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Dual targeting of eIF4E by blocking MNK and mTOR pathways in leukemia

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ABSTRACT

Dysregulation of mRNA translation leads to aberrant activation of cellular pathways that promote expansion and survival of leukemic clones. A key element of the initiation translation complex is eIF4E (eukaryotic translation initiation factor 4E). The mitogen-activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR) pathways play important roles in the regulation of eIF4E expression and downstream functional outcomes. Mitogen-activated protein kinase interacting protein kinases (Mnks) control translation by phosphorylation of eIF4E, whereas the mTOR kinase phosphorylates/de-activates the eIF4E inhibitor, 4E-BP1, to release translational repression. Both pathways are often abnormally activated in leukemia cells and promote cell survival events by controlling expression of oncogenic proteins. Targeting these pathways may provide approaches to avoid aberrant proliferation and neoplastic transformation.

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1. Introduction

Acute myeloid leukemia (AML) is a genetically heterogeneous leukemia characterized by subtypes with different molecular abnormalities and by the activation of multiple signalling pathways that promote cell survival and proliferation. Despite the currently available therapies, most subtypes of AML remain difficult to treat [1]. The control of mRNA translation plays a pivotal role in the regulation of expression of genes that are responsible for many cellular processes such as cell proliferation, differentiation and apoptosis. Translation processes are tightly regulated. The critical step for initiating translation of mRNAs is the availability of eIF4E (eukaryotic translation initiation factor 4E) to participate in the eukaryotic initiation complex 4F, along with RNA helicase eIF4A and the scaffolding protein eIF4G [2,3] (Fig. 1). eIF4E is a key component of this complex because it recognizes and directly binds the 5′-cap of the mRNA structure, which includes a 7-methylguanosine (m^7G) moiety [4,5]. The eIF4G scaffolding protein also binds to mRNA by interaction with eIF4E and the m^7G cap structure. This complex also includes the eIF4B protein that helps in the RNA-helicase function of eIF4A, thus regulating the translation of mRNAs that contain 5′-UTRs (untranslated regions) [6,7]. The study of eIF4E has become a major focus in cancer research due to its key role in controlling translation of mRNAs that lead to the expression of tumor-associated proteins, such as c-Myc, cyclins D1 and D3, and Mcl-1 (Myeloid cell leukemia 1). The activity of these proteins has been linked to proliferation of leukemic cells and other type of malignant cells [8–10]. In contrast, the activation of eIF4E plays a minor role in the expression of mRNAs for housekeeping genes, such as GAPDH (glyceraldehyde-3-phosphate dehydrogenase) and β-actin [11]. In addition to its role in translation, eIF4E also seems to facilitate the nucleocytoplasmic transport of certain mRNAs, which is enhanced by eIF4E phosphorylation. This process enables the production of proteins that are involved in cell cycle progression and cell survival [12]. This could represent an independent mechanism required for expression of oncogenic proteins and potentially provide a unique cellular target for therapeutic approaches.

The function of eIF4E is strictly regulated in cells under normal physiological conditions and is controlled by its repressor proteins, 4E-BPs (eIF4E-binding proteins), whose function does not allow formation of eIF4F complex [8]. eIF4E activity can be regulated by two major signalling pathways which play critical roles in leukemogenesis, the MAPK (Mitogen-activated protein kinases) and mTOR (mammalian target of rapamycin) pathways [13,14]. The selective targeting of these pathways, alone or in combination with other therapies, could conceptually increase the anti-leukemic activity of the currently available and generally insufficient treatments for

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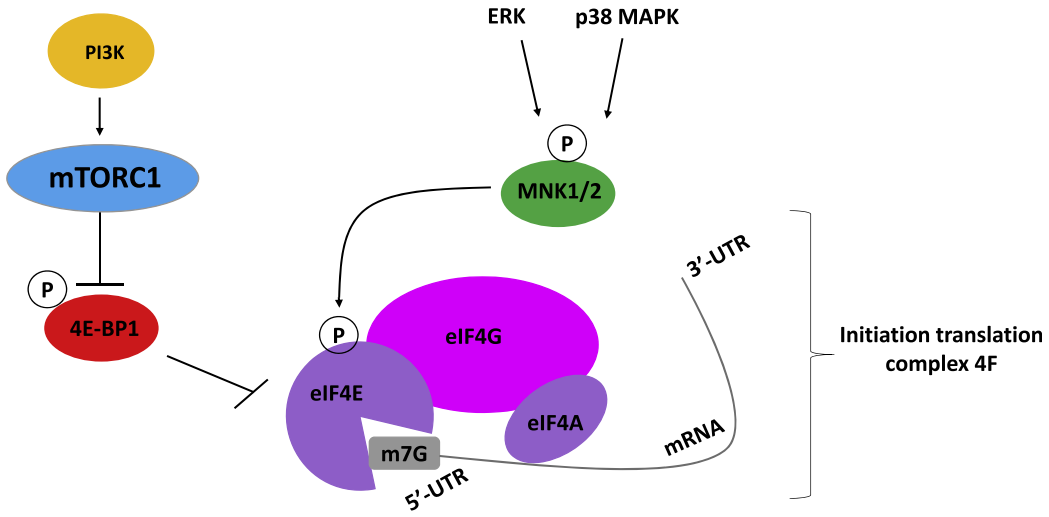

Fig. 1. Schematic illustration depicting the cellular pathways that lead to eIF4E activation.

patients with AML and has been the major focus of study by different groups in the field.

