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Tumor Cell Recovery from Senescence Induced by Radiation with PARP Inhibition

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Abstract

Inhibitors of poly(ADP-ribose) polymerase (PARP) are clinically used as single-agent therapy for tumors with BRCA1 or BRCA2 mutations. One approach to expanding the use of PARP inhibitors to a wider range of tumors is to combine them with cytotoxic chemotherapy or radiotherapy. Preclinical studies in experimental animals and tumor cells in culture indicate that PARP inhibition modestly sensitizes most tumor cells to ionizing radiation. Studies of cell behavior after these combined treatments show that radiosensitization is manifested predominantly in an increase in prolonged growth arrest and senescence, with little or no contribution from apoptosis. The secretory phenotype associated with senescence can target these tumor cells for immune surveillance, and therefore increased senescence can effectively contribute to tumor control. However, the possible recovery of senescent cells and re-entry into cell cycle after prolonged arrest also needs to be considered. Such recovery could lead to tumor recurrence, yet may not be reflected in short-term assays commonly used to assess radiosensitization.

PARP AS A TARGET FOR RADIOSENSITIZATION

In mammalian cells, DNA polymerase beta (Polβ) and poly(ADP-ribose) polymerase (PARP) have been implicated in base excision repair (BER) and single-strand break (SSB) repair. Polβ$^{-/-}$PARP-1$^{-/-}$ double-mutant mice are viable, but appear to be highly sensitive to DNA-alkylating agents or gamma radiation (1), raising the possibility that BER, and PARP in particular, can be targeted for chemo/radiosensitization of cells. The PARP enzyme acts as a “molecular sensor” to identify DNA SSBs. If PARP activity is compromised, SSBs

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Authors' note. One of the few papers in the literature that appears to make a compelling case for therapy-induced senescent cells activating an immune response is by Meng et al., where senescence was induced by radiation (12 Gy) + the PARP inhibitor, veliprab, in the syngeneic B16SIY mouse melanoma cell line. Depletion of CD8 positive T cells markedly reduced the effectiveness of the combination treatment when measuring tumor volume over a period of 40 days (Supplementary Fig. S1). However, somewhat paradoxically, the T-cell depletion also suppressed expression of the beta galactosidase marker and senescent morphology in the tumor cells.

Meng Y, Efimova EV, Hamzeh KW, Darga TE, Mauceri HJ, Fu YX et al. Radiation-inducible immunotherapy for cancer: senescent tumor cells as a cancer vaccine. Mol Ther 2012; 20:1046–55.

collapse replication forks, which results in the formation of double-strand breaks (DSBs) (2), the most dangerous cytotoxic lesions. In recent years, there has been extensive interest in the possibility of enhancing the response to cancer therapies through the use of PARP inhibitors, a class of agents that interfere with BER and therefore with DNA repair (2–5). The development of PARP inhibitors as agents to treat tumors with certain sensitizing genetic lesions is based on the idea that cells with defects in DSB repair, such as BRCA-deficient cells, are more dependent on PARP and BER to maintain genomic integrity (6). The concept of "synthetic lethality", first articulated by Dobzhansky in 1946 as a situation in which mutations in two genes have little or no effect individually but the combination results in cell death, is thus well illustrated by PARP inhibition in BRCA-deficient cells (7). This synthetic lethal approach has been validated in studies that show striking single-agent activity of PARP inhibitors in preclinical models of BRCA1 and BRCA2 inactivation *in vitro* and *in vivo* (2, 3). In patients with hereditary BRCA mutations, PARP inhibitors would be highly selective for tumor tissues (expected to be completely BRCA deficient) compared with normal tissues (expected to be heterozygous at the BRCA locus). In addition, the observation that cells deficient in other critical homologous recombination (HR) proteins are sensitive to PARP inhibitors provides the rationale for testing PARP inhibitors in other cancers (8). For instance, with the recent finding that the tumor suppressor PTEN is important for expression of the repair protein RAD51, it was shown that PTEN-deficient cells are exquisitely sensitive to PARP inhibitors, providing a rationale for ongoing studies of PARP inhibitors in PTEN-deficient tumors (9).

