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Using immunotherapy to boost the abscopal effect

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Abstract

More than 60 years ago, the effect whereby radiotherapy at one site may lead to regression of metastatic cancer at distant sites that are not irradiated was described and called the abscopal effect (from 'ab scopus', that is, away from the target). The abscopal effect has been connected to mechanisms involving the immune system. However, the effect is rare because at the time of treatment, established immune-tolerance mechanisms may hamper the development of sufficiently robust abscopal responses. Today, the growing consensus is that combining radiotherapy with immunotherapy provides an opportunity to boost abscopal response rates, extending the use of radiotherapy to treatment of both local and metastatic disease. In this Opinion article, we review evidence for this growing consensus and highlight emerging limitations to boosting the abscopal effect using immunotherapy. This is followed by a perspective on current and potential cross-disciplinary approaches, including the use of smart materials to address these limitations.

Radiotherapy is a crucial part of the cancer treatment armamentarium[1]. However, radiotherapy is limited by normal tissue toxicity, and it is generally prescribed for treatment of localized tumours. Recent technological advances have focused on addressing the toxicity limitation, with advanced radiotherapy modalities aimed at achieving greater therapeutic effectiveness (that is, greater tumour cell killing with less normal tissue toxicity and less time under treatment compared with previous approaches)[2,3]. These advanced radiotherapy technologies and approaches include intensity-modulated radiation therapy (IMRT), image-

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guided radiotherapy (IGRT), high dose rate (HDR) brachytherapy, stereotactic ablative body radiotherapy (SABR), proton therapy and carbon ion radiotherapy.

For example, IMRT allows the creation and delivery of precise radiation doses that conform to the target tumour while minimizing the dose delivered to neighbouring healthy tissues[2]. The increase in conformality and tighter treatment margins engendered an increased need for accuracy to circumvent the potential to miss the tumour owing to organ motion and/or variability in patient setup. IGRT works to assuage this need by allowing imaging of the target immediately before or even during treatment to guide a more geographically precise delivery of the dose[2]. Improved accuracy and greater understanding of radiation biology have in turn made dose escalation feasible, and this has allowed for further improvement in the therapeutic ratio for several tumour sites. The advent of SABR is partly a consequence of this, allowing for hypofractionated treatment with precise delivery of very high radiotherapy doses with short overall treatment times. Other advanced radiotherapy approaches employ high-energy protons or carbon ion beams. The main advantage of therapy with such charged particle beams is the ability to more precisely localize the radiation dosage[4]. Intra-operative radiotherapy is another advanced modality where a concentrated dose of radiotherapy is administered to a tumour bed during surgery to kill any residual cancer cells after the tumour has been removed[4]. In addition to advanced external beam radiotherapy modalities, HDR brachytherapy has been developed to allow short-distance radiotherapy of cancers, including skin, cervical, prostate and breast cancers, with minimal toxicities to healthy tissue. With these remarkable developments, radiotherapy can currently provide benefit in the treatment of over 50% of patients with cancer when used alone or in combination with other treatments such as surgery (for example, intra-operative radiotherapy) or chemotherapy (chemoradiotherapy)[1].

While advances in radiotherapy technologies have largely focused on minimizing toxicity and improving the therapeutic ratio when treating localized tumours, there have also been recent developments relevant to the abscopal effect that provide a promising frontier in extending the use of radiotherapy to treatment of both localized and metastatic disease. The term ‘abscopal’ was first introduced in 1953 by Mole[5,6] to describe an immune-mediated response to radiation by tumour cells located distant from the irradiated site[5–8]. Over the years, the rare abscopal effect has been reported for several cancers, including melanoma[9], renal cell carcinoma[10], breast cancer[7], hepatocellular carcinoma[11] and other metastatic solid tumours[12]. A recent review estimates that there have been 46 case reports of the abscopal effect from radiotherapy alone between 1969 and 2014 (REF. 13). There is now a growing consensus from many studies indicating that combining radiotherapy with immunotherapy provides an opportunity to boost abscopal response rates. This Opinion article examines the growing evidence behind this consensus and discusses some of the emerging limitations, as many institutions worldwide are increasingly testing this combination strategy. This is followed by a perspective on current and potential cross-disciplinary approaches, including the use of smart biomaterials to address these limitations and extend this benefit to more patients.

Boosting the abscopal effect

Following the first description of the abscopal effect[5], initial case reports were recorded for melanoma and papillary adenocarcinoma when using radiotherapy alone in 1973–1975 (REFS 14,15) (FIG. 1). In 1979, it was shown that cell killing by ionizing radiation contains an immune-mediated component, with the degree of integrity of the host immune system determining the radiosensitivity of a tumour[16]. In a syngeneic mouse model of fibrosarcoma, the radiotherapy dose required to control tumour growth was determined in mice that were T cell competent compared with those that were T cell depleted. It was found that the average radiation dose required to control tumour growth in 50% of the mice was lower for the T cell-competent mice than for the T cell-deficient mice. In addition, the likelihood of developing metastasis in T cell-deficient mice was increased, demonstrating an association between immune status, local response to radiotherapy and metastasis.

Since then, several studies have demonstrated that there is a direct connection between the abscopal effect and mechanisms involving the immune system[17–19]. For example, in a bilateral syngeneic mouse model of breast cancer, treatment with a combination of radiotherapy on one flank and systemic delivery of the immunoadjuvant FMS-like tyrosine kinase receptor 3 ligand (FLT3L) led to a significant growth delay of the irradiated tumour as well as the non-irradiated tumour compared with untreated control mice. This abscopal effect was dependent on the presence of T cells[17], suggesting that radiotherapy can increase the immunogenicity of a tumour and hence can be used to improve immunotherapy effectiveness or vice versa. Regarding the latter, results indicating that the use of immunotherapy could help in boosting the abscopal effect during radiotherapy were reported by a number of preclinical studies[20–25] (TABLE 1). These studies also examined different schedules for fractionation and dosing as well as different combinations of radiotherapy and immunotherapy.

In a clinical trial that tested radiotherapy in combination with an immunoadjuvant, granulocyte–macrophage colony-stimulating factor (GM-CSF), for the treatment of multiple types of confirmed solid metastatic cancer, an abscopal response occurred in approximately 30% of patients[12]. In a different study on melanoma, radiotherapy in combination with an immunotherapy comprising antibodies against cytotoxic T lymphocyte-associated antigen (CTLA4) and programmed cell death 1 ligand 1 (PDL1) increased abscopal response rates[26]. Currently, many ongoing studies are investigating the combination of radiotherapy and immunotherapy to improve treatment outcomes for different indications[27].

Abscopal response mechanism

Although the biological mechanism underlying the abscopal effect is yet to be fully understood, several studies have helped to elucidate how combining radiotherapy with immunotherapy would boost this effect. When a tumour is irradiated, the cellular stress or injury in the tumours may lead to the liberation of neoantigens, here referred to as tumour-associated antigens (TAAs), in the context of necrotic and apoptotic tumour cells and debris. A substantial increase in the number and diversity of TAAs can stimulate a tumour-specific immune response, with TAAs engulfed by antigen-presenting cells (APCs) and then presented to $CD8^+$ T cells. The $CD8^+$ T cells can then recognize and attack both the primary

tumour and metastatic disease[28] (FIG. 2). Irradiated tumour cells may also release cellular danger-associated molecular patterns (DAMPs) and cytokines that enhance traffic of immune cells[29]. Collectively, these events promote tumour cell elimination by primed $CD8^+$ T cells[30,31].

The rarity of the abscopal effect suggests that even primed antitumour $CD8^+$ T cells are unable to overcome the suppressive effect of the tumour microenvironment[29,30]. Immunosuppressive cytokines released by tumours, such as transforming growth factor-β (TGFβ), and surface receptors expressed on T cells, such as CTLA4, can inhibit the function of T cells. M2 macrophages, myeloid-derived suppressor cells (MDSCs) and immature dendritic cells (DCs) may also suppress T cell functions[29,30]. Tumour elimination could be further inhibited by $CD4^+$ T cells with regulatory function (also called regulatory T (T_{reg}) cells).

