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Brief Reviews

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Intratumoral Delivery of Immunotherapy—Act Locally, Think Globally

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Immune mechanisms have evolved to cope with local entry of microbes acting in a confined fashion but eventually inducing systemic immune memory. Indeed, in situ delivery of a number of agents into tumors can mimic in the malignant tissue the phenomena that control intracellular infection leading to the killing of infected cells. Vascular endothelium activation and lymphocyte attraction, together with dendritic cell–mediated cross-priming, are the key elements. Intratumoral therapy with pathogen-associated molecular patterns or recombinant viruses is being tested in the clinic. Cell therapies can be also delivered intratumorally, including infusion of autologous dendritic cells and even tumor-reactive T lymphocytes. Intralesional virotherapy with an HSV vector expressing GM-CSF has been recently approved by the Food and Drug Administration for the treatment of unresectable melanoma. Immunomodulatory monoclonal Abs have also been successfully applied intratumorally in animal models. Local delivery means less systemic toxicity while focusing the immune response on the malignancy and the affected draining lymph nodes. ***The Journal of Immunology*****, 2017, 198: 31–39.**

More than 100 years ago, the surgeon William Coley found that in some cases of soft tissue sarcoma there were regressions following erysipelas. Facing similar cases in his practice, he proceeded to cause such risky infections on purpose, observing some successful responses. To make it safer he went on to use bacterial-derived material (Coley's toxins) to locally inject tumor masses (1, 2). Since then, we have learned that the results obtained by Coley were related to a systemic antitumor immune response following local delivery of the ill-defined microorganisms and bacterial toxins.

These empiric ideas have found application for superficial urothelial carcinoma, which is often treated by transurethral instillation of bacillus Calmette–Guérin. Today this procedure remains the adjuvant treatment of choice, due to its ability to prevent both local and distant relapses (3).

The type of immunity that can deal with a tumor is related to the evolutionary mechanisms shaped to combat intracellular pathogens such as viruses and mycobacteria. To perform such a critical function, the immune system is equipped with the ability to kill infected cells while inhibiting the spread of pathogens to other cells and distant organs. Therefore, in immunotherapy, one of the goals is to make the tumor, with its Ags, to look like an intracellular pathogen–infected tissue. To achieve this, several strategies are possible that would locally release and activate the biochemical signals derived from pathogen presence and unprogrammed cell destruction. These notions build on the ideas of Charles Janeway and Polly Matzinger who elaborated on the concept that the immune system has evolved to respond against infection and agents causing tissue damage (4, 5).

Following in Coley's footsteps, we can now deliver into tumors molecularly defined pathogen-associated molecular patterns (PAMPs), safe recombinant viruses or bacteria as well as inflammatory and immune mediators. Interventional radiologists and laparoscopic surgeons have evolved the tools to gain access for injection to almost every organ in the human body and several lesions can be simultaneously or sequentially injected, expecting impact not only on the treated lesion, but also on distant non-injected tumor sites or subclinical undetected metastases (i.e., minimal residual disease). In a way, the strategy aims to turn the treated lesion into a sort of vaccine against the untreated metastasis. This concept has been summarized as in situ vaccination (6, 7). Following a term coined by the radiotherapy community, effects of local treatment can be observed outside the localized irradiation/treatment fields, the so-called abscopal effects (8).

Cross-priming of tumor Ags

Presentation of tumor Ags to T lymphocytes able to differentiate into CTL and IFN-γ producing Th1 cells is a critical

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Abbreviations used in this article: DC, dendritic cell; PAMP, pathogen-associated molecular pattern; poly I:C, polyinosinic-polycytidylic acid; STING, stimulator of IFN genes.

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point to start efficacious antitumor immunity. Tumor cells perform poorly as Ag presenting cells and this step needs the contribution of professional APCs of dendritic cell (DC) lineage (9, 10).

