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A wholesale approach to disarm multiple myeloma

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Comment on Li et al, page 2926

In an original preclinical study published in this issue of *Blood Advances*, Li et al[1] provide proof-of-principle evidence of the therapeutic efficacy of a novel approach against multiple myeloma (MM). The authors explored the therapeutic potential of the combined inhibition of exportin 1 (XPO1), using selinexor, a compound recently approved for refractory myeloma,[2] and eukaryotic translation initiation factor (eIF) 4E (eIF4E) to achieve more potent antitumor effects. This preclinical study offers interesting insights into myeloma pathobiology and has potentially relevant therapeutic implications.

The established concepts of oncogene and nononcogene addiction are formidable frameworks to decipher cancer cell biology and devise new therapies.[3] MM cells, the malignant counterparts of long-lived professional antibody secretors, epitomize both addictions, with both general and plasma cell–specific oncogenic mechanisms and stress phenotypes. A notable example is that myeloma pathobiology has revealed that proteosynthetic and proteocatabolic stress entail actionable vulnerabilities (eg, proteasome activity) that can be successfully targeted, resulting in radical improvement of therapeutic outcomes.[4] However, despite effective therapies, patients with myeloma typically relapse and develop refractory disease because of clonal outgrowth of cancer subpopulations that gain proliferative and/or prosurvival advantage and chemoresistance from complex genetic and epigenetic alterations that ultimately result in overexpression of oncoproteins and/or inactivation of oncosuppressors.[5] Studies exploring new therapeutic avenues to correct these aberrations are thus highly needed.

Eukaryotic cells have evolved mechanisms that control the traffic of macromolecules between the cytoplasm and the nucleus to maintain cellular homeostasis. Attesting to the importance of such control, nuclear-cytoplasmic traffic is often subverted in cancer cells to evade cell- cycle checkpoints and acquire chemotherapeutic resistance.[5] The multisubunit nuclear pore complex, embedded in the nuclear envelope, is estimated to translocate hundreds of macromolecules per minute in both directions through specialized carrier proteins that mediate energy-dependent transport of cargoes exceeding 40 kDa, including proteins and RNAs. Most carriers belong to a functional group sensibly referred to as the *caryopherin* family, which includes importins and exportins. Some recognize specific signals: 4 (out of >10 known) importins recognize positively charged nuclear localization signals, whereas only XPO1 (also referred to as Chromosome Region Maintenance 1), out of 7 exportins hitherto identified, recognizes a leucine-rich hydrophobic nuclear export signal (NES). Thus, XPO1 is the only exportin that mediates the nuclear export of NES-containing proteins, including key tumor suppressors such as TP53, p21, p27, BRCA1/2, pRB, FOXO, and IκB, thereby hindering their nuclear activities.[6,7]

XPO1 is overexpressed in both solid and hematologic cancers, including MM, and its overexpression has been shown to be associated with disease progression, treatment resistance, and inferior overall or progression-free survival. Thus, XPO1 is an attractive therapeutic target against cancer.[7] Of particular interest in myeloma, XPO1 has been implicated in acquired resistance to the first-in-class proteasome inhibitor, bortezomib. Indeed, XPO1 was found to be overexpressed in bortezomib-resistant cancer cells, with differentially expressed proteins including a cluster of recognized XPO1 interactors, and its genetic suppression rescued chemosensitivity.[8] The recent Food and Drug Administration approval of the small molecule covalent XPO1 inhibitor, selinexor, for use in previously treated MM[2] encourages the comparison of combinations with standard-of-care and targeted therapies, aiming to overcome acquired resistance and improve therapeutic outcomes.

XPO1 also mediates the cytoplasmic transport of eIF4E, a critical factor involved in tumorigenesis and cancer progression that shuttles messenger RNAs with highly complex 5′ untranslated regions, including the oncogene-coding transcripts *MYC*, *BCL6*, *BCL2*, and *MCL1*, thereby promoting their

translation.[9] Thus, the antimyeloma efficacy of XPO1 blockade is likely accounted for, in part, by the inhibition of eIF4E. Further attesting to eIF4E as an attractive antimyeloma target itself, Li et al[10] previously found that its expression is elevated in malignant plasma cells, as compared with healthy counterparts, and stimulates the translation of C/EBPβ, a transcription factor that transactivates master determinants of plasma cell identity and fitness, such as IRF4, XBP-1, and Blimp-1, and proved eIF4E required for myeloma growth in xenografts.

Taken together, the pleiotropic targets and multiple mechanisms of action of XPO1 and eIF4E, their interconnectedness, and their broad predicted impact on plasma cell oncogenic and stress-adaptive pathways led Li et al to hypothesize that the combined inhibition of XPO1 and eIF4E could synergistically affect plasma cell survival by achieving deeper suppression of nuclear export and translation of oncoproteins while empowering nuclear oncosuppressive activities, a wholesale approach strongly opposing plasma cell fitness and triggering cell death.

The results obtained substantiate the therapeutic potential of the combined approach, with significant synergies observed in vitro on myeloma cell proliferation and survival.[1] Intriguing details include: the observation that XPO1 blockade inhibited eIF4E while decreasing its abundance via reduced protein stability; the demonstration that eIF4E is a key mediator of the protumoral activity of XPO1, because its genetic inhibition overcame primary resistance of myeloma cell lines to selinexor, whereas its overexpression induced resistance; and the evidence that rocaglamide, an inhibitor of eIF4A, a partner of eIF4E in the translation initiation complex eIF4F, recapitulated the antiproliferative and death-inducing synergies with selinexor already documented with eIF4E knockdown in vitro.

Interestingly, in the in vivo setting, eIF4E silencing alone was sufficient to profoundly reduce myeloma growth and restore the survival of xenograft recipient mice; whereas, in contrast, eIF4E silencing in vitro synergized with selinexor but had limited effects on proliferation and none on apoptosis when administered alone. Moreover, the effects of eIF4E silencing were so potent in xenograft recipient mice that the possible synergistic effect of combined eIF4E and XPO1 inhibition observed in vitro could not be formally addressed in vivo.[1]

In summary, the synergies described encourage further inquiry into the pleiotropic impact of deranged nuclear-cytoplasmic trafficking and protein translational control on plasma cell pathobiology. Dedicated unbiased strategies and curiosity-driven efforts may disclose circuits extending beyond canonical oncogenic pathways, with potentially relevant insights into specific stress-adaptive strategies. For example, strategies related to endoplasmic reticulum, mitochondrial, or proteostatic stress. Therefore, this study may inspire efforts to better understand and disentangle the complex interconnections between oncogene and nononcogene addictions in cancer biology.

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