For a range of tumour types, preclinical studies (TABLE 1) consistently show that combining radiotherapy with immunotherapy substantially improves abscopal response rates compared with using radiotherapy or immunotherapy alone. From these studies, it is also evident that different immunotherapeutic agents can boost abscopal responses by targeting different aspects of the immune-mediated response[9,17,27]. For example, FLT3L can be used to recruit and stimulate APCs[17,18,32], anti-CD40 can be employed to increase activation of APCs[33], and anti-CTLA4 or antibodies against programmed cell death protein 1 (PD1) can act as immune checkpoint inhibitors, increasing the T cell activity directed against tumour cells[23,26,34].

Abscopal response factors

Preclinical studies indicate that appropriate timing, dosage and combinations are likely crucial to the success of combining radiotherapy and immunotherapy. Many studies have reported substantial abscopal responses when administering immunotherapy after radiotherapy[17,18,20–26,33–40]. However, the optimal timing is not clear. In one study on colorectal carcinoma, anti-CTLA4 was effective in generating abscopal responses when given before radiotherapy[36], which is explained by the depletion of T_{reg} cells in response to anti-CTLA4; meanwhile, in another study using the syngeneic mammary carcinoma 4T1 model, anti-CTLA4 administered after radiotherapy generated substantial abscopal responses[20]. Most ongoing trials utilize concurrent immune checkpoint blockade with radiotherapy[27]. More preclinical studies and clinical trials investigating the timing for different immunotherapy and tumour types will further clarify the issue of optimal timing.

On the basis of the preclinical studies (TABLE 1), the optimal dosing and fractionation strategy for each cancer type has not been determined yet, as both single and fractionated radiotherapy doses have been reported to boost abscopal responses when combined with different immunotherapies[23,34,41]. For example, a preclinical study combining radiotherapy with anti-CTLA4 for breast and colon cancer models concluded that 3 fractions of 8 Gy and 5 fractions of 6 Gy are superior to a single ablative dose of 20 Gy (REF. 23). However, other work in breast and colon cancer models has also shown synergy when using a single fraction of radiotherapy with other immunotherapies[18,25,26,33,34,36,39,40,42,43].

Multiple preclinical studies have investigated different dose and fractionation regimens in colon cancer (MC38 and colon26)[23,42], breast cancer (TUBO, 67NR, TSA and FM3A)[17,23,34,40], squamous cell carcinoma (SCCVII)[21], sarcoma (MethA)[42] and large-cell lung carcinoma[42]. Generally larger doses per fraction were associated with abscopal effects. An optimal dose range is likely to exist, below which immune stimulation might be suboptimal and above which immunosuppression prevails[44]. Seminal studies using breast cancer models showed that the DNA exonuclease 3 repair exonuclease 1 (TREX1) inhibits immune activation[45,46]. TREX1 is induced by radiation doses above 12–18 Gy in different colorectal carcinoma and breast cancer cell lines, and it attenuates immunogenicity by degrading double-strand DNA that accumulates in the cytosol upon radiation[47]. Further investigations of dosage and combinations of radiotherapy with immunotherapy are needed to determine the optimal thresholds or range[48]. Currently, a wide range of dose and fractionation schedules is being utilized in clinical studies of metastatic tumours. A recent review highlights the ongoing clinical trials testing these different combinations of radiotherapy with immunotherapy[27].

Many studies investigating the abscopal effect have used bilateral subcutaneous tumour mouse models, in which the treated tumours on one flank of the animals represented primary tumours in patients and the untreated control tumours on the other flank of the animals represented metastasis[17,20–23,26,33–38]. Clearly, these subcutaneous tumours are a limited recapitulation of the tumour microenvironments of primary and metastatic tumours in patients. Still, these studies have advanced the understanding of the abscopal effect, and some results have been confirmed in clinical trials. For example, in one recent study[26], patients with melanoma received hypofractionated radiotherapy targeting a single index lesion, in combination with systemic delivery of anti-CTLA4. When unirradiated lesions were analysed, this treatment showed a partial response as best response in 18% of the patients. When mice with bilateral subcutaneous melanoma tumours received radiotherapy on one flank and systemic delivery of anti-CTLA4, a response rate of about 17% was observed in unirradiated tumours of the other flank, consistent with the clinical trial outcomes. Nevertheless, relatively higher rates of abscopal response or efficacy in mice treated with the combination therapy compared with single-therapy-treated mice or untreated controls observed in many other preclinical studies[17,23,33,40–42] have not been confirmed in clinical trials. Additional investigations in animal models that are more representative of patient tumours, such as orthotopic tumour mouse models, would be valuable (reviewed in REF. 49).

Limitations

A number of limitations have emerged from the available experimental and clinical data testing the combination of radiotherapy and immunotherapy. One obvious limitation is the prevailing lack of sufficient understanding of the mechanism underlying the abscopal effect. A greater understanding is needed to best leverage the abscopal effect and benefit a larger proportion of patients.

Immunosuppression

Even when combining radiotherapy with immunotherapy, the development of a robust abscopal response can still be stifled by the widespread presence of immunosuppression or tolerance at tumour sites. Low immunogenicity of tumour antigens at the local site of irradiation and the prevalence of immunosuppressive cells (for example, MDSCs and T_{reg} cells) and/or of immunosuppressive cytokines (for example, interleukin-10 (IL-10) and TGFβ) work together to limit the abscopal response elicited even by combination approaches. An excellent example of this is a recent study in melanoma combining radiotherapy with anti-CTLA4 that led to a limited abscopal effect, as described above[26]. This study found that radiotherapy and anti-CTLA4 led to upregulation of PDL1 on tumour cells, mediating T cell exhaustion and explaining at least in part the limited abscopal responses observed. Immune-mediated abscopal effects are also likely to be affected by such factors as the patient's degree of myelosuppression, overall tumour burden and the neutrophil:lymphocyte ratio in addition to the patient's prior exposure to radiotherapy or cytotoxic chemotherapy[27]. The depletion of immune cells, or lymphopaenia, observed in most patients with cancer is likely to decrease the chances of an effective immune response. Hypoxic regions within tumours can also contribute to immunosuppression[50]. For example, chemokines induced by tumour-associated hypoxia enable recruitment of immunosuppressive T_{reg} cells, as shown in ovarian cancer[51]. Hypoxia is also known to alter the capacity of APCs in antigen presentation and can make tumour cells more resistant to T cell-mediated killing, as shown in a murine model of breast cancer[52]. In general, any factors that suppress the immune system may hamper the development of robust abscopal responses.

Toxicities

While rational combinations of radiotherapy and immunotherapy could overcome immunosuppression and lead to vigorous antitumour T cell responses[14,18], the systemic and overlapping toxicities from such a combination could be a substantial obstacle[30,53]. Immune-related adverse events that can be severe or life-threatening have been seen following treatment with immunomodulatory agents such as ipilimumab and anti-PD1 antibodies[53,54]. Combining radiotherapy with immunotherapy, which affects different steps in the immune response, might increase the likelihood of these adverse events[48]. Immune-related adverse events of concern include dermatological, gastrointestinal, hepatic, endocrine and other, less common inflammatory events[55]. For example, early studies combining radiotherapy with interferon-α (IFNα) in pancreatic cancer were promising[56], but the phase II trial showed unacceptably high rates of toxicity using this treatment[57].

Unfortunately, preclinical studies investigating toxicities do not adequately predict the range of pathology that is observed in humans. For example, hypophysitis, a somewhat common side effect of ipilimumab, was not anticipated from experimental studies in mouse models[48,49]. Initial clinical experience suggests that routine palliative radiotherapy is likely to be well tolerated in the setting of anti-CTLA4 and anti-PD1 therapy[58], and ongoing clinical trials for different indications[27] will help provide the needed additional prospective data on toxicities and efficacy.

Overcoming immunosuppression

Strategies under investigation for improving outcomes when combining radiotherapy with immunotherapy include promoting cross-priming of tumour-specific $CD8^+$ T cells, stimulating the immune effector function of T cells primed by radiotherapy and neutralizing the immunosuppressive effects of the tumour microenvironment[30]. Ongoing studies are investigating optimal timing, dosage and combinations with different immunotherapeutic agents relevant to these strategies[26,27,47,59]. As an example, an approach to overcome immunosuppression is to use multiple immunotherapeutic agents, as highlighted in a recent melanoma study describing PDL1-mediated immunosuppression when tumours were treated with a combination of radiotherapy and anti-CTLA4, as described above, and employing a combination of anti-CTLA4 and anti-PDL1 to overcome this immunosuppression[26]. The study showed that radiotherapy increases the diversity of the T cell receptor repertoire of intratumoural T cells and that anti-CTLA4 inhibits immunosuppressive T_{reg} cells, while the addition of PDL1 blockade reverses T cell exhaustion to mitigate the decrease in the $CD8^+$ T cell:T_{reg} cell ratio and further encourage oligoclonal T cell expansion. Hence, radiotherapy combined with immunotherapeutic agents that have different mechanisms of action might boost abscopal response rates.