Initially, the toxicity of PARP inhibitors to HR-deficient cells was proposed to reflect an accumulation of SSBs due to lack of PARP-dependent SSB repair, followed by their conversion during S phase into DSBs that were not rejoined due to lack of homologous recombination (2, 3). It is now apparent that the mechanism is more complex, as maximal toxicity requires both PARP and the non-homologous end joining (NHEJ) DSB repair pathway. A comparison of the potencies of various PARP inhibitors suggests that persistent trapping of PARP on damaged DNA is more important than mere inhibition of SSB repair (10–12). Further, inappropriate channeling of the replication-associated DSBs into NHEJ, rather than simply an increase in their persistence, appears to account for most of the toxicity (13–16). Figure 1 show a diagrammatic summary of the primary concepts presented in this review.

While there is evidence that PARP inhibitors alone might have utility against tumors that are intrinsically DNA DSB repair deficient, the focus of this review is on the literature describing the interaction of PARP inhibitors with radiation treatment. Specifically, we analyze the recent literature to address whether this treatment strategy results in growth arrest and/or cell death and the implications of those outcomes for clinical use of these agents.

INCREASE IN DNA DAMAGE

One fundamental underlying premise for the incorporation of PARP inhibitors into radiation therapy is that while tumor cells have the capacity to repair the bulk of radiation-induced DNA damage alone, inhibition of PARP allows SSBs to progress to DSBs. These DSBs are

largely replication-dependent, as reflected in the reported finding that blocking replication largely eliminates PARP inhibitor-mediated radiosensitization of most cells (17, 18). The downstream consequences, including modes of cell death or growth arrest, could thus differ substantially from those of DSBs induced directly by radiation alone. For example, if, as in BRCA1-deficient cells, these replication-associated DSBs are misjoined by NHEJ, γ-H2AX foci would presumably disappear as free DSB ends are eliminated, yet cryptic potentially lethal damage would remain and its lethality would not be expressed until the cell attempts to enter mitosis. Moreover, production of these DSBs will only continue during the time PARP inhibitors are still present, which is typically limited to 24 h or less due to their toxicity.

Studies that have addressed the impact of PARP inhibitors with radiation treatment on DNA damage have, not surprisingly, provided clear evidence of increased damage; this result has generally been based on γ-H2AX foci formation and/or the comet assay (19–23). While most published studies have not attempted to actually distinguish between the induction of DNA SSBs and DSBs, the detection of γ-H2AX foci that are not resolved is generally considered to be a reliable indicator of unrepaired DSBs (24, 25). Moreover, neutral comet assays, which provide a more direct and specific measure of DSBs than γ-H2AX foci, also indicate that PARP inhibition increases radiation-induced damage (18). Nevertheless, it might be relevant to monitor the DNA damage induced by radiation with PARP inhibition for extended periods of time to reliably establish that the breaks are prolonged and essentially irreparable. This suggestion relates to the fact that, as indicated below, the incorporation of PARP inhibition with radiation has generally not demonstrated cell killing that might be expected with unrepaired DNA DSBs; instead, studies have shown that this experimental strategy tends to lead to inhibition of tumor cell proliferation and, in a number of studies, to the induction of a state of senescence (18, 26–28).

Our laboratories have confirmed that PARP inhibitors do not increase radiation-induced apoptosis in HCT-116 colon carcinoma cells, but instead markedly enhance growth arrest and senescence (18). In this context, a tumoristatic effect could be considered a less desirable outcome than a tumoricidal effect since we have further determined that the growth arrest induced by radiation with PARP inhibition is transient (as is also the case with that induced by radiation alone) (18) in at least a fraction of the cells. Although recovery of the culture as a whole could reflect outgrowth of a few undamaged or lightly damaged cells rather than proliferation of transiently arrested, senescent cells, we have succeeded in separating from the treated cultures β-galactoside-expressing cells that appear morphologically senescent, yet resume proliferation after a short delay (18).

INDUCTION OF APOPTOSIS

Because cell death is an expected effect of combined radiation and PARP inhibition treatment, given that unresolved DNA DSBs are being generated, it is logical to evaluate the promotion of apoptosis upon treatment. Some published studies of apoptosis induction by radiation alone as well as combined radiation and PARP inhibition treatment have relied on surrogate markers, particularly the cleavage of caspases, which does not necessarily represent a direct measurement of the actual extent of apoptosis in the irradiated tumor cell

population. This would require assessment by such approaches as FACS analysis using propidium iodide/annexin or TUNEL assay. We have identified only one study where there was a significant increase in apoptosis from radiation treatment alone as well as from radiation treatment combined with a PARP inhibitor, but in only one of four cell lines examined (22). Otherwise, even in those studies demonstrating a statistically significant increase in apoptosis for radiation treatment with PARP inhibitors compared to radiation treatment alone, the extent of apoptosis has generally not been sufficient to account for the degree of radiosensitization observed (29–32). Furthermore, studies have rarely included complementary experiments where pharmacological or genetic suppression of apoptosis induced by radiation treatment with PARP inhibition was demonstrated to attenuate or reverse radiosensitization. Our own recent studies support the conclusion that neither radiation alone nor radiation with PARP inhibition results in a significant degree of apoptosis, which we have confirmed by demonstrating that radiosensitization is not altered by caspase inhibition (18).

