In this issue of *Clinical Cancer Research*, Ko and colleagues (1) report that they have developed a novel strategy to specifically target eIF4E activity in ovarian tissue by fusing 4EBP1 peptides to an agonist of the gonadotropin-releasing hormone (GnRH).

The levels and activity of the eukaryotic translation initiation factor eIF4E are elevated in many human malignancies (2). eIF4E overexpression in tissue culture leads to oncogenic transformation, in xenograft mouse models to increased tumor size, invasion, and metastases, and in transgenic mouse models to cancers of distinct histological origins (2). Elevated eIF4E levels correlate with poor prognosis in many cancers including those of the breast and head and neck (2). eIF4E modulates gene expression at (at least) two levels: cap-dependent translation and nuclear mRNA export (3). In the nucleus, eIF4E promotes the export of specific mRNAs to the cytoplasm, thereby increasing the cytoplasmic concentration of these transcripts available to the translation machinery. Such mRNAs include mdm2 and cyclin D1. In the cytoplasm, eIF4E, through its interactions with eIF4G, recruits transcripts to the ribosome enhancing the efficiency of the given transcript’s translation. Transitionally sensitive mRNAs include vascular endothelial growth factor (VEGF). Not all mRNAs are sensitive to eIF4E at both levels. However, mRNAs sensitive to eIF4E at either level tend to be involved in proliferation and survival (3).

The nuclear and cytoplasmic functions of eIF4E are tightly regulated by the cell (3). Regulation is redundant, with many different types of regulators playing key roles. With the exception of PML and the arenavirus Z protein, which bind eIF4E through their RING domains, eIF4E regulators contain conserved eIF4E binding sites defined by YXXXXLΦ, in which X is any residue and Φ any hydrophobic (3). The binding partners, the eIF4E binding protein 1 (BP1) and eIF4G both contain this motif and use it to bind eIF4E. In this way, BP1 blocks the eIF4E-eIF4G association and inhibits translation. This binding site is also used by tissue specific regulators of eIF4E, including nearly 200 homeodomain proteins (3). More recent studies indicate that the BPs may also modulate the subcellular distribution of eIF4E, influencing its nuclear functions (4). BPs are themselves found in the nucleus as well as the cytoplasm, further suggesting that their regulatory roles are likely broader than first thought. Importantly, the redundancy in its regulators is important in keeping the oncogenic potential of eIF4E in check. For example, BP1−/− mice do not get cancers more readily than controls (5).

Given the prevalence of eIF4E overexpression and its role in driving oncogenic transformation in model systems, many groups have worked to develop strategies to effectively target eIF4E. There is at least one weakness that can be exploited. Cancer cells with elevated levels of eIF4E seem to have developed an oncogene addiction to eIF4E (6, 7). For example, a physical mimic of the natural ligand of eIF4E, ribavirin, preferentially inhibits the growth of primary acute myeloid leukemia (M4/M5 AML) specimens with elevated eIF4E levels relative to specimens with normal levels of eIF4E (e.g., M1/M2 AML) or normal controls (7). Ribavirin activity is being tested in a phase II clinical trial of poor prognosis AML with some patients achieving complete or partial remissions and with no treatment-related toxicities observed (8).

In a prostate cancer mouse model, antisense oligonucleotides to eIF4E reduced eIF4E levels and suppressed xenograft tumor growth (6). Other modes to repress eIF4E expression using RNA interference or antisense RNAs were reported in breast cancer and separately head and neck cancer xenograft mouse models (9, 10). Finally, a suicide gene therapy strategy successfully targeted head and neck cancer cells in a mouse model. In this model, a long complex 5’ untranslated region was placed upstream of the suicide gene, making its production more efficient in cells that had elevated eIF4E levels (11).