Intratumoural administration of immunotherapeutic agents in combination with radiotherapy has been shown to be effective in overcoming immunosuppression in lymphoma[60,61]. This is particularly relevant when using immunotherapies that target specific immune cells within the tumour microenvironment; hence, it may be preferable to deliver these agents locally into the tumour rather than systemically. Local delivery of the immunotherapeutic agent allows for much higher or more potent concentrations in the tumour microenvironment than via systemic delivery. In one example of intratumoural delivery, toll-like receptor (TLR) agonists were administered to generate potent abscopal responses in combination with low-dose radiotherapy[62]. In particular, 15 patients with non-Hodgkin lymphoma were treated with radiotherapy (2×2 Gy) at a single site with concomitant intratumoural administration of 6 mg synthetic CpG oligodeoxynucleotides, which act as a TLR9 agonist. The results after 12 weeks showed objective abscopal responses at distant non-treated sites in 4 of the 15 patients[62].

Strategies that can minimize hypoxia in the tumour microenvironment could also help overcome immunosuppression and radioresistance. For example, hypoxia-inducible factor modulators such as dimethyloxalylglycine (DMOG)[63] can inhibit immunosuppressive hypoxic signalling[50,63]. Furthermore, the use of charged particle radiotherapy might promote uniform cell killing in tumours that have heterogeneous radiosensitivity as a result of intermittent normoxic and hypoxic regions within the tumour. This approach takes advantage of high linear energy transfer (LET), which uses dense ionization tracks that inflict direct DNA damage, showing high biological effectiveness because of less dependency on oxygenation of tissues[64]. Increased generation of neoantigens by higher LET radiation may also increase the potential for generating an abscopal response.

Most reported cases of the abscopal effect occur in immunogenic tumours[7,9,65,66]. A high level of tumour immunogenicity is important for favourable treatment outcomes, and

treatment strategies should focus on developing combination therapies that increase immunogenicity through increasing immunogenic cancer cell death[67–69]. Such strategies aim at inducing a specific level of cell death that can generate sufficient neoantigens, and specific danger signals, to help overcome the condition of local immunosuppression which is characteristic of established tumours[70]. Studies indicate that tumour immunogenicity may be increased by the use of protons or carbon ion radiotherapy and α-particles, which are considered to have high LET[71].

The combination of radiotherapy with anticancer vaccines and checkpoint inhibitors has been shown to overcome immunosuppression and to increase response rates in preclinical models[72]. For example, a promising strategy involving sequential combination of radiotherapy, vaccination and anti-PDL1 in a mouse model of pancreatic cancer converts non-T-cell-inflamed cancers into T cell-inflamed cancers and mediates regression of established pancreatic tumours[72]. Other groups are also investigating the use of irradiated tumour cell vaccines as a strategy to boost therapeutic outcomes[73–75]. In one such study using a B16 melanoma model[74], it was shown that irradiated tumour cells that were genetically modified to express murine GM-CSF stimulated potent, long-lasting and specific antitumour immunity. The study demonstrated the potential for clinical use of genetically modified tumour cells as anticancer vaccines. The treatment of tumour-bearing mice with radiotherapy combined with dendritic cell (DC)-based vaccines has shown substantial increases in antitumour efficacy compared to tumour-bearing mice treated with single therapies or untreated controls, in mouse models of squamous cell carcinoma, melanoma and fibrosarcoma[21,25,39] (TABLE 1).

Using smart materials technologies

Smart materials technologies, including nanoparticles and smart radiotherapy biomaterials (SRBs)[76], provide great opportunities to address the above limitations to priming the abscopal effect (BOX 1). There are a number of reasons why smart materials may help overcome immunosuppression.

Box 1

Smart materials technologies for boosting the abscopal effect

Contemporaneous developments in smart materials technologies offer potential solutions for addressing limitations of immunosuppression and toxicity. Smart materials[76] are designed to be sensitive to specific stimuli (for example, tumour microenvironment, pH, the wavelength or intensity of incident radiation or an electrical or magnetic field) and to then respond in active ways, including changing their structure for drug delivery, priming an immune response or other functions that have the potential to cogently improve treatment outcomes. Examples of smart materials technologies worth consideration, with perspective on boosting the abscopal effect with minimal toxicities, include nanoparticles and smart radiotherapy biomaterials (SRBs)[2,76,108].

One distinctive feature of nanoparticles highlighted in oncological applications is their potential for improving the therapeutic index of a drug by increasing effectiveness and/or reducing toxicities (reviewed in REF. 108).

Beside nanoparticles, it has been proposed that currently used inert radiotherapy biomaterials (fiducials, spacers, beacons, and so on) can be replaced with SRBs loaded with drugs for therapy modulation[76,109]. The currently used inert radiotherapy biomaterials have only one function, which is to ensure geometric accuracy during treatment[109]. They could be replaced with multifunctional SRBs, which provide geometric accuracy but can also deliver drug payloads[110]. Currently proposed SRB designs incorporate smart polymer components[76,111,112] that can sense and actuate or change structure to release payloads incorporated in their polymer matrix in a controlled way.

Following implantation, as currently done for inert radiotherapy biomaterials, the SRBs can be activated by the tumour microenvironment or other stimuli to sustainably release the payloads in situ and directly into the tumour (FIG. 2). During radiotherapy, antigens from the dying tumour cells could serve as an in situ vaccine, working in conjunction with the released immunotherapeutic agent to potentiate the immune-mediated abscopal effect.

Targeted nanoparticles could be loaded with potent immunotherapeutic payloads that can be delivered controllably or sustainably during radiotherapy to prime abscopal responses more efficaciously, overcoming immunosuppression. A recent review highlights studies showing that the use of nanoparticles to deliver immunotherapy can boost antitumour immune responses[77]. In one study using a mouse model of melanoma, targeted delivery of CpG oligodeoxynucleotides by nanoparticles to DCs in the draining lymph node increased the $CD8^+$ T cell:T_{reg} cell ratio, delaying tumour growth compared with mice receiving immune adjuvant-free nanoparticles[78]. In another study using a mouse model of melanoma, nanoparticles were used to deliver CTLA4-targeting small interfering RNA (siCTLA4) into T cells at tumour sites, resulting in increased T-cell mediated antitumour immune responses in mice receiving siCTLA4-loaded nanoparticles compared with melanoma-bearing mice receiving control nanoparticles[79]. The combination of this therapy with radiotherapy promises to boost the abscopal effect more effectively.

High-atomic-number nanoparticles such as gold nanoparticles may also be employed to increase tumour immunogenicity by leveraging the photoelectric effect, in which radiation can induce the emission of micrometre-range photoelectrons and Auger electrons[2]. These Auger electrons have high LET and the potential to inflict more irreparable mutations upon tumour cell DNA, which could help by increasing tumour immunogenicity or overcoming immunosuppressive hypoxia[2,80,81].

A merit of using nanoparticles is that they could also serve as imaging contrast agents, which could be valuable in image-guided drug delivery of immunotherapy to boost the abscopal effect. Nanoparticles such as gadolinium nanoparticles have the potential to improve radiotherapy[82,83] but also provide magnetic resonance imaging (MRI) contrast, which would resonate with recent IGRT developments towards MRI-guided radiotherapy[82,84,85]. The use of nanoparticles with image contrast capability could also facilitate non-invasive monitoring of the effect of radiotherapy and immunotherapy

combinations on tumour progression, as shown in recent studies, with nanoparticles designed to allow tracking of cancer-specific T cells in vivo[86,87].