GROWTH ARREST VERSUS CELL DEATH

In the reviewed literature where tumor cells were treated with radiation combined with PARP inhibitors, either in cell culture studies or in tumor-bearing animal experiments, the primary effect of the combination treatment almost uniformly reflected growth arrest rather than cell death (18, 19, 21, 22, 27–29, 33–35). Consequently, it does appear that modes of cell death such as apoptosis or necrosis may play, at most, only minor roles in the overall response to the combination treatment. In this context, when clonogenic assays are utilized to assess the effect of combined radiation and PARP inhibition, it should be recognized that growth arrest, if sufficiently prolonged, would be interpreted as reproductive death and would be indistinguishable from apoptosis or other modes of actual cell disintegration. Similarly, in assays where cell number is monitored in culture or tumor volume is measured *in vivo*, a prolonged delay in growth, followed by proliferation, is often observed (18, 19, 21, 22, 27–29, 33–35). However, it is generally unclear whether outgrowth resulted from a large fraction of cells that re-entered cell cycle after a long period of arrest, or from a minute fraction of cells that continued to proliferate with little or no arrest, and rarely has any attempt been made to distinguish between these two scenarios.

SENESCENCE

Given that the primary outcome of treatment with radiation and PARP inhibitor appears to be the promotion of a state of growth arrest as opposed to cell death, it is reasonable that, as reported in a number of studies, radiosensitization might be a consequence primarily of an increase in the extent of senescence (18, 27, 28). This outcome could also be a direct consequence of the fact that senescence has been shown to be the primary response to clinically relevant doses of radiation (36, 37). Again, in our own recent work combining radiation with PARP inhibitors, in HCT-116 colon carcinoma cells we observed a pronounced increase in the extent of senescence, as determined by β-galactosidase staining, release of IL-6 and morphological alterations (18).

As (chemotherapy and radiation induced) senescence has traditionally been considered an irreversible form of growth arrest (37), cells irradiated in the presence of a PARP inhibitor could prove to be reproductively dead, which would be a desirable outcome in cancer treatment even if the tumor cells do not formally die by e.g., apoptosis, necrosis or mitotic catastrophe. Furthermore, senescent cells have been reported to secrete factors that activate an immune response that is ultimately the basis for their recognition and elimination (38–40). Finally, it is possible that prolonged and functionally irreversible senescence may ultimately be succeeded by some other form of cell death, such as apoptosis, even if the latter is not a primary response to the combination treatment.

An alternative view that we recently reported on (41) is that senescence may actually prove to be reversible, even if only for a small subpopulation of tumor cells. In this scenario, senescent cells may actually not be functionally and reproductively dead but only in a prolonged state of (reversible) growth arrest, which is in some ways reminiscent of the stem cell population. At some subsequent time, and under the influence of an as yet undefined stimulus, the cells could recover proliferative function, allowing for resurgence of the tumor (and disease recurrence).

Sabisz and Skladanowski (42) reported in their studies that using A549 non-small cell lung cancer cells that regrowth from drug-induced premature senescence is associated with the presence of stem cells. In addition, Salmina *et al.* (43) present data in support of the premise that radiation induces senescence and a transient polyploid state, where polyploid tumor cells overcome senescence by upregulation of OCT4 and NANOG, characteristic of germ cell lines. Finally, studies by Chitikova *et al.* (44) using rat embryonic fibroblasts, also support the possibility that reversion of senescence is associated with polyploidy and expression of the stem cell marker OCT3/4.

If, in fact, senescent cells are actually in a state of pseudodormancy (either at the primary tumor site or at some distant site to which the cells have metastasized), then senescence could instead represent a pathway whereby tumor cells are able to escape the potential cytotoxic effect of radiation. Our recent work is consistent with the premise that senescence induced by either radiation alone or in combination with PARP inhibition is reversible, a finding that raises reservations as to the potential utility of this therapeutic strategy.

