Editorial Commentary

Tackling the HuRdle of radioresistance: a radiation perspective on the RNA-binding protein HuR

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RNA-binding proteins are key post-transcriptional gene expression regulators. They are involved in a broad variety of cellular processes, including proliferation, differentiation, and migration. While they play important roles in fine-tuning physiological cell behavior, they may also contribute to the development and progression of a wide range of diseases if dysregulated (1). One prominent example is cancer, where RNA-binding proteins have been implicated in a variety of oncogenic pathways, functionally influencing cell invasion, migration, proliferation, therapy resistance, and numerous other functions (1,2). Ultimately, RNA-binding protein expression may influence outcomes in different cancers (3).

One of the more prominent RNA-binding proteins—more than 1,200 have been verified in humans (1), a number that continues to grow (4)—is the RNA-binding protein human antigen R (HuR) (5). In a highly commendable effort, Finan *et al.* have summarized recent findings on the HuR protein in different human cancers with a focus on its translational relevance. The review broadly underlines that cytoplasmatic HuR localization promotes tumorigenesis and increases stress resistance in human cancer cells, making HuR a potential therapeutic target. Different targeting mechanisms are discussed in detail, indicating the scientific relevance of this approach (5).

At the heart of this translational work is the question whether HuR targeting strategies may support and improve cancer therapy. We appreciate the authors' efforts to highlight studies that combine HuR targeting with traditional cancer therapies (5). Multiple other recent reviews have similarly discussed targeting HuR protein expression or function (6-8). Many studies show a synergistic effect between HuR targeting and chemotherapy in multiple different settings, including in breast, lung, colorectal, prostate, liver, pancreatic cancer and others (9).

Radiotherapy is another mainstay of cancer therapy: roughly half of cancer patients receive radiation treatment during the course of their disease (10). Treatment is administered in a broad variety of cancers, including in many patients with metastatic or locally advanced tumors (10). Consequently, improving efficacy of radiation treatment remains a major priority in cancer care (11). Radiotherapy has oftentimes been combined with chemotherapy, but increasing evidence suggests that concomitant application of targeted therapies may also increase treatment effectiveness (11). Accordingly, translational research identifying radiosensitizers holds significant promise (11).

In this setting, Finan *et al.* note that some findings relate HuR targeting to cancer radiosensitization (5). Expanding on these thoughts, we want to more closely evaluate the HuR protein and its combination with radiation therapy, focusing on some key questions.

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What is the evidence for HuR-associated radiosensitization?

As discussed by Finan *et al.*, two *in vitro* studies in solid tumors showed that human colon cancer and breast cancer cells were more sensitive to radiotherapy after small interfering RNA (siRNA)-based HuR knockdown (12,13). A similar finding was made in non-cancerous human cells, including skin (14) and oral keratinocytes (15). A recent study in esophageal cancer confirmed a radiosensitizing effect *in vivo* and *in vitro* (16). HuR knockout mice showed a significant sensitization to whole-body radiotherapy (17). Finally, 15,16-Dihydrotanshinone-I (DHTS), a HuR inhibitor, successfully sensitized cells to radiotherapy in an *in vivo* cervical cancer model (18). No other data seems currently available on other solid or any hematologic malignancies.

What are the underlying molecular mechanisms of HuR-associated radioresistance?

Molecular mechanisms have been investigated to a substantial degree, mainly focusing on ties between HuR expression and stress response as well as DNA damage repair. DNA damage may induce cytosolic translocation of HuR via activation of the damage proteins checkpoint kinase 1 (CHK1) and p38 mitogen-activated protein kinase (p38 MAPK) (19,20). HuR may then further increase DNA damage protein translation (19). Most studies found an increased level of DNA double strand breaks in HuR low-expressing cells (12,13,16). This finding was associated with increased caspase activation (12,16,18), decreased kinesin light chain-2 (21) and Snail (16), and decreased expression of the genomic stability marker AT-rich interactive domain-containing protein 1A (ARID1A) (21) and WEE1 (22) as well as the repair markers ataxia-telangiectasia mutated (ATM), Ku80, and RAD51 (19). HuR has also been associated with cancer stem cells (23) which have been linked to a specific gene expression profile and are known to be highly radioresistant (24). One potential additional resistance mechanism could be the HuR-associated stabilization of Musashi-1 (25), another RNA-binding protein, that is known to be associated with radioresistance (26,27). Based on these findings it seems likely that HuR acts through a multitude of mechanisms to induce DNA damage repair and reduce radiotherapy efficacy, making it an attractive therapeutic target.

What about combination treatment toxicity?

There is a substantial amount of evidence regarding HuR-associated DNA stabilization. However, far fewer studies have investigated radiotherapy and HuR targeting, as discussed above. Only three *in vivo* studies combined radiotherapy and HuR inhibition (16-18), two of which were performed in a cancer model. One used a lentiviral construct for knockdown of HuR in esophageal cancer cells before injection into mice and did not collect toxicities (16). The other used a HuR inhibitor, DHTS, in cervical cancer, reporting that no toxicities were noted after intraperitoneal injection of DHTS (18). Only one study described increased toxicities after HuR knockout and whole-body irradiation in mice (17). Notably, the animals did not bear tumors. Finan *et al.* concluded that combination treatment of radiotherapy and HuR targeting may result in unfavorable side effects, calling into question the rationale behind this combination (5). However, modern radiotherapy is tailored to the tumor region and significant efforts are made to spare organs at risk. Additionally, HuR knockout cells may not be representative of clinical inhibition models. And finally, most importantly, as noted in the review, targeting HuR inhibitor application to cancer cells would substantially alleviate concern for side effects. These delivery efforts are currently under investigation (28). Hence, we believe the combination of HuR targeting and radiation treatment remains promising.

However, some challenges have to be resolved before clinical assessments become feasible. First, inhibitor specificity needs to be demonstrated as targeting individual RNA-binding proteins may prove challenging. Off-target effects may increase toxicity and reduce outcomes such as treatment tolerance and quality of life. Second, downstream effects need to be fully studied to preclude unwanted side effects. While HuR is one of the most-investigated RNA-binding proteins, it remains far from fully understood. Third, a targeted delivery needs to specifically transport HuR inhibitors to cancer cells. HuR targeting is likely to negatively impact non-cancerous cells given its ubiquitous expression and its important role in physiological cell development (5). This is supported by the increased normal-tissue toxicity in irradiated HuR knockout mice (17). Fourth, delivery needs to accomplish a meaningful inhibition of HuR in the target cells to achieve clinically relevant results.

In sum, there is a substantial body of evidence to support the DNA-stabilizing function of the HuR

protein. In our view, this offers a clear rationale for the combination of HuR inhibitors and radiotherapy given radiation-induced DNA damage. Few, yet encouraging studies have demonstrated the value of combination treatment in cancer cell eradication, two of which were conducted *in vivo*. We agree with Finan *et al.* (5) in their assessment of the potential value of HuR targeting as a complement to traditional cancer therapy. However, some important pre-clinical hurdles remain, most importantly cancer-specific delivery of HuR inhibitors. In this setting, substantial progress will still have to be made before clinical assessment is feasible. At this time, we commend Finan *et al.* (5) for keeping the spotlight on the translational aspects and the long-term clinical potential of HuR research in cancer chemotherapy and radiation.

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