Clearly, more strategies need to be developed to target eIF4E, and ideally, strategies will target the cancer cells reducing the impact on eIF4E, an essential gene, in normal cells. The study by Ko and colleagues developed tissue specific therapy to eIF4E (Fig. 1). They exploited the observation that more than 80% of epithelial ovarian cancers (EOC) express the receptor for GnRH. They designed an inhibitor of BP1 based on previous crystal structures ensuring that the peptide used would be optimized for eIF4E binding. Their studies show that when BP1 peptide
Culjkovic B, Topisirovic I, Borden KL. Controlling presence of the GnRH receptor, the fusion peptide was observed and ascites in mice. Tumor burden was lowered by an impressive [Dlys6]GnRH-4EBP1 inhibited the growth of ovarian tumors and thus are effected by the treatment.

Fig. 1. A schematic representation of the strategy developed by Ko et al. to target cells expressing GnRH. The GnRH agonist, [Dlys6]GnRH, is represented as a sphere and the BP1 peptide as a line. The GnRH receptor is represented as a half moon. Only cells expressing the GnRH receptor take up [Dlys6]GnRH-4EBP1 and thus are effected by the treatment.

is fused to the gonadotropin agonist [Dlys6]GnRH, that the fusion peptide effectively enters only cells that express the GnRH receptor and reduces the elf4E-elf4F4 association. Consistently, cap-dependent translation of luciferase was impaired. It will be interesting in future to monitor the extent to which translationally sensitive endogenous mRNAs, such as VEGF, are targeted by this therapy. Their data show that [Dlys6]GnRH-4EBP1 did not affect the translation of elf4E, elf4G, or actin, consistent with the specificity seen for elf4E translation targets. These studies were likely more successful than previous studies using BP1 peptides because of the inclusion of an extended BP1 fragment to more effectively target the elf4E-binding surface. Also, the targeting strategy avoided previously observed toxicity issues with these peptides.

Im impartantly, the authors show that the administration of [Dlys6]GnRH-4EBP1 inhibited the growth of ovarian tumors and ascites in mice. Tumor burden was lowered by an impressive five-fold in treated mice relative to controls. Consistent with the presence of the GnRH receptor, the fusion peptide was observed in mouse ovaries as well as in the xenograft. However, the fusion peptide was absent from other tissues in the mouse. There did not seem to be any BP1-related toxicity in these animals. These findings could profoundly impact the treatment of EOC. Studies of elf4E knockdown in breast cancer and in head and neck cancer found an additional benefit when cis-platin was added to the elf4E knockdown treatment (9, 10). Given that this is usually used in EOC, future studies of the benefit of a combination of cis-platin and [Dlys6]GnRH-4EBP1 could be interesting. The very strength of this elegant strategy may also turn into an Achilles’ heel. In particular, how effective will this strategy be against metastases, which may not express the GnRH receptor? Further, will resistance arising from downregulation of the GnRH receptor become an issue?

There are some features of BP1 functionality that are counterintuitive, and thus, strategies targeting BP1 may need to be adjusted accordingly. For instance, both elf4E and BP1 are reported to be highly elevated in breast carcinomas (12). Here, BP1’s phosphorylation is also highly elevated. The fusion peptide may not be phosphorylated in the absence of the rest of the BP1 protein. In this way, the BP1 peptide could be a more potent suppressor of elf4E than the endogenous BP1 protein. Studies in esophageal cancers reported higher levels of BP1-elf4E complexes than in normal controls, again a counterintuitive observation (13). Thus, formation of more BP1-elf4E complexes may not be sufficient in all cases and other strategies to target elf4E or target collaborating pathways may be needed.

In summary, Ko and colleagues have developed an elegant strategy to effectively target ovarian cancer by fusing BP1 peptides to the GnRH receptor agonist [Dlys6]GnRH. Such novel strategies combining inhibition of elf4E and tissue targeting will hopefully lead to the translation of new, targeted therapies into the clinic.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

KLBB is grateful for helpful discussions with Dr. Biljana Culjkovic.

References

Tissue Targeting in Cancer: eIF4E's Tale

Katherine L.B. Borden


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