AUTOPHAGY

Studies from our laboratory as well as those by other research groups have demonstrated that when senescence occurs, it is often preceded by autophagy; that is, autophagy has been shown to accelerate the induction of senescence (by oncogenes and by chemotherapy), although it is also clear that senescence can occur even when autophagy has been abrogated (41). Whether this relationship also exists for radiation has not been fully resolved. Nevertheless, autophagy can actually be considered as a “first responder” to different forms of stress, such as that which occurs under conditions of nutrient deprivation, but also consistently in response to ionizing radiation. Given the evidence for the increased senescence induced by radiation with PARP inhibitors, it appeared likely that the radiosensitization observed under these experimental conditions would also be associated

with the induction of autophagy. Since autophagy is generally considered to be a transient and reversible phenomenon, if autophagy is the mechanism of radiation sensitization by PARP inhibition, then the sensitization may prove to be transient as well, contributing to and/or facilitating proliferative recovery of the tumor cells from the accompanying state of senescence.

In our recently published work, we did, in fact, find that induction of autophagy correlated with the extent of senescence as well as the persistence of DNA damage based on γ-H2AX foci formation (18). Unexpectedly, however, inhibition of autophagy utilizing either pharmacologic or genetic approaches failed to alter the extent of radiosensitization by the PARP inhibitors, ostensibly via the promotion of senescence. These studies demonstrated dissociation between the induction of autophagy and senescence in response to radiation and unequivocally indicated that autophagy was not responsible for radiosensitization by PARP inhibition.

POTENTIAL CLINICAL RAMIFICATIONS

As indicated above, if the inclusion of PARP inhibitors with radiation in cancer therapy fails to result in tumor cell death, but instead leads to a state of growth arrest (associated with senescence), the critical question becomes whether the growth arrest is sustained and irreversible or transient and reversible. If the former, then having reproductively dead tumor cells is an appropriate and useful clinical outcome. If the latter, while this treatment approach might be useful in the short term by suppressing tumor growth initially, it might be lacking the decisive outcome that would also prevent (or at least delay or attenuate) reemergence of the tumor cell population that would otherwise lead to disease recurrence. Clinically, this could be detrimental to the long-term survival of the patient, since recovery of self-renewal capacity could be a precursor to active disease recurrence.

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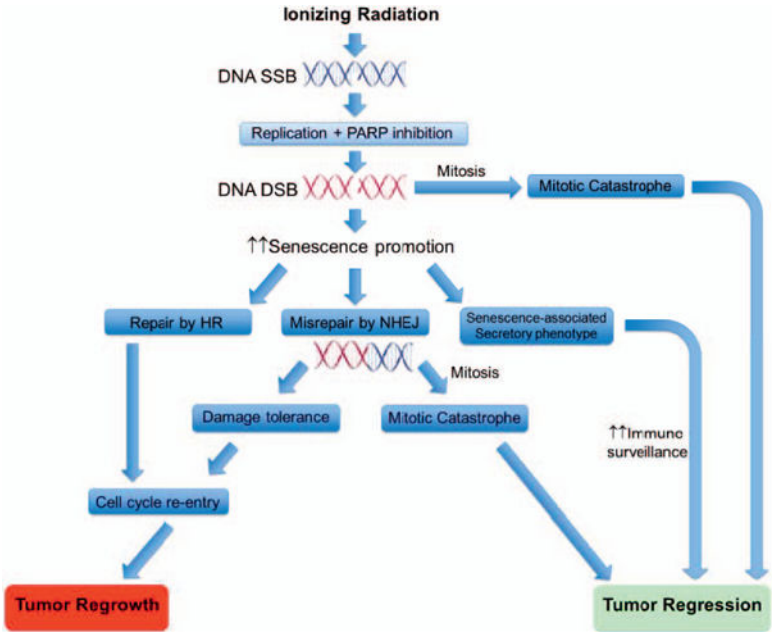

FIG. 1.

Divergent outcomes of radiation-induced senescence and its enhancement by PARP inhibitors. Senescence, at least initially, is maintained by signaling from unrepaired DSBs. PARP inhibitors block SSB repair, thus increasing the chances of collision with a replication fork to generate additional DSBs. PARP inhibition also promotes misjoining of these DSBs by NHEJ, which may be undetectable and inconsequential until the cell attempts to divide, at which point dicentric and other aberrant chromosomes could induce mitotic catastrophe. Alternatively, senescence, through the senescence-associated secretory phenotype, may promote cell death by triggering immune surveillance. However, some senescent cells may ultimately repair persistent damage or develop tolerance to it, and again begin to proliferate.