The classical scheme borrowed from vaccination experiments involves DCs taking up Ags in peripheral tissues (11) and sensing pathogen presence (9) or cell destruction/inflammation by means of innate receptors. Subsequently, DCs need to migrate to regional lymph nodes to encounter naive and central memory T cells. More recent evidence suggests a key role for functionally specialized DC subsets, which are equipped to cross-present Ags to CTL precursors (12, 13). This subtype is known to be BATF3-dependent, $XCR1^+$ DCs in mice (14). In humans, these cells are primarily represented by $XCR1^+$, $CLEC9a^+$, $CD141^+$ DCs (15) and have been shown to be strong producers of IL-12 following stimulation with polyinosinic–polycytidylic acid (poly I:C) (16). These specialized subsets are endowed with the ability to divert engulfed cell-associated Ags to the MHC class I Ag–presenting pathway (10) and to produce high amounts of IL-12 in response to the presence of pathogens (mainly RNA viruses) (17, 18).

Ag presentation mechanisms are conceivably poorly operational in tumor tissue, giving rise to peripheral tolerance rather than to type I tissue-destructing immunity. In this regard, the tumor is rich in immunosuppressive factors for DC function such as TGF-β (19), oxidized lipids (20), IL-10 (21, 22), etc. Hence, potentiation of these Ag-cross-priming functions in tumors may turn them into a vaccine. In line with this, release of Ags surpassing the ability of macrophages to clear cell debris and making DCs believe that they are dealing with a virally infected tissue is an alternative to promote cross-presentation of tumor Ags both locally and in tumor-draining lymph nodes (23, 24). It has been documented that the local production of IFN-α/β is critical for these phenomena resulting in Ag cross-priming (25, 26) as well as a number of eat me signals and alarmins such as extracellular ATP and high mobility group box 1, biochemical events that converge in what is known as immunogenic cell death (27, 28).

Local delivery of pathogen-associated molecular patterns

Recognition of the presence of pathogens beyond epithelial barriers is mediated by an intricate set of innate receptors that detect moieties exclusively or selectively expressed by viruses and/or *prokaryotae* (29). These receptors mainly involve TLR on the plasma membrane and in endosomal compartments, cytoplasmic receptors for viral nucleic acids [RIG-I, MDA-5 and the stimulator of IFN gene (STING) system], and the intracellular NOD-family of receptor-complexes. Interestingly, these sets of receptors are entangled, and in many cases shared by the molecular machineries that detect stressful or unwanted cell death (30, 31) expected to occur under intracellular infectious conditions. Stressful cell death can be artificially induced by microwaves, heat, ionizing radiation, and other physical-chemical agents.

In this regard, transplantable mouse tumor models injected locally with TLR4 agonists such as LPS (32) and monophosphoryl lipid A (33) undergo regressions that are mediated by an anti-tumor immune response. In humans, such an approach has not yet been reported, but the intratumoral delivery of the synthetic TLR4 agonist G100 is being evaluated in an ongoing clinical trial (NCT 02501473, Table I) that is exploring its effect against Merkel cell carcinoma and soft tissue sarcoma, in the latter case combined with radiotherapy. Similarly, there are TLR4 endogenous agonists such as the nuclear protein HMGB1, and this pathway is turned on upon stressful cell death. Indeed, for cell death to be immunogenic, this pathway is critical in mouse models (34). In fact, following adjuvant chemotherapy for breast cancer, subjects with hypofunctional TLR4 alleles have worse overall survival (34). Injecting cytokines as recombinant proteins directly into the tumor has been attempted. For instance, IL-2 injected in cutaneous melanoma lesions is known to be locally effective but provides little systemic benefit (35).

Bacterial DNA is sensed by the presence of unmethylated CpG motifs by endosomal TLR9 and can be mimicked by oligonucleotides optimizing these CpG sequences in which those cytosines are not methylated (36, 37). Intratumoral delivery of CpG oligonucleotides is active against mouse models (38, 39) and the group of R. Levy has carried out seminal work injecting CpG oligonucleotides into human lymphoma lesions to achieve objective clinical responses when combined with low-dose limited field radiotherapy (40).

