Disrupting adaptive proteostasis to overcome proteasome inhibitor resistance

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Despite therapeutic advances over the past decade, multiple myeloma (MM) remains an incurable plasma cell malignancy. Even in the era of modern immunotherapies, only approximately one-third of patients with relapsed or refractory disease achieve a durable remission.[1] Overcoming therapeutic resistance, or enhancing the efficacy of approved agents, does therefore remain one of the major challenges of current myeloma research. Among currently approved drug classes, proteasome inhibitors (PI) represent a cornerstone of MM therapy, with established roles in both frontline and relapsed/refractory regimens.[2] Their broad utilization, however, has been accompanied by the frequent emergence of resistance, which limits efficacy in later lines of therapy. PI resistance is multifactorial, encompassing genetic alterations in proteasome subunits,[3] influences exerted by the tumor microenvironment,[4] and the activation of compensatory proteostasis mechanisms. In particular, upregulation of molecular chaperones, notably heat shock proteins (HSP), has been recognized as a critical cytoprotective adaptation mechanism. Prior studies have shown that proteasome inhibition triggers chaperone induction, thereby facilitating stabilization of misfolded proteins and preventing aggregation.[5,6] While targeting HSP has long been proposed as a means to sensitize myeloma cells to PI, translation to the clinic has been limited by toxicity and a narrow therapeutic window.

In this issue of *Haematologica*, Besse and colleagues[7] provide mechanistic and translational evidence that inhibition of insulin receptor and insulin-like growth factor-1 receptor (INSR/IGF-1R) signaling disrupts a pivotal adaptive proteostasis program that underlies PI resistance in MM. By repurposing the clinically approved anaplastic lymphoma kinase (ALK) inhibitor ceritinib, the authors outline a rational strategy to suppress the protein folding response that mitigates proteotoxic stress following exposure to carfilzomib.

Insulin and IGF-1 are established growth factors in MM, with signaling through their respective receptors promoting cell survival and resistance to PI.[8] Although the importance of these pathways in myeloma biology has long been recognized,[9] up to now efforts to target them therapeutically have not yielded clinical benefit.

Ceritinib, a second-generation ALK inhibitor approved for ALK-rearranged non-small cell lung cancer, exhibits selective cytotoxicity in MM despite the absence of ALK expression in plasma cells, prompting questions about its mechanism of action in this context.

Through an elegant combination of *in vitro*, *ex vivo* and *in vivo* experiments, together with kinase profiling and functional genomic analyses, Besse and colleagues demonstrate that ceritinib's activity in MM is mediated by off-target inhibition of INSR and IGF-1R. Inhibition of this axis attenuates PI3K/Akt/mTORC1 signaling, a pathway the authors show to be essential for maintaining elevated levels of HSP70 and other chaperones. Importantly, PI3K/Akt/mTOR signaling is also known to contribute to microenvironment-mediated treatment resistance in MM, and its inhibition could both diminish protein folding capacity as well as disrupt protective microenvironmental influences, thereby resensitizing myeloma cells to proteasome inhibition.[10]

A particularly important aspect of this work is the demonstration that proteasome inhibition alone fails to dismantle proteostasis in PI-resistant myeloma models. Carfilzomib continues to elicit a robust chaperone response even in resistant cells, enabling tolerance of impaired protein degradation. Ceritinib selectively abrogates this protective program, converting proteasome inhibition from a manageable stress into a lethal insult (Figure 1).

This dual targeting strategy – simultaneous impairment of protein degradation and protein folding – constitutes a mechanistically coherent approach to overcoming PI resistance. Notably, ceritinib does not directly inhibit the proteasome; rather, it prevents the compensatory response that buffers proteasome dysfunction, thereby acting synergistically with carfilzomib.

The authors show that INSR and IGF-1R expression is in-

creased in relapsed/refractory MM compared with newly diagnosed disease, suggesting that reliance on this pathway may intensify with disease progression and therapeutic pressure. This observation raises the possibility that patients with advanced or refractory disease may derive particular benefit from this combination strategy. Furthermore, the identification of mTORC1 regulatory components, such as NPRL3, DDIT4, and FOXO1, as modifiers of ceritinib sensitivity and as prognostic markers underscores the centrality of mTORC1-driven proteostasis in myeloma biology and

