role of DYRKs in cell cycle control via regulation of protein stability have been obtained in pioneering studies of DYRK1B.\(^2,3\) DYSK1B destabilizes cyclin D1 by phosphorylating a threonine residue close to the C terminus.\(^2,3\) A recent report suggests that DYRK1A can also catalyze this phosphorylation, leading to nuclear export and proteasomal degradation of cyclin D1.\(^2,4\) The exact site of phosphorylation (Thr286 or Thr288) is controversial,
Table 1. Evidence for a role of DYRKs as regulators of protein stability

| Kinase | Protein (phosphorylation sites) | GSK3 priming | Function | Comments | Ref. |
|--------|---------------------------------|--------------|----------|----------|------|
|        |                                 |              |          |          |      |
| **Protein degradation** |                                 |              |          |          |      |
| DYRK2  | c-Jun (S239)                    | yes          | regulation of S-phase entry | DYRK2/GSK3 initiate ubiquitination via Fbw7 E3 ligase | 12   |
| DYRK2  | c-Myc (S62)                     |              | regulation of S-phase entry | DYRK2/GSK3 initiate ubiquitination via Fbw7 E3 ligase | 12   |
| DYRK2  | GLI2 (S385, S1011)              |              | effector of hedgehog pathway | DYRK2 reduces GLI2 levels, MG132 inhibitable | 17   |
| DYRK2  | katanin p60 (S42, S109, T133)   |              | control of mitotic transition | DYRK2 serves as a scaffold for EDVP E3 ligase | 14   |
| MBK-2  | MEI-1 (katanin)                 |              | oocyte-to-embryo transition | MBK-2 initiates APC dependent degradation | 21,22|
| MBK-2  | OMA-1 (T239), OMA-2             | yes          | oocyte-to-embryo transition | MBK-2/GSK3 initiate ubiquitination by CUL2-based E3 ligase | 19,20|
| DYRK1B | cyclin D1 (T286 or T288)        | no           | regulation of S-phase entry | phosphorylation initiates SCF<sup>B-<sub>crystallin</sub></sup>-mediated degradation | 23, 26|
| DYRK1A | REST                            |              | neuronal differentiation | no direct evidence for phospho-degron; degraded via SCF<sup>β<sub>−<sub>TrCP</sub></sup></sub> | 35   |
| DYRK1A | CRY2 (S557)                     | yes          | component of circadian clock | SCF<sup>β<sub>−<sub>TrCP</sub></sup></sub>-independent, MG132 sensitive | 54   |
| HIPK2  | CtBP (S422)                     |              | transcriptional co-repressor | HIPK2 is required for the UV-induced decrease in CtBP | 55   |
| HIPK2  | ZBTB4 (T783, T795, T797)        |              | regulator of p21 expression | HIPK2 is required for the UV-induced decrease in ZBTB4 | 56   |
| HIPK2  | ΔNp63 (T397)                    |              | prosurvival factor | HIPK2 is required for DNA damage-induced degradation of ΔNp63 | 57   |
| HIPK2  | β-catenin (S33, S37)            | no           | effector of Wnt pathway | phosphorylation initiates SCF<sup>β<sub>−<sub>TrCP</sub></sup></sub>-mediated degradation | 58   |
| HIPK2  | Siah2 (S26, S28, S36)           | no           | E3 ligase involved in hypoxic regulation | phosphorylation reduces the half-life of Siah2 | 59   |
| Yak1   | cyclin B2                       |              | regulatory subunit of CDK | genetic evidence for enhanced APC-dependent degradation of cyclin B2 | 50   |
| **Protein stabilization** |                                 |              |          |          |      |
| DYRK1B | p27<sup>kip1</sup> (S10)        |              | CDK inhibitor | phosphorylation enhances stability of p27 (by preventing nuclear export) | 24, 47|
| HIPK2  | HPV16E7 (Thr5, Thr7)            |              | Viral oncoprotein | phosphorylation enhances stability | 48  |
| DYRK1A | Presenilin 1 (T354)             |              | component of gamma secretase complex | phosphorylation enhances stability | 60  |
| DYRK1A | RCAN1 (T192)                    |              | inhibition of NFAT activation by calcineurin | phosphorylation enhances stability | 61  |
| **Protein interaction** |                                 |              |          |          |      |
| DYRK1A/B | DCAF7 (= WDR68)              |              | putative substrate receptor of CUL4-type E3 ligases | scaffold of HIPK2 complexes; DYRK1A recruits DCAF7 to the nucleus | 40,41|
| HIPK2  | CUL9 ( = PARC)                  |              | atypical E3 ligase | identified in interaction screen | 43  |
| DYRK1A | RNF216                          |              | E3 ligase | identified in interaction screen | 43  |
| DYRK2  | DCAF1 ( = VprBP)                |              | substrate receptor of CUL4-type E3 ligases | identified by tandem affinity purification | 14  |
| Yak1   | Hrt1 ( = ROC1)                  |              | E2 recruiting subunit of SCF | identified in interaction screen | 41  |