Plasmids or RNAs encoding for cytokines can be of use while also providing the innate response to bacterial nucleic acids. Recent evidence with a plasmid encoding single chain IL-12 that is in vivo electroporated into cutaneous melanoma has shown strong signs of clinical activity (41).

dsRNA is mimicked by poly I:C and is detected by endosomal TLR3 and the intracellular sensors RIG-I and MDA-5 (42, 43). Pharmaceutical formulations of poly I:C have been used to treat transplantable mouse tumors, yielding good results particularly when combined with checkpoint inhibitors (44, 45). A stabilized formulation of poly I:C (poly ICLC, Hiltonol) is being used as monotherapy or in combination for intratumoral delivery in a number of clinical trials (46). Another promising nanocomplexed poly I:C agent is also under late preclinical development (47). Because TLR3 is the main PAMP receptor in $XCR1^+$ cross-priming DCs (15, 48), there are trials that combine sFlt-3L to expand the numbers of such DCs combined with intratumoral Hiltonol (NCT 01924689).

TLR7/8 natural agonists are single-stranded RNA molecules with viral features. Chemical agonists such as imiquimod (49) and resiquimod (50) have been developed. Imiquimod, which is formulated as a cream, is active against basal cell carcinoma, melanoma and other skin neoplasms (51) as well as against common warts. Local imiquimod has been used successfully in immunotherapy combinations to treat transplantable mouse models (52, 53), and has been combined with radiotherapy for breast cancer in the clinic (54).

More recently, the STING pathway was found to be critical for antitumor immunity (55). This molecular system detects cytosolic dsDNA through cGAS, which produces cyclic dinucleotides as second messengers, leading to STING activation (56, 57). Intratumoral injection of STING-agonist dinucleotides unleashes a powerful and often curative tumor response against transplantable mouse models (55) and human STING agonists are undergoing clinical development in this setting (NCT 02675439). An intact type I IFN system is critical for both TLR-3 and STING agonists (58). Indeed, the

group of T. Gajewski has found that STING detection of some form of tumor DNA is critical for the baseline immune response against many tumors (59).

Local virotherapy and gene therapy

Viral vectors have been considered vehicles to deliver genes. However, they are sensed by the immune system and elicit strong immune responses (60–62). In this regard, recombinant replicative viruses have been engineered to selectively kill malignant cells in what is called oncolytic virotherapy (60). The original work for each replication-conditional virus relied on a peculiar biochemical feature of the tumor cells to selectively sustain viral replication. However, it is now fully realized that the main mechanism of action of oncolytic viruses is mediated by the ensuing antitumor immune response against viral-infected cells (60). In this regard, both oncolytic viruses and viral vectors are most often genetically engineered to express cytokines or other proimmune factors (63–66).

Intratumoral delivery of bacteria such as *Clostridium* spp. (67) and virus-based agents (66, 68–70) has been extensively tested in transplantable mouse models achieving good local results, while rarely showing efficacy on distantly implanted lesions. One of the problems with viral vectors carrying structural proteins is that the immune response tends to be dominant against the foreign viral Ags, whereas the rules dictating epitope spreading to tumor Ags are not well understood.

In this scenario, it is quite possible that the most potent viruses at eliciting an antitumor immune response would be RNA viruses such as Newcastle Disease Virus (71–73), Sindbis virus (74) or Semliki forest virus (74, 75). These and other virus types (e.g., vaccinia, herpes virus) have proven to be most effective when they are engineered to encode for immune-promoting genes such as IL-12 and GM-CSF (68, 76–78). In all cases these agents are dramatically enhanced in their therapeutic performances by concomitant administration of PD1/PD-L1 and CTLA-4 blocking Abs (73, 79) as well as anti-CD137 or anti-OX40 agonist Abs (80, 81).