The use of SRBs[76] for sustained delivery of immunotherapeutic payloads could also help overcome immunosuppression, especially given the persistent and contemporaneous presence of antigen and adjuvant signalling in the tumour microenvironment, which may not be attainable in the case of intratumoural delivery of immunotherapy that can diffuse away fairly rapidly. The advantage of a sustained delivery is predicated on promising results from vaccine studies, which have shown that sustained delivery of a vaccine using biomaterials elicits increased proliferation of antigen-specific $CD8^+$ T cells compared with the effect elicited by delivery of the same vaccine through injections[88]. Consistent with expectations from these studies, preliminary data indicate an increase in abscopal responses in Lewis lung carcinoma-tumour-bearing mice treated with radiotherapy in combination with anti-CD40 delivered through SRBs compared with mice receiving radiotherapy in combination with anti-CD40 delivered through injections (W.N., O.C.I. and J.D.S., unpublished observations). Besides this, the use of SRBs for sustained in situ delivery of payloads is a relatively more convenient way to deliver immunotherapeutic agents than repeated intratumoural injections[49].

Another merit of using SRBs is that the use of polymers such as poly(lactic-co-glycolic-acid) (PLGA) or chitosan as components of these SRBs could itself have a major effect in priming an immune response. Recent studies[89,90] have shown that these particular polymers, used in prototype SRBs[76], support the maturation of DCs. Studies also showed that DCs treated with PLGA and chitosan films supported higher levels of T cell proliferation than control DCs[91–93]. In parallel, biomaterials have been shown to increase the immunogenicity of antigens. For example, adsorption of ovalbumin to PLGA scaffolds has been found to support antibody-mediated immune responses[94–96]. Taken together, there is compelling evidence from these studies that intelligently engineered SRBs may engender pro-immunogenic activity, which would be helpful in overcoming the commonly encountered local immunosuppression of established tumours.

Minimizing toxicities

Dose optimization and focused delivery

To minimize toxicities when combining radiotherapy and immunotherapy, a standard strategy is to use as low as reasonably possible doses of radiotherapy and immunotherapy that would engender optimal therapeutic outcomes. With respect to radiotherapy, retrospective studies highlight that conformal radiation dose delivery, with the radiotherapy beam shaped to tightly conform to the tumour margins, is crucial for minimizing toxicity[53,97]. The use of advanced conformal radiotherapy treatment modalities such as IMRT, SABR or proton therapy would allow for substantial reductions in radiation toxicity. HDR brachytherapy or short-distance radiotherapy, which brings radioactive sources close to tumour tissue, is specifically designed to reduce toxicity to neighbouring healthy tissue. A recent study on colorectal carcinoma has shown that HDR brachytherapy combined with anti-PD1 or anti-CD137 monoclonal antibodies engendered abscopal responses[35]. Thus,

such a combination approach could also be further developed with potential to minimize toxicity.

With respect to immunotherapy, the route of administration is crucial in determining toxicity. A major rationale for the approach of intratumoural delivery is that it can allow for reduction of systemic toxicity. This approach is supported by results from different studies[60,61]. As already mentioned, intratumoural administration of an escalated dose of CpG oligodeoxynucleotides in combination with low-dose radiotherapy was well tolerated in a trial of patients with follicular lymphoma[61]. In another study, intratumoural administration of ipilimumab at one-hundredth of the systemic dose was found to be active, safe and well tolerated in lymphoma[60,98]. These studies indicate that the relative safety of intratumoural therapies offers advantages as we move into a future with increasing combination therapies. An acknowledged limitation of the intratumoural therapy approach is that it is limited to specific, accessible tumour types where direct intratumoural administration of the immunotherapy is feasible. Overall, more studies investigating the optimal dosing or scheduling to optimize both radiotherapy and immunotherapy dose and manner of administration are needed.

Delivery through smart materials

It has been demonstrated that the use of targeted biocompatible gold nanoparticles loaded with immunotherapeutic agents can improve the delivery and safety of immunotherapy[77]. The use of such high-atomic-number nanoparticles could also avail efforts to minimize radiation toxicity[2]. Radiation-induced photoelectrons and Auger electrons can substantially boost local damage to tumour cells, allowing a reduction in the dose or number of fractions of primary radiation to be administered. As such, this could minimize radiation toxicity to normal tissues and/or lymphopaenia. Reducing the number of treatment fractions could also help improve patients' compliance and reduce the financial cost of treatments. Besides gold nanoparticles, platinum-based chemotherapy drugs (for example, cisplatin or carboplatin) loaded on nanoparticles could also provide a multi-pronged approach for combining chemoradiotherapy with immunotherapy, potentially resulting in more potent local and metastatic tumour cell killing with reduced toxicities.

An advantage of using SRBs is that the direct and sustained delivery of the respective immunotherapeutic agent has potential to substantially minimize systemic or overlapping toxicities[99]. For example, the clinical use of agonistic anti-CD40 antibodies has been blocked by dose-limiting toxicities[100]. CD40 is expressed by B cells, macrophages and DCs throughout the body, and systemic administration leads to immune-related adverse events, such as cytokine release syndrome and liver toxicity. An agonistic anti-CD40 antibody delivery system based on a slow-release agent would cause fewer side effects than systemic therapy[99,100]. SRB delivery systems offer great promise in the context of combining radiotherapy with immunotherapy.

Biomarkers

Studies designed to monitor different biomarkers should also provide valuable information to improve our understanding of boosting abscopal responses. Validated biomarkers could

help inform patient selection, monitor treatment response or help identify optimal treatment strategies to overcome immunosuppression with minimal toxicities. Studies investigating the combination of radiotherapy and immunotherapy could introduce biomarkers (for example, measurement of tumour-associated macrophages, MDSCs and T_{reg} cells) to facilitate the design and fine-tuning of approaches. For example, recent preclinical evidence suggests that TREX1 induction could guide the selection of optimal radiation dose and fractionation in patients treated with radiotherapy and immunotherapy[47].

Because determining the optimal dose or BED includes comparison of the rates of tumour cell killing for different fractionations or schedules in radiotherapy, it also informs what timing or schedules are best in generating an abscopal effect. A recent review[44] supports the use of SABR treatment schedules. Machine learning and modelling applied to data from clinical trials[27] could shed further light on the optimal BED and timing for different tumour tissue types.

TABLE 2 summarizes the merits and demerits of different approaches that have been discussed for boosting the abscopal effect. Evidently, studies that will continue to advance mechanistic understanding of the abscopal effect will avail efforts in developing these approaches. Besides the understanding that T cells are required to mediate the abscopal effect during radiotherapy[17], cytokine release has been suggested as another mechanism to mediate the abscopal effect[101]. This has been supported by the fact that the production of tumour necrosis factor in the irradiated tumour microenvironment in mice can reduce the number of immunosuppressive MDSCs[34].

Another potential marker predictive of response to immunotherapy and radiotherapy is the induction of calreticulin. Sublethal radiation exposure of tumour cells enhanced antigen processing and increased calreticulin expression on human breast, lung and prostate carcinoma cells compared with untreated control cells[102]. In these different carcinoma types, tumour cells that had been exposed to radiotherapy were significantly more sensitive to T cell killing, suggesting that the increased T cell killing is a consequence of direct interaction of the exposed calreticulin with T cells. It was also reported that knockdown or depletion of calreticulin in cancer cells resulted in decreased T cell killing of calreticulin-deficient cancer cells compared with control cells[102].

The promise of intratumoural therapy

The preclinical studies in TABLE 1 employ subcutaneous tumours in mice as the primary site and report positive abscopal responses. These outcomes suggest that subcutaneous tumours can be treated with radiotherapy and immunotherapy to modulate robust abscopal responses that can inhibit tumour growth or metastatic progression in distant untreated sites, and they offer a strategy in which subcutaneous tumours or metastasis in patients could be targeted as the primary site to prime or modulate a robust abscopal response. Such patients may then benefit from the advantages of intratumoural delivery or use of SRBs whose main limitation is access to the primary tumour site. A substantial number of patients with cancer with cutaneous metastasis could benefit from such a subcutaneous modulation approach. In one retrospective study of 7,316 patients covering a range of tumour types, 367 patients

(5%) showed incidence of cutaneous metastasis[103]. In another study[104], 1,080 patients out of 20,380 patients with a range of cancer types had cutaneous metastasis. Given the potential benefit, such a therapy approach is worth further investigation, using animal models with both subcutaneous tumours and orthotopic tumours with metastasis.

