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Radioprotection and Molecular Therapy

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The dose limiting toxicities of Ionizing Radiation (IR) in radiosensitive normal tissues, such as bone marrow, intestine, and skin, precludes the delivery of curative or effective palliative doses of radiation in many cases. Despite of the intense research effort in the past to find new effective and well-tolerated radioprotectors, only one drug has been approved by FDA for this indication. One of the critical challenges for this research area is the inherent dilemma associated with radioprotection in radiation therapy, i.e., the need to protect normal tissues without diminishing the therapeutic effect of IR on cancer cells. An even more challenging task for researchers is to find radioprotectors that may simultaneously sensitize cancer cells to IR. Traditional radioprotective strategies rely upon counter measures that prevent IR injuries (such as free radical scavengers) or stimulating the post-IR growth with growth factors [1]. These approaches largely do not discriminate normal and cancer cells. The only currently FDA approved radioprotective drug, Amiphostine, mitigates radiation toxicities through mechanisms such as free radical scavenging and induction of intracellular hypoxia [2]. Although Amiphostine has not been reported to protect tumor cells from the effect of IR, other side effects associated with Amiphostine have precluded its wide clinical use [2].

It is apparent that to develop successful radioprotectors with strict selectivity on normal tissues, a better understanding of the radiobiology of cancer and normal cells is required. Of particular importance is the difference in the survival mechanisms between cancer and normal cells. A body of knowledge has accumulated in the recent past regarding different possible outcomes of irradiated cells, which include Cell Cycle Arrest (CCA), senescence, apoptosis, and reproductive cell death (mitotic catastrophe). These distinct events are activated by IR through a multitude of cell signaling factors, such as p53, chk1/2, ceremide, and NF-κB [3,4]. Although IR-induced DNA damage and ROS generation occur in all tissues, the signaling pathways that transduce these stresses are complex and often crosstalk to form a complex network. The presence and regulation of these pathways can have some important tissue-dependence, and many differ in important ways between normal and tumors [5,6]. For instance, p53, a key regulator in cell apoptosis and senescence to IR, is frequently mutated or deleted in cancer cells, hence contributing to cancer cells' resistance to radiation therapy [3].

There are important differences between the different post-IR events with regard to tissue physiological functions. Senescence, apoptosis, and mitotic catastrophe result in tissue deficit and dysfunction. In particular, these events lead to stem cell loss, and affect tissue regeneration after massive post-IR cell death. As a result, the most radiosensitive tissues are those that have a high turnover rate, and the acute post-IR symptoms occur within the turnover time. In contrast, reversible CCA blocks cells with DNA damage from entering mitosis and dying from mitotic catastrophe [7]. In doing so, CCA allows cells to repair DNA damage prior to reentering the cell cycle, and thereby increases cell survival and helps to maintain the stem cell dependent tissue regeneration. The protective role of CCA has been elegantly demonstrated in mice that have p53 deletion in intestinal epithelium, which prevents CCA in this tissue. Following lethal doses of subtotal body radiation, these mice have a much lower rate of survival than wild type control mice, whereas mice over expressing p53 have an increased survival rate [8,9]. IR-induced apoptosis in the intestinal epithelial cells with p53 deletion is decreased [9], and blocking apoptosis by epithelium-specific knockout of bax and bak1 did not affect mouse survival [8]. Therefore, the predominant effect of p53 activation in intestinal epithelium is CCA-mediated radioprotection. In contrast, in many cancer cells with wild type p53, the predominant effect of p53 activation is to sensitize cells to IR-induced senescence and apoptosis, whereas CCA is present but limited [10,11]. These findings therefore demonstrate some of the important differences between cancer and intestinal cells in their responses to IR even when both tissues have wild type p53, and suggest the potential utility of p53 activators for intestinal protection in patients receiving radiation therapy for treatment of abdominal and pelvic cancers. In consistence with this concept of CCA-dependent and tissue-dependent radioprotectors, there has been reports of CCA-inducing drugs (such as indomethacin [12,13] and Darinaparsin [14]) that radioprotect normal tissues, but cause predominantly apoptosis in cancer cells, and even sensitize cancer cells to radiation.

Given the protective role of CCA in post-IR cell survival, it is conceivable that agents that induce CCA would increase cell survival by enhancing post-IR CCA. Perhaps more importantly, as a signaling process that involves transactivation of downstream factors (such as p21, GADD45A, and 14-3-3sigma), it takes hours to over one day for full induction of CCA following IR. This induction process forms a window of time during which cells are not protected by CCA. Therefore, pre-IR induction of CCA may be necessary for optimal radioprotection. In support of this concept is the recent observation that mice treated with inhibitors of CDK4/6 had significantly improved post-IR hematopoietic functions due to the CCA protection of hematopoietic progenitor/stem cells, and this protection was most evident when the drugs were administered at 28 hours prior to IR [15]. Importantly, cancer cells that were Retinoblastoma protein (Rb) null, a downstream target of CDK4/6 that inhibits cell cycle (G1/S) progression, were not protected from the IR effect. Since Rb is often mutant in various cancers, this finding provides a novel radioprotective approach to enhance the therapeutic index of radiation therapy of Rb mutant or null cancers.

CCA is under the control of a multitude of signaling factors and associated pathways, such as CDK4/6 inhibitors (such as p15, p16,

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p18, and p19), ATM (or ATR)/p53/21 pathways, CDK4/6/Rb/E2F, and oncogene MYC. Many of these factors (such as p53 and Rb) are defective in cancer cells due to mutation or epigenetic inhibition, and therefore, may be candidates of pharmacologic targets for selective induction of CCA in normal cells. These drugs are expected to induce a transient and reversible CCA that lasts for days until the completion of post-IR DNA damage repair. Ideally, the patients will be treated with IR at the peak of the drug-induced CCA. Targeting therapy based on the molecular difference between normal and cancer cells is a promising novel strategy for selectively protecting normal tissues from the effects of IR without radioprotecting tumor cells.

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