In the clinic, an HSV-1 modified oncolytic virus encoding GM-CSF (T-vec, talimogene) has been granted Food and Drug Administration approval for unresectable melanoma when used by intratumoral injection of accessible lesions (76). This translational development represents a milestone in cancer therapeutics and is especially promising in combination with immune checkpoint blocking mAbs, and such combination clinical trials are already underway (NCT02263508, NCT02626000). A recent report on a phase I clinical trial with locally delivered T-vec in conjunction with systemic anti-CTLA-4 mAb (Ipilimumab) achieved a promising overall response rate of 50%, most of which were durable (82). Vectors based on vaccinia virus encoding GM-CSF are also under clinical development (JX-594) with promising results (83, 84). Oncolytic viruses based on adenovirus have also been repeatedly tried in the clinic, but to date their performance has been deemed unsatisfactory (85, 86).

The innate response to viral PAMPs is conceivably important for the outcome by means of inducing IFN-α/β in response to their viral nucleic acids (75, 87) and causing cytopathic immunogenic tumor cell death. Viral RNA is sensed by TLR3, TLR7, and TLR8 in the endosomes and by RIG-I and MDA5 in the cytosol (88, 89). This innate sensing of viral nucleic acids is critical for the therapeutic outcome.

Intratumoral immunostimulatory mAbs

Immunomodulatory mAbs tampering with immune cell receptors constitute a revolution in cancer therapy of unprecedented efficacy (90, 91). The usual mode of delivery is systemic, because this route produces predictable pharmacokinetics and is considered to achieve full receptor occupancy even in the tumor (92), although in at least two cases full receptor occupancy was not reached in the tumor microenvironment after full doses of anti PD-1 mAb (93).

There are three potential advantages if the activity of such Abs is confined to the tumor microenvironment: 1) the most relevant sites of action are on the surface of lymphocytes already infiltrating the tumor or present in the tumor microenvironment; 2) tissue penetration of systemically administered mAb is poorly defined in cancer; and 3) systemic autoimmune and inflammatory side effects can be limited with lower systemic exposure (94). Another potential advantage of local administration is that it likely targets the lymphoid tissue downstream of lymphatic drainage from the injected tumor.

All these principles have been tested in transplanted mouse tumor models including treatment with anti-CTLA-4 (95), anti-CD40 (96, 97), anti-OX40, and anti-CD137 (98, 99) mAbs. In some cases, mAbs have been formulated in emulsions to cause a depot effect and slow release, to maximize local bioavailability (97). Alternatively it might be possible to generate targeted bi- or multispecific Ab–based moieties, given systemically but becoming enriched in the tumor microenvironment (100). However, the best targeting technology still achieves limited local enrichment.

The more systemic toxicity an immunostimulatory Ab presents, the more advisable it seems to deliver it locally. Local delivery permits combinations as described for anti-PD-1 plus anti-CD137 (101) or for anti-CTLA-4 plus anti-OX40 (37). In our opinion, the use of anti-CD137 and superagonist anti-CD40 mAbs (NCT02379741) by intratumoral routes makes sense in light of their systemic toxicity profile (102–105).

Delivering immune cells inside tumors

Cell therapy strategies in immunotherapy involve ex-vivo culture and/or differentiation of immune cells under good manufacturing practices. For instance, DCs have often been used to formulate therapeutic cancer vaccines given through intradermal or i.v. routes (106). Other approaches that have been attempted to maximize bioavailability include intranodal injections (ultrasound-guided injection inside lymph nodes) (107–109).