Conclusions

Many decades after the rare abscopal effect was first described, research developments provide increasing evidence that the use of radiotherapy with immunotherapy could boost the abscopal effect. Persisting challenges in overcoming established cancer immunosuppression and mitigating dose-limiting toxicities remain. Many studies are ongoing to address these limitations and to better understand how to optimize combinations of radiotherapy and immunotherapy. With parallel developments in smart materials technologies, there is great motivation for more cross-disciplinary research, which can leverage these discoveries to address current limitations and boost the application of radiotherapy to the treatment of both local and metastatic disease. Metastasis accounts for over 90% of cancer-related death and suffering[105–107]. Hence, boosting radiation-induced abscopal response rates could substantially impact patient care far beyond the patients who now benefit from radiotherapy or immunotherapy alone. Overall, there is a considerable impetus for more concerted research collaborations combining radiotherapy and immunotherapy with smart materials science in boosting the abscopal effect, thereby improving patient outcomes and saving more lives.

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References

1. Atun R, et al. Expanding global access to radiotherapy. Lancet Oncol. 2015; 16:1153–1186. [PubMed: 26419354]
2. Ngwa W, et al. Targeted radiotherapy with gold nanoparticles: current status and future perspectives. Nanomedicine. 2014; 9:1063–1082. [PubMed: 24978464]
3. Chang JY, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in Stage I or Stage III non-small-cell lung cancer. Int J Radiat Oncol. 2006; 65:1087–1096.
4. Baumann M, et al. Radiation oncology in the era of precision medicine. Nat Rev Cancer. 2016; 16:234–249. [PubMed: 27009394]
5. Mole RH. Whole body irradiation — radiobiology or medicine? Br J Radiol. 1953; 26:234–241. [PubMed: 13042090]
6. Andrews, JR. The Radiobiology of Human Cancer Radiotherapy. Univ. Park Press; 1978.
7. Hu ZI, McArthur HL, Ho AY. The abscopal effect of radiation therapy: what is it and how can we use it in breast cancer? Curr Breast Cancer Rep. 2017; 9:45–51. [PubMed: 28344743]
8. Siva S, MacManus MP, Martin RF, Martin O. A Abscopal effects of radiation therapy: a clinical review for the radiobiologist. Cancer Lett. 2013; 356:82–90. [PubMed: 24125863]
9. Postow MA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med. 2012; 366:925–931. [PubMed: 22397654]

10. Wersall PJ, et al. Regression of non-irradiated metastases after extracranial stereotactic radiotherapy in metastatic renal cell carcinoma. Acta Oncol. 2006; 45:493–497. [PubMed: 16760190]
11. Ohba K, et al. Abscopal regression of hepatocellular carcinoma after radiotherapy for bone metastasis. Gut. 1998; 43:575–577. [PubMed: 9824589]
12. Golden EB, et al. Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. Lancet Oncol. 2015; 16:795–803. [PubMed: 26095785]
13. Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. Curr Probl Cancer. 2016; 40:25–37. [PubMed: 26582738]
14. Kingsley DP. An interesting case of possible abscopal effect in malignant melanoma. Br J Radiol. 1975; 48:863–866. [PubMed: 811297]
15. Ehlers G, Fridman M. Abscopal effect of radiation in papillary adenocarcinoma. Br J Radiol. 1973; 46:220–222. [PubMed: 4706791]
16. Stone HB, Peters LJ, Milas L. Effect of host immune capability on radiocurability and subsequent transplantability of a murine fibrosarcoma. J Natl Cancer Inst. 1979; 63:1229–1235. [PubMed: 291749]
17. Demaria S, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. Int J Radiat Oncol Biol Phys. 2004; 58:862–870. [PubMed: 14967443]
18. Chakravarty PK, et al. Flt3-ligand administration after radiation therapy prolongs survival in a murine model of metastatic lung cancer. Cancer Res. 1999; 59:6028–6032. [PubMed: 10626784]
19. Camphausen K, et al. Radiation abscopal antitumor effect is mediated through p53. Cancer Res. 2003; 63:1990–1993. [PubMed: 12702593]
20. Demaria S, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. Clin Cancer Res. 2005; 11:728–734. [PubMed: 15701862]
21. Akutsu Y, et al. Combination of direct intratumoral administration of dendritic cells and irradiation induces strong systemic antitumor effect mediated by GRP94/gp96 against squamous cell carcinoma in mice. Int J Oncol. 2007; 31:509–515. [PubMed: 17671676]
22. Lee Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood. 2009; 114:589–595. [PubMed: 19349616]
23. Dewan MZ, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res. 2009; 15:5379–5388. [PubMed: 19706802]
24. Nikitina EY, Gabrilovich DI. Combination of gamma-irradiation and dendritic cell administration induces a potent antitumor response in tumor-bearing mice: approach to treatment of advanced stage cancer. Int J Cancer. 2001; 94:825–833. [PubMed: 11745485]
25. Kim KW, et al. Direct injection of immature dendritic cells into irradiated tumor induces efficient antitumor immunity. Int J Cancer. 2004; 109:685–690. [PubMed: 14999775]
26. Twyman-Saint Victor C, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015; 520:373–377. [PubMed: 25754329]
27. Kang J, Demaria S, Formenti S. Current clinical trials testing the combination of immunotherapy with radiotherapy. J Immunother Cancer. 2016; 4:51. [PubMed: 27660705]
28. Grass GD, Krishna N, Kim S. The immune mechanisms of abscopal effect in radiation therapy. Curr Probl Cancer. 2016; 40:10–24. [PubMed: 26612692]
29. Barker HE, Paget JTE, Khan AA, Harrington KJ. The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. Nat Rev Cancer. 2015; 15:409–425. [PubMed: 26105538]
30. Vatner RE, Cooper BT, Vanpouille-Box C, Demaria S, Formenti SC. Combinations of immunotherapy and radiation in cancer therapy. Front Oncol. 2014; 4:325. [PubMed: 25506582]
31. Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases — elimination, equilibrium and escape. Curr Opin Immunol. 2014; 27:16–25. [PubMed: 24531241]

32. Habets TH, et al. Fractionated radiotherapy with 3 × 8 Gy induces systemic anti-tumour responses and abscopal tumour inhibition without modulating the humoral anti-tumour response. PLoS ONE. 2016; 11:e0159515. [PubMed: 27427766]
33. Hao Y, et al. Enhancing radiotherapy for lung cancer using immunoadjuvants delivered in situ from new design radiotherapy biomaterials: a preclinical study. Phys Med Biol. 2016; 61:N697–N707. [PubMed: 27910826]
34. Deng L, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest. 2014; 124:687–695. [PubMed: 24382348]
35. Rodriguez-Ruiz ME, et al. Brachytherapy attains abscopal effects when combined with immunostimulatory monoclonal antibodies. Brachytherapy. 2017; 16:1246–1251. [PubMed: 28838649]
36. Young KH, et al. Optimizing timing of immunotherapy improves control of tumors by hypofractionated radiation therapy. PLoS ONE. 2016; 11:e0157164. [PubMed: 27281029]
37. Habets THPM, et al. Fractionated radiotherapy with 3 × 8 Gy induces systemic anti-tumour responses and abscopal tumour inhibition without modulating the humoral anti-tumour response. PLoS ONE. 2016; 11:e0159515. [PubMed: 27427766]
38. Yasuda K, Nirei T, Tsuno NH, Nagawa H, Kitayama J. Intratumoral injection of interleukin-2 augments the local and abscopal effects of radiotherapy in murine rectal cancer. Cancer Sci. 2011; 102:1257–1263. [PubMed: 21443690]
39. Teitz-Tennenbaum S, et al. Radiotherapy potentiates the therapeutic efficacy of intratumoral dendritic cell administration. Cancer Res. 2003; 63:8466–8475. [PubMed: 14679011]
40. Kanegasaki S, Matsushima K, Shiraishi K, Nakagawa K, Tsuchiya T. Macrophage inflammatory protein derivative ECI301 enhances the alarmin-associated abscopal benefits of tumor radiotherapy. Cancer Res. 2014; 74:5070–5078. [PubMed: 25038226]
41. Marconi R, et al. A meta-analysis of the abscopal effect in preclinical models: is the biologically effective dose a relevant physical trigger? PLoS ONE. 2017; 12:e0171559. [PubMed: 28222111]
42. Shiraishi K, et al. Enhancement of antitumor radiation efficacy and consistent induction of the abscopal effect in mice by ECI301, an active variant of macrophage inflammatory protein-1alpha. Clin Cancer Res. 2008; 14:1159–1166. [PubMed: 18281550]
43. Filatenkov A, et al. Ablative tumor radiation can change the tumor immune cell microenvironment to induce durable complete remissions. Clin Cancer Res. 2015; 21:3727–3739. [PubMed: 25869387]
44. Bernstein MB, Krishnan S, Hodge JW, Chang JY. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? Nat Rev Clin Oncol. 2016; 13:516–524. [PubMed: 26951040]
45. Stetson DB, Ko JS, Heidmann T, Medzhitov R. Trex1 prevents cell-intrinsic initiation of autoimmunity. Cell. 2008; 134:587–598. [PubMed: 18724932]
46. Wilson R, et al. MicroRNA regulation of endothelial TREX1 reprograms the tumour microenvironment. Nat Commun. 2016; 7:13597. [PubMed: 27886180]
47. Vanpouille-Box C, et al. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun. 2017; 8:15618. [PubMed: 28598415]
48. Vanneman M, Dranoff G. Combining immunotherapy and targeted therapies in cancer treatment. Nat Rev Cancer. 2012; 12:237–251. [PubMed: 22437869]
49. Dranoff G. Experimental mouse tumour models: what can be learnt about human cancer immunology? Nat Rev Immunol. 2011; 12:61–66. [PubMed: 22134155]
50. McNamee EN, Korns Johnson D, Homann D, Clambey ET. Hypoxia and hypoxia-inducible factors as regulators of T cell development, differentiation, and function. Immunol Res. 2013; 55:58–70. [PubMed: 22961658]
51. Facciabene A, et al. Tumour hypoxia promotes tolerance and angiogenesis via CCL28 and Tregcells. Nature. 2011; 475:226–230. [PubMed: 21753853]
52. Doedens AL, et al. Macrophage expression of hypoxia-inducible factor-1 alpha suppresses T-cell function and promotes tumor progression. Cancer Res. 2010; 70:7465–7475. [PubMed: 20841473]
53. Tang C, et al. Combining radiation and immunotherapy: a new systemic therapy for solid tumors? Cancer Immunol Res. 2014; 2:831–838. [PubMed: 25187273]

