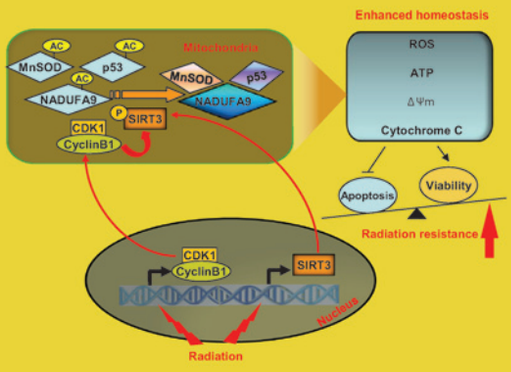
Molecular Cancer Therapeutics

Highlights

September 2015 • Volume 14 • Number 9

Selected Articles from This Issue



Targeting CDK1-Mediated SIRT3 Enhances Tumor Response to Radiotherapy

Liu *et al.* Page 2090

Tumor adaptive resistance to therapeutic radiation remains a barrier for further improvement of local cancer control. SIRT3, a member of the sirtuin family of protein deacetylases, prevents cell aging by promoting mitochondrial metabolic homeostasis. Liu and colleagues discovered that SIRT3 was transcriptionally regulated by NF-κB upon radiation, and its enzymatic activity was further enhanced via phosphorylation by mitochondria-localized Cyclin B1–CDK1 complex. Phosphorylation of SIRT3 by CDK1 was required for mitochondrial functions as well as cell survival upon therapeutic radiation shown by *in vitro* and *in vivo* radiation tests. Thus, targeting CDK1-mediated SIRT3 phosphorylation is a potential effective approach to enhance tumor response to radiotherapy.

HSP90 Is a Potential Therapeutic Target in Cholangiocarcinoma

Shirota *et al.* Page 1985

Cholangiocarcinoma is a highly malignant carcinoma with poor prognosis. The molecular chaperone, heat shock protein 90 (HSP90), plays an important role in the posttranslational maturation and activation of many critical oncogenic proteins. Here, Shirota and colleagues discovered that the expression of HSP90 was significantly associated with 5-year survival for intrahepatic and extrahepatic cholangiocarcinoma. Furthermore, HSP90 inhibitor NVP-AUY922 showed potent anti-cholangiocarcinoma effect *in vitro* and *in vivo*. These data indicate that HSP90 expression is an independent prognostic factor, and that NVP-AUY922 may be an effective treatment option for a subset of patients with cholangiocarcinoma.

Small Molecule MDM2 Inhibitor Augments Radiation Response

Werner and Huang *et al.* Page 1994

There is compelling clinical rationale to identify molecular targeting agents that enhance tumor response to radiation. Agents that target MDM2 and p53 are excellent candidates to modulate radiosensitivity. Werner, Huang, and colleauges demonstrate that AMG 232, a potent small molecule MDM2 inhibitor, augments radiation response across a spectrum of human tumors using *in vitro* and *in vivo* model systems. Combined AMG 232 and radiation treatment resulted in inhibition of DNA damage repair and induction of senescence, apoptosis, and autophagy. This work previews a promising combination treatment approach for tumors harboring functional p53.

Antitumor Effect of MEHD7945A in Combination with Radiation

Li and Huang *et al.* Page 2049

Increasing evidence implicates EGFR and HER3 in the modulation of tumor cell response to radiation. In this study, Li, Huang, and colleagues investigate the effect of a dual-specific antibody (MEHD7945A) that simultaneously targets EGFR and HER3 to radiation response in head and neck and lung cancers. The authors found that MEHD7945A enhanced radiation response in both *in vitro* and *in vivo* model systems, possibly through an increase of γ-H2AX associated with DNA double-strand breaks and a significant reduction of markers related to tumor proliferation and vasculature. These data suggest the potential value of MEHD7945A as a radiation sensitizer in future clinical trial designs.

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Mol Cancer Ther 2015;14:1973.