In DC therapy, approaches have been followed to deliver DCs inside tumors (110, 111). The most successful schemes in mouse models involved DCs transfected to express IL-12 (110) or local DC activation with other immunostimulatory genes (112). Such an approach has been transferred to the clinic with limited success (113). One of the caveats is that the tumor microenvironment is highly suppressive for their function (114). More refined strategies ought to involve tumor tissue destruction before intralesional delivery of such

Table I. Ongoing clinical trials on intratumoral delivery of immunotherapy

	Agent	Combination	Tumor Histotype	Trial ID	Status
PAMPs and analogs	CpG (PF-3512676)	Radiotherapy	Non-Hodgkin lymphoma	NCT00880581	Recruiting
	CpG (SD-101)	Pembrolizumab	Melanoma	NCT02521870	Recruiting
		Ipilimumab, radiotherapy	Non Hodgkin lymphoma	NCT02254772	Recruiting
		Radiotherapy	Hodgkin or non-Hodgkin lymphoma	NCT01745354	Recruiting
		Radiotherapy	Non-Hodgkin lymphoma	NCT02266147	Recruiting
	CpG (IMO-2125)	Ipilimumab	Melanoma	NCT02644967	Recruiting
	CpG (CMP-001)	Pembrolizumab	Melanoma	NCT02680184	Recruiting
	Glucopyranosyl lipid adjuvant in stable emulsion (G100)	Radiotherapy	Merkel-cell carcinoma	NCT02035657	Recruiting completed
	Glucopyranosyl lipid adjuvant in stable emulsion (G100)	Radiotherapy, pembrolizumab	Non-Hodgkin lymphoma	NCT02501473	Recruiting
	Lefitolimod (MGN1703)	Ipilimumab	Solid tumors	NCT02668770	Recruiting
	Poly-I:CLC (Hiltonol)	Intratumoral rhuFlt3L, radiotherapy	Non-Hodgkin lymphoma	NCT01976585	Recruiting
			Melanoma and non-melanoma skin cancer, sarcoma, head and neck squamous carcinoma	NCT02423863	Recruiting
	Imidizaquinoline derivative (MEDI9197)		Solid tumors	NCT02556463	Recruiting
	Clostridium Novyi-NT spores		Solid tumors	NCT01924689	Recruiting
	Allogenic CD4+ memory Th1-like T cell (Allostim)	Cryoablation	Colorectal cancer	NCT02380443	Not yet recruiting
	Cyclic dinucleotides (MIW815)		Solid tumors or lymphoma	NCT02675439	Recruiting
Cytokines	Vector-encoded IL-12		Melanoma	NCT01502293	Not yet recruiting
			Head and neck squamous carcinoma	NCT02345330	Not yet recruiting
			Breast cancer	NCT02531425	Recruiting
Dendritic cells	Activated allogenic DC (INTUVAX)		Gastrointestinal stromal tumors	NCT02686944	Not yet recruiting
	Activated DC	Chemotherapy	Breast cancer	NCT02018458	Recruiting
	Autologous DC expressing CCL21 (Ad-CCL21-DC)		Non-small cell lung cancer	NCT01574222	Not yet recruiting
	Autologous DC pulsed with keyhole limpet hemocyanin	Recombinant adenovirus expressing TNF-α or radiotherapy	Pancreatic cancer	NCT00868114	Not yet recruiting
	Autologous DC	Intratumoral GM-CSF and rituximab, radiotherapy	Non-Hodgkin lymphoma	NCT02677155	Recruiting
	Autologous DC	Cryotherapy	Prostate cancer	NCT02423928	Recruiting
Virotherapy	Parvovirus [^{1}H] (ParvOryx)		Pancreatic cancer	NCT02653313	Recruiting
	Vaccinia-virus encoding GM-CSF (Pexa Vec)	Targeted therapy	Hepatocellular carcinoma	NCT02562755	Recruiting
	Measles virus vaccine encoding carcinoembryonic Ag (MV-CEA)		Glioblastoma	NCT00390299	Recruiting
	Replication-competent adenovirus expressing PH20 hyaluronidase (VCN-01)	Chemotherapy	Pancreatic cancer	NCT02045589	Recruiting
	Mutant replication-competent HSV-1 (HSV1716)		Non–central-nervous system solid tumors	NCT00931931	Recruiting
	Coxsackievirus A21 (CAVATAK)	Ipilimumab	Melanoma	NCT02307149	Recruiting
	Telomerase-specific replication-competent adenovirus (Telomelysin)		Hepatocellular carcinoma	NCT02293850	Recruiting
	Replication-deficient adenovirus encoding inducible IL-12	Veledimex	Glioblastoma or high grade glioma	NCT02026271	Recruiting
			Breast cancer	NCT02423902	
	Replication-deficient adenovirus encoding IFN-γ (ASN-002)		Basal-cell carcinoma	NCT02550678	Recruiting
	Mutant replication-competent HSV-1 (HF10)	Ipilimumab	Melanoma	NCT02272855	Recruiting
	Replication-competent adenovirus encoding CD40L and 4-1BBL	Chemotherapy	Pancreatic cancer	NCT02705196	Not yet recruiting
	Vesicular stomatitis virus-expressing IFN-β		Hepatocellular carcinoma	NCT01628640	Recruiting
	Replication-competent HSV-1 virus encoding GM-CSF (T-VEC)		Melanoma	NCT01740297	Recruiting
			Breast cancer	NCT02658812	Not yet recruiting
	Replication-competent adenovirus (DNX-2401)	Temozolomide	Glioblastoma	NCT01956734	Not yet recruiting
		IFN-γ	Glioblastoma or gliosarcoma	NCT02197169	Recruiting
	Vaccinia GM CSF/thymidine kinase-deactivated virus (Pexa Vec)	Sorafenib	Hepatocellular carcinoma	NCT02562755	Recruiting