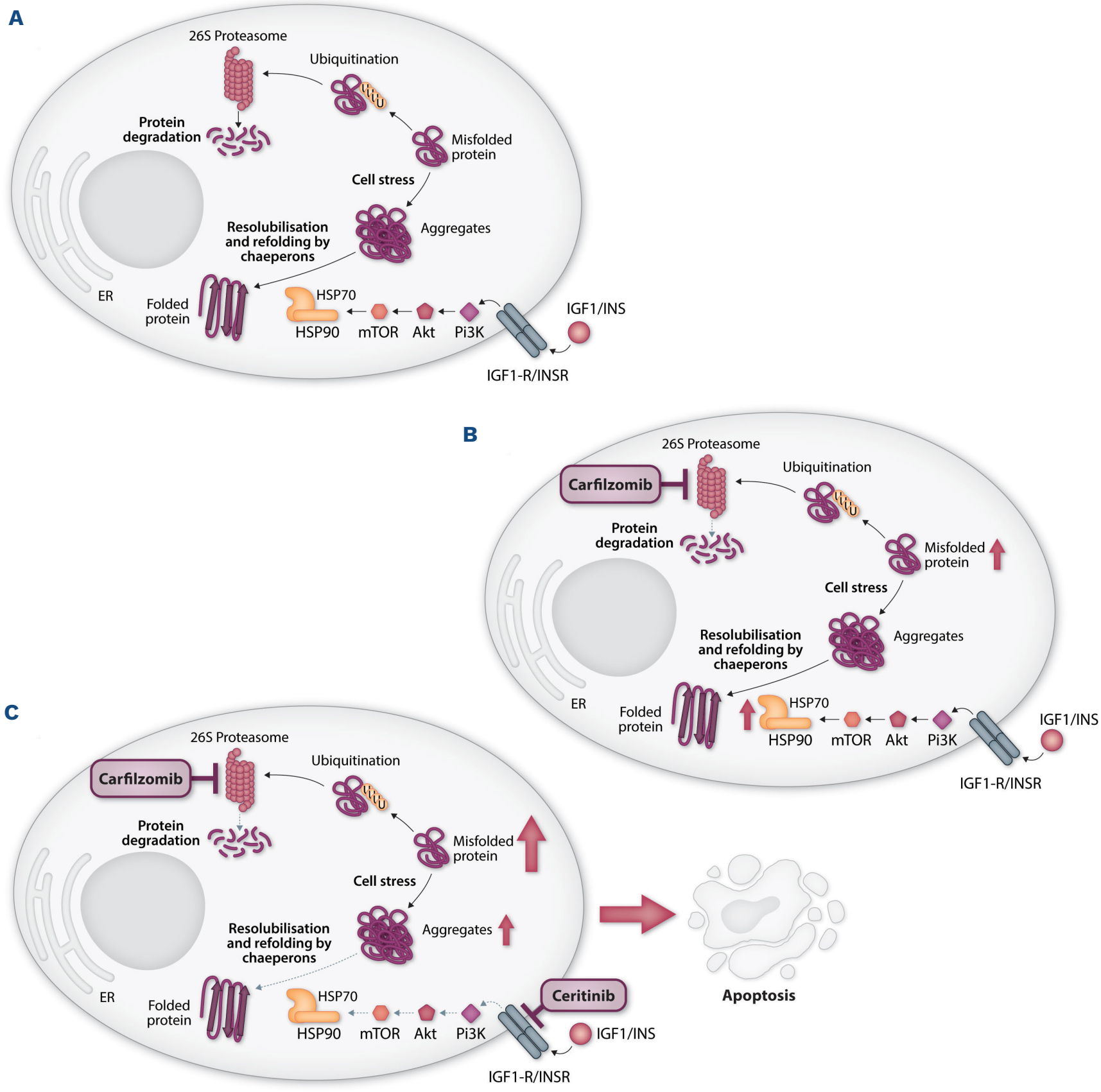


Figure 1. Schematic representation of proteasome inhibition and interactions of carfilzomib and ceritinib in disrupting proteostasis. (A) Interaction of the proteasome with heat shock proteins (HSP) and with the IGF1-R/INSR axis. Although IGF1-R and INSR are two distinct receptors, for simplicity they are depicted together. (B) Proteasome inhibition reduces protein degradation and causes an accumulation of misfolded proteins. This in turns increases the synthesis of HSP (HSP70 and HSP90) as a protective mechanism. The IGF1-R/INSR axis enhances this effect. (C) Dual inhibition of the proteasome via carfilzomib and of the IGF1-R/INSR axis via ceritinib triggers apoptosis by simultaneous impairment of protein degradation and protein folding. ER: endoplasmic reticulum; HSP: heat shock protein; mTOR: mammalian target of rapamycin; Akt: protein kinase B; Pi3K: phosphatidylinositol 3-kinase; IGF1/INS: insulin-like growth factor-1/insulin; IGF1-R/INSR: insulin-like growth factor-1 receptor/insulin receptor.

suggests avenues for biomarker-guided patient selection in future clinical studies.

Several aspects of this work underscore its translational relevance. The synergy between ceritinib and carfilzomib is consistently observed in PI-naïve and PI-resistant cell lines, in primary samples from patients with relapsed/refractory MM and plasma cell leukemia, and in an orthotopic bone marrow xenograft model. Ceritinib exerts minimal toxicity toward healthy donor peripheral blood mononuclear cells and does not exacerbate metabolic toxicity *in vivo*, despite targeting insulin signaling pathways. Moreover, because ceritinib is already approved for the treatment of non-small cell lung cancer, its clinical repurposing could be achieved relatively easily.

Despite the novelty and therapeutic potential of this approach, important questions remain. The long-term metabolic consequences of INSR inhibition in myeloma patients, particularly in combination with corticosteroids, warrant careful evaluation. In addition, while xenograft models recapitulate key aspects of tumor–bone marrow interactions, they do not fully capture the complexity of the human microenvironment and immune landscape, which may influence treatment response. It will also be important to determine whether more selective IGF-1R/INSR inhibitors can replicate ceritinib's effects, or whether its broader polypharmacology contributes to its efficacy.

In summary, Besse and colleagues provide compelling evidence that PI resistance in MM can be overcome not by intensifying proteasome inhibition, but by disabling the cellular programs that sustain survival in the face of proteotoxic stress. By repurposing ceritinib to suppress IGF-1R/INSR-driven protein folding responses, this study identifies a therapeutically actionable nexus between metabolism, proteostasis, and drug resistance. These findings reinvigorate interest in IGF-1R/INSR targeting – not as monotherapy, but as a strategic partner to proteasome inhibition – and provide a strong mechanistic rationale for clinical evaluation of ceritinib–carfilzomib combinations in relapsed and refractory MM.

Disclosures

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