54. Michot JM, et al. Immune-related adverse events with immune checkpoint blockade: A comprehensive review. Eur J Cancer. 2016; 54:139–148. [PubMed: 26765102]
55. Naidoo J, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol. 2015; 26:2375–2391. [PubMed: 26371282]
56. Picozzi VJ, Kozarek RA, Traverso LW. Interferon-based adjuvant chemoradiation therapy after pancreaticoduodenectomy for pancreatic adenocarcinoma. Am J Surg. 2003; 185:476–480. [PubMed: 12727570]
57. Picozzi VJ, et al. Multicenter phase II trial of adjuvant therapy for resected pancreatic cancer using cisplatin, 5-fluorouracil, and interferon-alfa-2b-based chemoradiation: ACOSOG Trial Z05031. Ann Oncol. 2011; 22:348–354. [PubMed: 20670978]
58. Bang A, et al. Multicenter evaluation of the tolerability of combined treatment with PD-1 and CTLA-4 immune checkpoint inhibitors and palliative radiation therapy. Int J Radiat Oncol Biol Phys. 2017; 98:344–351. [PubMed: 28463153]
59. Yasmin-Karim, S., Moreau, M., Ngwa, W. AAPM 59th Annual Meeting & Exhibition; Denver, CO. 2017. MO-DE-605-6
60. Pierce RH, Campbell JS, Pai SI, Brody JD, Kohrt HEK. In-situ tumor vaccination: bringing the fight to the tumor. Hum Vaccin Immunother. 2015; 11:1901–1909. [PubMed: 26055074]
61. Kohrt HE, et al. Dose-escalated, intratumoral TLR9 agonist and low-dose radiation induce abscopal effects in follicular lymphoma. Blood. 2014; 124:3092. [PubMed: 25193870]
62. Brody JD, et al. In situ vaccination with a TLR9 agonist induces systemic lymphoma regression: a phase I/II study. J Clin Oncol. 2010; 28:4324–4332. [PubMed: 20697067]
63. Hams E, et al. The hydroxylase inhibitor dimethyloxallyl glycine attenuates endotoxic shock via alternative activation of macrophages and IL-10 production by B1 cells. Shock. 2011; 36:295–302. [PubMed: 21844787]
64. Tinganelli W, et al. Kill-painting of hypoxic tumours in charged particle therapy. Sci Rep. 2015; 5:17016. [PubMed: 26596243]
65. Blankenstein T, Coulie PG, Gilboa E, Jaffee EM. The determinants of tumour immunogenicity. Nat Rev Cancer. 2012; 12:307–313. [PubMed: 22378190]
66. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunol Res. 2013; 1:365–372. [PubMed: 24563870]
67. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunogenic cell death in cancer and infectious disease. Nat Rev Immunol. 2016; 17:97–111. [PubMed: 27748397]
68. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Reply: Immunosuppressive cell death in cancer. Nat Rev Immunol. 2017; 17:402–402.
69. Zitvogel L, Kroemer G. Subversion of anticancer immunosurveillance by radiotherapy. Nat Immunol. 2015; 16:1005–1007. [PubMed: 26343538]
70. Ma Y, et al. How to improve the immunogenicity of chemotherapy and radiotherapy. Cancer Metastasis Rev. 2011; 30:71–82. [PubMed: 21298323]
71. Gorin JB, et al. Antitumor immunity induced after α irradiation. Neoplasia. 2014; 16:319–328. [PubMed: 24862758]
72. Zheng W, et al. Combination of radiotherapy checkpoint blockade resistance and vaccination overcomes checkpoint blockade resistance. Oncotarget. 2016; 7:43039–43051. [PubMed: 27343548]
73. Le DT, et al. A live-attenuated listeria vaccine (ANZ-100) and a live-attenuated listeria vaccine expressing mesothelin (CRS-207) for advanced cancers: phase I studies of safety and immune induction. Clin Cancer Res. 2012; 18:858–868. [PubMed: 22147941]
74. Dranoff G, et al. Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity. Proc Natl Acad Sci USA. 1993; 90:3539–3543. [PubMed: 8097319]
75. Garnett-Benson C, Hodge JW, Gameiro SR. Combination regimens of radiation therapy and therapeutic cancer vaccines: mechanisms and opportunities. Semin Radiat Oncol. 2015; 25:46–53. [PubMed: 25481266]