The table lists the DYRK substrates that are either destabilized or stabilized by phosphorylation and DYRK interacting proteins related to ubiquitin E3 ligases. The table includes proteins that are not related to cell cycle control as well as target proteins of HIPK2 that are not further discussed in the text.
but it is clear that in this case, DYRK1A and DYRK1B do not act as priming kinases for GSK3. Phosphorylation on Thr286 by GSK3 in S phase is known to induce the cytoplasmic ubiquitination of cyclin D1 catalyzed by SCFβTrCP. The resulting phosphodegron motif is recognized by Fbw7, which acts as the substrate receptor of an SCF complex (SKP1/cullin1/Fbw7/Rbx), initiating ubiquitination by the E2 ligase and subsequent proteasomal degradation. Likewise, c-Jun is ubiquitinated after sequential phosphorylation at thr239 and Ser243 by DYrK2.

The importance of cyclin D1 proteolysis, in the sense that loss of cyclin D1 causes accumulation of p27 (see below), is highlighted by the fact that mutations in the cyclin D1 phosphodegron have been observed in human tumors. It is worth mentioning that cyclin D2 and cyclin D3 are also phosphorylated on corresponding C-terminal threonines (Thr280 and Thr283, respectively) to trigger their UPS-dependent degradation. It remains to be determined whether DYRK1A and/or DYRK1B also phosphorylate these cyclins.

The RE1-silencing transcription factor (REST) is expressed in dividing neural progenitors and acts as a repressor of neuronal differentiation and positive regulator of proliferation. The neurodevelopmental effects of DYRK1A in Down syndrome may in part be due its effect on REST, since DYRK1A overexpression reduces REST protein levels through facilitating ubiquitination and subsequent degradation. REST is regulated by phosphorylation and subsequent ubiquitin-mediated proteolysis in a SCFβ-TrCP3 E3 ligase-dependent manner, but it remains to be shown whether DYRK1A acts on this pathway. Reduced REST levels due to DYRK1A overexpression were documented from undifferentiated embryonic stem cells to adult brain and are predicted to favor cell cycle exit and differentiation of neural progenitor cells.

Another strong indication that DYRK1A and DYRK1B are functionally linked is that both of them, as well as HIPK2 (but not DYRK2), have repeatedly been shown to interact with DDB1 and CUL4-associated factor 7 (DCAF7, also called WDR68 or Han11). DCAFs are a family of more than 50 proteins that function as adaptor proteins of the CUL4-DDB1 ubiquitin ligases to mediate substrate specificity. The specific function of DCAF7 as a receptor subunit of E3 ligase complexes is unknown, but one might speculate that it mediates the interaction either between the kinase and its substrate or between the kinase and an E3 ligase. Another protein interacting with DYRK1A is cullin 9, which seems to be part of an atypical cullin-based E3 ligase complex and regulates p53.

### Stabilization of Target Proteins by DYRK1A and DYRK1B

In addition to targeting specific proteins for proteasomal degradation, DYRK1A or DYRK1B can stabilize other proteins by phosphorylation. The most pertinent example in this context is the phosphorylation by DYRK1B of p27 in G0 phase of the cell cycle. Phosphorylation on Ser10 stabilizes p27 in quiescent cells by maintaining the protein within the nucleus, where it inhibits CDK2. The physiological importance of Ser10 phosphorylation was shown in lymphocytes from p27S10A/S10A-knock-in mice, where protein turnover of p27 in G0 phase, but not in S phase, was markedly enhanced compared with wild-type cells. Phosphorylation of Ser10 in G0 phase or upon mitogenic stimulation is catalyzed by other kinases and has different functional consequences as compared with G0 phase. Recently, HIPK2 has also been shown to phosphorylate Ser10 and stabilize p27 in asynchronously growing cell lines. Further work will be necessary to uncover the contribution of the individual kinases in different cell types and different phases of the cell cycle.

The E7 oncoprotein of human papilloma virus type 16 (HPV16E7) is another substrate of DYRK1A and has been reported to be stabilized by phosphorylation on Thr5 and Thr38. HPV16E7 induces the degradation of retinoblastoma family of proteins (pRb, p107 and p130) and promotes S phase entry. Phosphorylation by DYRK1A increased the half-life of HPV16E7 and enhanced the transforming potential of HPV16-infected cells. This effect is in striking contrast to the antiproliferative effects of DYRK1A or DYRK1B that result from phosphorylation of cyclin D1 or p27. Thus, the viral oncoprotein virtually hijacks and reprograms a cellular pathway that normally inhibits cell division.
E3 ligases, but also of the mechanism by which DYRKs can reduce the turnover of specific substrates (such as p27Kip1).

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