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Stressing Out Melanoma with an anti-GRP78 compound

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Melanoma incidence has risen dramatically and while targeted therapy with BRAF or MEK inhibitors provides an initial response, acquired resistance to such treatments compromises a durable response. Accumulating evidence suggests that targeting unfolded protein response (UPR) signaling has potential as novel therapy with potent efficacy, broad responses and an ability to overcome BRAF inhibitor resistance (Chevet et al., 2015). Cerezo and colleagues describe the development of a novel compound that targets the endoplasmic reticulum chaperone, GRP78/BiP and exhibits anti-melanoma activity.

The endoplasmic reticulum (ER) is an organelle that coordinates with a variety of extracellular and intracellular stimuli and integrates oncogenic stress and survival in the tumor microenvironment. Misfolded protein accumulation in the ER triggers activation of the UPR, a signaling pathway composed of 3 transmembrane signal transducers (Inositol Requiring Enzyme 1, Ire1; Protein kinase RNA (PKR)-like ER kinase, PERK; Activating Transcription Factor 6, ATF6). Critically, the activity of all three transducers is governed through direct binding to GRP78/BiP (Figure 1). UPR activation occurs following GRP78 release from the luminal domains of UPR transducers, at which point GRP78 engages in refolding/chaperoning activity under conditions of stress. Importantly, activation of the UPR while initially pro-survival, switches to pro-death under conditions of continual or unrelenting stress. As such, agents that specifically increase ER stress within a tumor context have therapeutic potential.

During the past decade, a growing body of work implicates the UPR and particularly PERK in promoting tumor progression (Bu and Diehl, 2016). Consequently, the first highly specific PERK inhibitors have been developed (GSK2606414)(Axten et al., 2012). As an alternative to targeting one arm of the UPR, Cerezo et al report the identification of a compound that targets the master UPR regulator, GRP78. GRP78 makes an attractive target not only because it governs the activity of all three UPR branches, but in addition is overexpressed in every cancer in which it has been examined adding broad therapeutic value. HA15, a thiazole benzenesulfonamide, was demonstrated to bind and inhibit GRP78 where biochemical data reveal specific disruption of UPR transducer-GRP78 complexes resulting in constitutive UPR signaling and cell death exclusively in cancer cells (Figure 1).

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The HA15 mechanism of action proposed by this study suggests that HA15 binding to GRP78 triggers release of all three ER mediators and also induces a partial inhibition of GRP78 ATPase activity. GRP78 knockout of both alleles causes embryonic lethality in mouse development (Luo et al., 2006), and adults maintain a basal level of GRP78 in major organs. Given HA15 spares fibroblasts from cytotoxicity, along with no detrimental effects in HA15 treated mice, we can speculate that HA15 doesn't interfere significantly with GRP78-folding activity or other normal physiological functions.

HA15 treatment generated both autophagy and apoptosis, which correlated with reduced melanoma progression in vivo. The potent anti-melanoma activity depended upon the induction of the UPR key player Chop. Depletion of Chop inhibited apoptosis and autophagy thereby compromising the HA15 cytotoxicity on melanoma cells. Chop represents a point of convergence for all three UPR signaling branches: PERK activates Chop transcription via PERK-eIF2 α -ATF4 axis while Ire1 and ATF6 indirectly regulate Chop expression. Chop, as a transcription factor, modulates a wide range of genes whose protein products regulate autophagy. Autophagy has been implicated as a double sword in cancer development, either activating or inhibiting cell death in a context-dependent manner. Ultimately, the cytotoxic effects of HA15 appear to prevail over the cytoprotective functions of the UPR due to the intensity and duration of the stress.

Importantly, HA15 is effective in naïve melanoma and BRAF inhibitor resistant melanoma. Previous reports suggest that Vemurafenib promotes mutant BRAF binding to GRP78 and triggers chronic ER stress and autophagy, resulting in Vemurafenib resistance in melanoma (Ma et al., 2014). Interestingly, HA15 can override this effect and provide an unresolved ER stress contributing to ER stress mediated melanoma death.

While it seems likely that HA15 will also be subject to resistance, such resistance has not yet been observed. The HA15 anti-tumor effect is not only limited to melanoma treatment. The authors expanded the study to a wide range of tumors, including prostate, breast and colon cancers. HA15 exerts cytotoxicity to all these cancer types in a similar way. Impressively, HA15 overcomes gemcitabine resistance in pancreatic cancer and imatinib resistance in myeloid leukemia. Given the therapeutic index and the facts that HA15 is able to suppress melanoma (and other types of tumors) growth regardless of BRAF mutation status, metastasis status, as well as BRAF inhibitor resistance status, with no side effects on normal tissue and no required resistance, HA15 has great potential to be a next-generation anti-melanoma therapy.

Notably, the duration and observation interval for HA15 treatment is only 2 weeks. Thus, additional work is required to assess the long-term tumor benefit of HA15 on melanoma progression. Furthermore, whether this compound has appropriate pharmacokinetic properties, adequate for clinical trial remains to be evaluated. Although further studies are yet needed to evaluate the potential clinical utility of HA15, it is hopeful that HA15 or a related compound will provide another entry for melanoma-targeted therapy, particularly with respect to acquired resistance to BRAF inhibitors.

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Figure 1. Mechanisms of HA15 targeting melanoma cells. HA15 potentially binds and inhibits GRP78 activity in the ER

All three ER stress transducers PERK, IRE-1 and ATF6, when released from GRP78 binding undergo a conformational change. Their activation directly or indirectly triggers Chop accumulation, which represents a point of convergence for all three UPR signaling branches. As a key transcription factor, Chop mediates expression of multiple autophagic and apoptotic gene, eventually resulting in melanoma cell death. The brown squiggles represent misfolded proteins.