(*Table continues*)

Table I. (*Continued*)

	Agent	Combination	Tumor Histotype	Trial ID	Status
	Recombinant fowlpox PANVAC (PANVAC-F)	Subcutaneous Recombinant vaccinia + GM-CSF	Pancreatic cancer	NCT00669734	Not yet recruiting
	Replication-deficient Sendai virus particle GEN0101		Prostate cancer	NCT02502994	Recruiting
	Adenoviral vector expressing HSV-tk (aglatimagene besadenovec)	Valaciclovir, FOLFIRINOX, radiotherapy	Pancreatic cancer	NCT02446093	Recruiting
MoAbs	Agonistic anti CD-40 Ab (ADC-1013)		Solid tumors	NCT02379741	Recruiting
	Agonistic anti-CD40 Ab (APX005M)	Pembrolizumab	Melanoma	NCT02706353	Not yet recruiting
Adoptive cell therapy	CD4 CARs (T1E28z)		Head and neck squamous carcinoma	NCT01818323	Recruiting

APCs. Moreover, tumors should be injected with DC subsets capable of mediating cross-priming (115, 116), because Ags should be uptaken from the tumor cells rather than exogenously given or uploaded (117). One potential advantage is that tumor neoantigens are expected to be immunogenically presented by these strategies that see tumor vaccination with DCs more as a "self-service buffet" than an "à la carte restaurant" (117). In transplanted tumor models in mice, intratumoral injection of DC synergized with radiotherapy (118). The use for this purpose of CD141+ DC that are specialized in cross-priming could be advisable even if the numbers of this subset complicate ex vivo isolation and no reliable differentiation culture is available from human precursors yet. However, increasing their numbers in peripheral blood by means of sFLT-3L pretreatment seems to be a feasible alternative to attain sufficient numbers (119).

Activated T and NK cells can also be administered intratumorally. This idea is still in its infancy but potentially could achieve a round of local activation upon Ag recognition and subsequent recirculation in search of distant tumor lesions. Again, the limiting factor is likely to be the presence of substances in the tumor such as TGF-β that will dampen and impair their performance (120, 121). Engineering the T cells with artificial Ag receptors (TCRs or CARs) with cytotoxic encoding gene-expression cassettes, or providing them with the molecular means to resist the local immunosuppressive factors could be instrumental to attaining clinical efficacy (122, 123). The main advantage of intratumoral delivery of these cells would be to bypass the need for a T cell entrance into the tumor, crossing endothelial barriers and the fact that a high local concentration of T cells will be present inside the directly treated lesions (124). Combining systemic and local delivery of adoptive T cell therapy would be an appealing alternative in this regard.