76. Ngwa W, et al. Smart radiation therapy biomaterials. Int J Radiat Oncol. 2017; 97:624–637.
77. Toy R, Roy K. Engineering nanoparticles to overcome barriers to immunotherapy. Bioeng Transl Med. 2016; 1:47–62. [PubMed: 29313006]
78. Thomas SN, Vokali E, Lund AW, Hubbell JA, Swartz MA. Targeting the tumor-draining lymph node with adjuvanted nanoparticles reshapes the anti-tumor immune response. Biomaterials. 2014; 35:814–824. [PubMed: 24144906]
79. Li SY, et al. Restoring anti-tumor functions of T cells via nanoparticle-mediated immune checkpoint modulation. J Control Release. 2016; 231:17–28. [PubMed: 26829099]
80. Kim MS, et al. Gold nanoparticles enhance anti-tumor effect of radiotherapy to hypoxic tumor. Radiat Oncol J. 2016; 34:230–238. [PubMed: 27730800]
81. Sinha N, et al. Brachytherapy application with in situ dose painting administered by gold nanoparticle eluters. Int J Radiat Oncol Biol Phys. 2015; 91:385–392. [PubMed: 25482302]
82. Detappe A, et al. AGuIX nanoparticles as a promising platform for image-guided radiation therapy. Cancer Nanotechnol. 2015; 6:4. [PubMed: 26345984]
83. Luchette M, Korideck H, Makrigiorgos M, Tillement O, Berbeco R. Radiation dose enhancement of gadolinium-based AGuIX nanoparticles on HeLa cells. Nanomedicine. 2014; 10:1751–1755. [PubMed: 24941464]
84. Low, DA. Advances in Radiation Oncology. Wong, JYC.Schultheiss, TE., Radany, EH., editors. Springer; 2017. p. 41-67.
85. Lux F, et al. Gadolinium-based nanoparticles for theranostic MRI-radiosensitization. Nanomedicine. 2015; 10:1801–1815. [PubMed: 25715316]
86. Meir R, et al. Nanomedicine for cancer immunotherapy: tracking cancer-specific T-cells in vivo with gold nanoparticles and CT imaging. ACS Nano. 2015; 9:6363–6372. [PubMed: 26039633]
87. Kalbasi A, June CH, Haas N, Vapiwala N. Radiation and immunotherapy: a synergistic combination. J Clin Invest. 2013; 123:2756–2763. [PubMed: 23863633]
88. DeMuth PC, et al. Vaccine delivery with microneedle skin patches in nonhuman primates. Nat Biotechnol. 2013; 31:1082–1085.
89. Park J, Babensee JE. Differential functional effects of biomaterials on dendritic cell maturation. Acta Biomater. 2012; 8:3606–3617. [PubMed: 22705044]
90. Park J, Gerber MH, Babensee JE. Phenotype and polarization of autologous T cells by biomaterial-treated dendritic cells. J Biomed Mater Res A. 2015; 103:170–184. [PubMed: 24616366]
91. Shokouhi B, et al. The role of multiple toll-like receptor signalling cascades on interactions between biomedical polymers and dendritic cells. Biomaterials. 2010; 31:5759–5771. [PubMed: 20452017]
92. Rogers TH, Babensee JE. The role of integrins in the recognition and response of dendritic cells to biomaterials. Biomaterials. 2011; 32:1270–1279. [PubMed: 21030075]
93. Ishii KJ, Coban C, Akira S. Manifold mechanisms of Toll-like receptor-ligand recognition. J Clin Immunol. 2005; 25:511–521. [PubMed: 16380815]
94. Bennewitz NL, Babensee JE. The effect of the physical form of poly(lactic-co-glycolic acid) carriers on the humoral immune response to co-delivered antigen. Biomaterials. 2005; 26:2991–2999. [PubMed: 15603794]
95. Matzelle MM, Babensee JE. Humoral immune responses to model antigen co-delivered with biomaterials used in tissue engineering. Biomaterials. 2004; 25:295–304. [PubMed: 14585717]
96. Babensee JE. Interaction of dendritic cells with biomaterials. Semin Immunol. 2008; 20:101–108. [PubMed: 18054498]
97. Ng SY, et al. Acute toxicity with intensity modulated radiotherapy versus 3-dimensional conformal radiotherapy during preoperative chemoradiation for locally advanced rectal cancer. Radiother Oncol. 2016; 121:252–257. [PubMed: 27751605]
98. Marabelle A, et al. Depleting tumor-specific Tregs at a single site eradicates disseminated tumors. J Clin Invest. 2013; 123:2447–2463. [PubMed: 23728179]
99. Fransen MF, et al. Effectiveness of slow-release systems in CD40 agonistic antibody immunotherapy of cancer. Vaccine. 2014; 32:1654–1660. [PubMed: 24508038]

100. Fransen MF, Sluijter M, Morreau H, Arens R, Melief CJM. Local activation of CD8 T cells and systemic tumor eradication without toxicity via slow release and local delivery of agonistic CD40 antibody. Clin Cancer Res. 2011; 17:2270–2280. [PubMed: 21389097]
101. Kaminski JM, et al. The controversial abscopal effect. Cancer Treatment Rev. 2005; 31:159–172.
102. Gameiro SR, et al. Radiation-induced immunogenic modulation of tumor enhances antigen processing and calreticulin exposure, resulting in enhanced T-cell killing. Oncotarget. 2014; 5:403–416. [PubMed: 24480782]
103. Lookingbill DP, Spangler N, Sexton FM. Skin involvement as the presenting sign of internal carcinoma: a retrospective study of 7316 cancer patients. J Am Acad Dermatol. 1990; 22:19–26. [PubMed: 2298962]
104. Krathen RA, Orengo IF, Rosen T. Cutaneous metastasis: a meta-analysis of data. South Med J. 2003; 96:164–167. [PubMed: 12630642]
105. Mehlen P, Puisieux A. Metastasis: a question of life or death. Nat Rev Cancer. 2006; 6:449–458. [PubMed: 16723991]
106. Chaffer CL, Weinberg RA. A perspective on cancer cell metastasis. Science. 2011; 331:1559–1564. [PubMed: 21436443]
107. Ahmad, A. Introduction to Cancer Metastasis. 1. Academic Press; 2016.
108. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer. 2016; 17:20–37. [PubMed: 27834398]
109. Cormack RA, Sridhar S, Suh WW, D'Amico AV, Makrigiorgos GM. Biological in situ dose painting for image-guided radiation therapy using drug-loaded implantable devices. Int J Radiat Oncol. 2010; 76:615–623.
110. Kumar R, et al. Nanoparticle-based brachytherapy spacers for delivery of localized combined chemoradiation therapy. Int J Radiat Oncol Biol Phys. 2015; 91:393–400. [PubMed: 25636762]
111. Stuart MA, et al. Emerging applications of stimuli-responsive polymer materials. Nat Mater. 2010; 9:101–113. [PubMed: 20094081]
112. Tada DB, et al. Chitosan film containing poly(D, L-lactic-co-glycolic acid) nanoparticles: a platform for localized dual-drug release. Pharm Res. 2010; 27:1738–1745. [PubMed: 20521086]

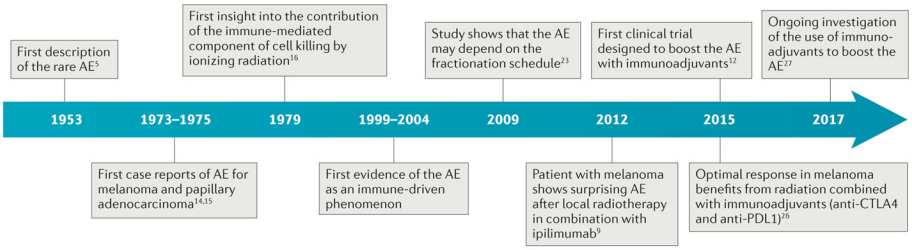

Figure 1. Historical timeline of some important developments regarding the abscopal effect

AE, abscopal effect; CTLA4, cytotoxic T lymphocyte-associated antigen; PDL1, programmed cell death 1 ligand 1.

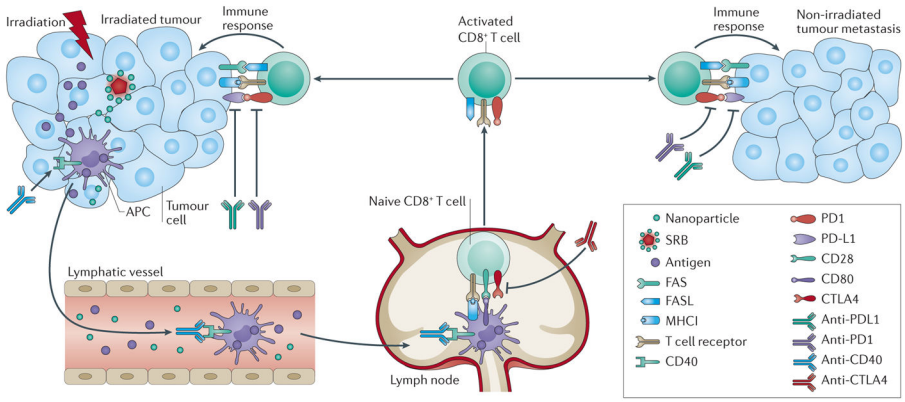

Figure 2. Mechanism of the abscopal effect

Radiation generates neoantigens from tumour cells. Antigens from damaged tumour cells can be taken up by antigen-presenting cells (APCs), which travel to the lymph node to prime the T cell-mediated abscopal effect. Activated T cells directed against tumour-specific antigens then infiltrate the primary tumour and non- irradiated tumour metastases. The use of smart radiotherapy biomaterials (SRBs) and nanoparticles provides promising avenues to boost abscopal response rates. Nanoparticles can amplify damage to the tumour cells owing to radiation-induced emission of micrometre-range missile-like photoelectrons and Auger electrons. Immunotherapeutic agents loaded in the SRBs and/or nanoparticles can be sustainably released to boost abscopal responses by targeting different aspects of the immune-mediated abscopal response process. For example, anti-CD40 monoclonal antibody could be employed to increase activation of the APCs, while antibodies against cytotoxic T lymphocyte- associated antigen (CTLA4), programmed cell death protein 1 (PD1) or PD1 ligand 1 (PDL1) can act as immune checkpoint inhibitors, increasing the T cell activity directed against tumour cells at irradiated as well as non-irradiated tumour sites. Please note that the relative sizes of SRBs, nanoparticles and immunotherapeutic agents as depicted are notproportional. FASL, FAS ligand; MHCI, major histocompatibility complex class I.