2. The oncogenic activity of eIF4E and its phosphorylation by MNKs

The oncogenic activity of eIF4E can be modified by its phosphorylation at Serine209 (Ser209) by the MAPK-interacting kinases MNK1 and MNK2 (Fig. 1). MNK1 and MNK2 belong to a family of serine/threonine protein kinases that are activated downstream of either ERK or p38 MAPK in response to extracellular factors (growth factors and stress) [9,15,16]. In human cells, two Mnk genes have been identified as *MNK1* and *MNK2*. Each one of these genes, after alternative splicing events, translate two protein isoforms: MNK1a, MNK1b, MNK2a, and MNK2b, respectively, which share a similar N-terminal region (involved in binding to eIF4G), but vary in their C-terminal domains [17,18]. The C-terminal regions of the longer MNK1a and MNK2a isoforms have a MAPK-biding site that allows their interaction/phosphorylation by ERK and p38 MAPK [19]. However, unlike MNK1a, which has a high affinity for both kinases, MNK2a has greater affinity for ERK. Moreover, the activation of ERK or p38 MAPK increases the low basal activity of MNK1a, but does not have a significant impact on the constitutive high basal activity of MNK2a [17,20]. On the other hand, the shorter b-isoforms of Mnks lack the MAP-kinase biding site in their C-terminal region. Initial studies have shown that basal activity of MNK1b is higher than that of MNK2b [17,21].

Recent studies have shown that phosphorylation and activation of eIF4E at Ser209 by MNK1/MNK2 is critical for eIF4E to promote oncogenic activity [22], but not essential for normal development [15,16]. As a proof of concept of this perspective, a study using Mnk1/2 double knockout PTEN −/− mice (T-cell-specific PTEN conditional knockout mice) showed resistance to lymphogenesis in these mice, when compared to the parental PTEN −/− mice [23]. Phosphorylation of eIF4E is also involved in development and progression of other type of cancer [11]. Notably, phosphorylation of eIF4E was shown to promote invasion, metastasis and epithelial to mesenchymal transition [24]. eIF4E is overexpressed in many types of cancer and in most cases is connected with poor prognosis (increased cancer recurrence and decreased patient survival) [11]. There has been accumulating evidence implicating Mnks in the pathophysiology of leukemogenesis. AML is often characterized by a collection of several mutations that support proliferation and survival of leukemic clones [25,26]. It has been shown that MNK1 activity is induced by several AML fusion genes and has an important role in hematopoietic proliferation [27]. A recent study on chronic myeloid leukemia (CML) provides evidence that targeting the MNK-eiF4E axis can inhibit the function of blast crisis leukemia stem cells (BC LSCs) by affecting production of β-catenin, without affecting normal hematopoietic stem cell functions [28]. Thus, Mnks can play an important role in leukemia progression and, therefore, future development of new small molecule inhibitors could be important for the treatment of leukemia.

3. Regulation of eIF4E by the mTOR pathway

The mTOR signalling cascade controls initiation of mRNA translation and plays significant roles in cellular processes such as protein synthesis, lipid production, cell growth and proliferation, and ribosome biogenesis [29,30]. This kinase is present in two unique, separate complexes: mTORC1 and mTORC2 [31]. In those complexes there are common and distinct subunits and effectors [32,33]. mTORC1 contains the common subunits mLST8 (mammalian lethal with sec13 protein 8) and Deptor (DEP domain-containing mTOR-interacting protein), and the unique components PRAS 40 (proline rich Akt substrate of 40 kDA) and Raptor (regulatory-associated protein of mTOR) [29,32,34]. The mTORC2 includes the unique subunits Rictor (rapamycin-insensitive companion of mTOR), mSin1 (mammalian stress activated protein-kinase interacting protein), and Protor, in addition to the common proteins mLST8 and Deptor [30]. A defining function of mTORC2 is the control of phosphorylation of AKT at Ser473, a site which is essential for activation of AKT and anti-apoptotic downstream effectors [31,32,35]. Additionally, mTORC2 regulates cytoskeletal organization and glucose and lipid metabolism [36]. It has also been shown that in addition to AKT, mTORC2 also phosphorylates SGK (glucocorticoid-regulated kinase) and PKCα (protein kinase C-α) [37–39].

mTORC1 is activated upstream by engagement of the PI3K/AKT cascade. PI3K (phosphoinositide 3-kinase) is a membrane-associated lipid kinase that when activated promotes conversion of phosphatidyl inositol 3,4 (PIP_2) to phosphatidyl inositol 3,4,5 (PIP_3) [29,40]. Once active, PI3K and PIP_3 bind PDK1 which phosphorylates AKT at Threonine 308 [41,42]. In its active form, AKT plays an important role in regulation of mTORC1 activity by phosphorylation of PRAS40 and tuberous sclerosis complex 2 (TSC2) [43–45].

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