It is also theoretically possible, although cumbersome from a regulatory point of view, to combine more than one immune cell type to be released intratumorally in such a way that the contribution of several cellular players could be required to achieve a maximal therapeutic response. It should not be forgotten that the antitumor concerts of the immune system perform more efficiently as an orchestra of cell types (125) than as a soloist recital.

Combinations with radiotherapy

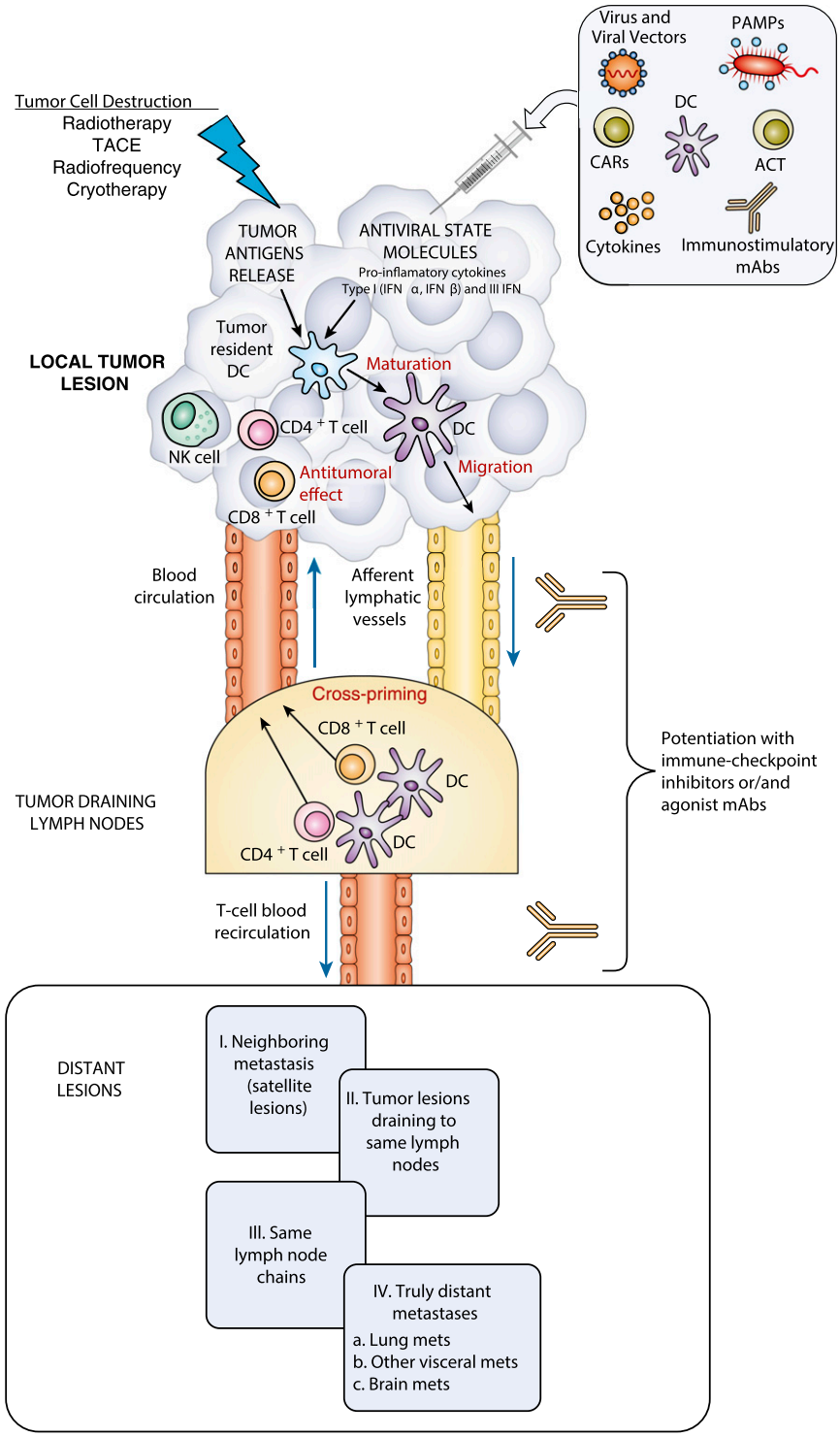
Radiotherapy of cancer is generally considered a local treatment without effect on non-irradiated metastases. However, recent research has defined that irradiation leads to immunogenic cell death and can be exploited to create in situ tumor vaccines (126, 127). Indeed, when radiotherapy is combined with anti-CTLA-4, anti-PD-1 or anti-CD137 mAbs cause distant (abscopal) effects (128) on non-irradiated tumors in mice, and, as in some instances already reported, in humans (129–132). Furthermore, local delivery of TLR7 or TLR9 agonists at a tumor site gives rise to systemic effects on non-irradiated lesions (40, 53, 54). Pilot clinical trials have been reported using both strategies and there are ongoing clinical trials testing radiotherapy plus immunotherapy combinations (Table I).