Table 1

Preclinical studies demonstrating the abscopal effect when using radiotherapy with immunotherapy

Tumour model (cell line injection into immunocompetent mice)	Radiotherapy dose	Immunotherapy type; dose; timing; administration route	Conclusion in regard to boosting the abscopal effect	Refs
Subcutaneous MC38 colon adenocarcinoma	3 × 8 Gy	Anti-PD1, anti-CD137 or both; 300 μg; after each radiotherapy fraction; intraperitoneal	Brachytherapy with immunotherapy can potentiate the abscopal effect	35
Subcutaneous CT26 colorectal carcinoma	20 Gy	• Anti-CTLA4; 250 μg; before radiotherapy; intraperitoneal • Anti-TNFRSF4; 250 μg; after radiotherapy; intraperitoneal	In combining radiotherapy and immunotherapy, ideal timing of radiotherapy is dependent on the mechanism of action of the respective immunotherapy utilized	36
Subcutaneous LLC	6 Gy	Anti-CD40; 20 μg; after radiotherapy; intratumoural	Intratumoural administration of anti-CD40 boosts the abscopal effect, and further research on the use of SRBs to boost this effect is justified	33
Subcutaneous 67NR mammary carcinoma	3 × 8 Gy	FLT3L; 10 μg × 10; after radiotherapy; intratumoural	Fractionated radiotherapy with FLT3L induces abscopal effects	32
Subcutaneous B16-F10 melanoma	20 Gy	Anti-CTLA4, anti-PD1, anti-PDL1; 200 μg per mouse; before, concurrent with and after radiotherapy; intraperitoneal	The combination of radiotherapy, anti-CTLA4 and anti-PDL1 promotes response and immunity through distinct mechanisms	26
Subcutaneous TSA mammary adenocarcinoma	3 × 8 Gy	Anti-CTLA4, anti-PD1, anti-PDL1; 200 μg per mouse; before, concurrent with and after radiotherapy; intraperitoneal	The combination of radiotherapy, anti-CTLA4 and anti-PDL1 promotes response and immunity through distinct mechanisms	26
• Subcutaneous TUBO mammary carcinoma • MCA38 colon carcinoma	12 Gy	Anti-PDL1; 200 μg × 4; before, concurrent with and after radiotherapy; intraperitoneally	There is close interaction between radiotherapy, T cells and PDL1 in boosting the abscopal effect	34
Subcutaneous colon26 adenocarcinoma	2 Gy × 5 consecutive days per cycle × 2 cycles	IL-2; 20,000 IU in 0.1 mL of PBS; after radiotherapy; intratumoural	Intratumoural injection of IL-2 boosts both the local and abscopal effects of local radiotherapy	38
• Subcutaneous TSA mammary adenocarcinoma • MCA38 colon carcinoma	20 Gy × 1, 8 Gy × 3 or 6 Gy × 5	Anti-CTLA4 antibody (9H10); 200 μg × 3; concurrent with or after radiotherapy; intraperitoneal	Fractionated but not single-dose radiotherapy in combination with anti-CTLA4 boosts the abscopal effect	23
• Subcutaneous 4T1 mammary carcinoma • Subcutaneous B16-CCR7 melanoma	2 × 12 Gy	Adenovirus-expressing TNFSF14 (also known as LIGHT); (2 × 1,010 virus particles); concurrent with and after radiotherapy; intratumoural	SABR combined with immunoadjuvant increases T cell priming in draining lymphoid tissues, leading to abscopal responses in a $CD8^+$ T cell-dependent fashion	22

Tumour model (cell line injection into immunocompetent mice)	Radiotherapy dose	Immunotherapy type; dose; timing; administration route	Conclusion in regard to boosting the abscopal effect	Refs
Subcutaneous SCCVII	4 10 Gy	DC; 1×10^6 cells; after radiotherapy; intratumoural	A combination of intratumoural DCs and radiotherapy can induce strong local and abscopal responses	21
Subcutaneous 4T1 mammary carcinoma	12 × 2 Gy	Anti-CTLA4; 200 μg × 3; after radiotherapy; intraperitoneal	Combining local radiotherapy with anti-CTLA4 is a promising new strategy against poorly immunogenic metastatic cancers	20
Subcutaneous 67NR mammary carcinoma	2 6 Gy	FLT3L; 0.5 mg per kg body weight × 10; after radiotherapy; intraperitoneal	T cells mediate the abscopal effect	17
Subcutaneous MCA-102 fibrosarcoma	15 Gy	DC; 1×10^6 cells; after radiotherapy; intratumoural	Direct injection of DCs into irradiated tumours can induce tumour-specific immunity	25
Subcutaneous D5 melanoma and/or MCA-205 sarcoma and MethA fibrosarcoma	42.5 Gy	DC; 1×10^6 cells × 4; before and after radiotherapy; intratumoural	Radiotherapy potentiates the therapeutic efficacy of DCs administered intratumorally	39
Subcutaneous C3 sarcoma and MethA fibrosarcoma	10 Gy × 3 5 cycles	DC; 2 4 × 10^6 cells per mouse; after radiotherapy; intravenous	The combination of radiotherapy and DC administration may be an attractive new approach to treat advanced cancer	24
Subcutaneous LLC	60 Gy	FLT3L; 500 μg per kg per day × 10 days; after radiotherapy; intraperitoneal	Radiotherapy combined with FLT3L improves survival and reduces pulmonary metastases	18

CTLA4, cytotoxic T lymphocyte-associated antigen; DC, dendritic cell; FLT3L, FMS-like tyrosine kinase receptor 3 ligand; IL-2, interleukin-2; IU, international units; LLC, Lewis lung carcinoma; PD1, programmed cell death protein 1; PDL1, PD1 ligand 1; SCC, squamous cell carcinoma; SABR, stereotactic ablative body radiotherapy; SRBs, smart radiotherapy biomaterials; TNFSF14, tumour necrosis factor ligand superfamily member 14; TNFRSF4, tumour necrosis factor receptor superfamily member 4.

Table 2

Merits and demerits or opportunities for future research regarding approaches for boosting the abscopal effect

Potential approaches	Merits	Demerits or research opportunities
Optimize doses, fractions and timing or sequence	• Potential to maximize immunogenicity and minimize immunosuppression • Increased understanding of the abscopal effect and appropriate BED	• Non-concurrent sequences may require more time • May be immunotherapy-dependent • May be tumour-dependent
Rational combination of radiotherapy with more than one immunotherapeutic agent	More than one aspect of the abscopal effect can be targeted to overcome immunosuppression	Risk of increasing toxicities because of additional immunotherapeutic agents
Intratumoural administration of immunotherapy	• Increase immunogenicity and overcome immunosuppression • Generate tumour-infiltrating lymphocytes • Minimize systemic and/or overlapping toxicities	Limited to specific tumour sites owing to need for direct access to tumours
Use of nanoparticles	• Can deliver potent immunotherapeutic payloads to specific sites with minimal off-target toxic effects • Can increase immunogenicity with high LET electrons • Localized boosting by high-*Z* nanoparticles could help reduce primary radiotherapy dose • Nanoparticles can serve as image contrast agents • Sustained delivery of immunotherapy from nanoparticles could help overcome immunosuppression	• Tumour penetration, cellular uptake and intracellular trafficking may not be uniform • Controllable and reproducible synthesis is a challenge
Use of SRBs	• In situ delivery minimizes toxicities • Obviates the need to choose a time sequence • Could be employed at no additional inconvenience to patients • Multifunctional design provides potential for image-guided drug delivery • Sustained delivery of immunotherapy could help overcome immunosuppression • Could be used in combination with nanoparticles or immunotherapy	• Limited to certain tumour types owing to need for direct access to tumours • More research needed for controllable and reproducible synthesis

BED, biologically effective dose; high-*Z*, high atomic number; LET, linear energy transfer; SRBs, smart radiotherapy biomaterials.