Radiotherapy is not the only physical therapy to cause immunogenic tumor destruction. Cryotherapy (52), radiofrequency (133), electrochemotherapy (134), and chemoembolization (135) all have potential in this regard. Studying the underlying biology will be of paramount importance, because, for instance, TGF-β induction by radiotherapy might be a serious drawback (136).

Conclusions

There are a number of immune mechanisms to be exploited by local delivery that would mimic infection by a pathogen (Fig. 1). The key aspect is that local intervention needs to exert systemic effects against distant metastases based on lymphocyte recirculation. The difficulty in achieving systemic effects would depend on factors such as proximity, similar lymphatic drainage, vascularization or truly anatomical distance. In tumor vaccination, it has been observed that the site of priming imprints recirculation patterns to T cells (137). This cellular behavior is dependent on chemokine and tissue homing receptors. Interestingly, DCs in each territory imprint the pattern of recirculation receptors to the T cells that they prime by cognate Ag presentation (138).

According to these ideas, the less related an anatomical location is to the distant non-treated tumors, the less prone to respond it will be. Indeed, this has been observed with T-vec (139). However, it becomes possible to administer the successful local treatment to other, still progressing, lesions if the originally injected lesion responds. Repetition might be less successful with viruses because of antiviral neutralizing immunity, but different



Classification of distant objective responses following local immunotherapy according to anatomical distance

FIGURE 1. Concept of local immunotherapy with systemic (abscopal) effect. Schematic representation of the mechanisms that, following local immunotherapy, can yield therapeutic systemic effects. The varying grades of difficulty in achieving responses in terms of anatomical distance are graded I–IV. ACT, adoptive T cell therapy; CARs, chimeric Ag receptors; mets, metastases; TACE, transarterial chemoembolization.

viruses could be rotated and intratumoral PAMPs in principle do not have this potential caveat of agent-neutralizing immunity.

Intratumoral delivery of immunotherapy offers advantages that call for its extensive clinical testing (Table I) and raise the need for new surrogate endpoints to monitor local and systemic efficacy. Pharmaceutical formulations of the agents and strategies of encapsulation, gene therapy or cell therapy need to be considered and developed. Local delivery of immunotherapy agents approved by the Food and Drug Administration and European Medicines Agency should be proposed and compared with systemic administration. Acting locally may pay off when treating cancer globally by means of combined immunotherapy strategies (140–142).

Disclosures

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