Biomaterials for Metastasis: Bridging the Gap between Basic and Translational Research

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Herein lies the issue of how to best approach cancer metastasis therapeutics in a focused, directed and efficacious manner. The lack of standardized means to efficiently deliver therapeutic cargo to metastatic sites calls for a paradigm shift in the way we view and treat metastasis. It is crucial to leverage the potential of nanomedicine to differentially combat cancer spread at each stage of the disease (primary tumor growth and formation of metastases) while considering the optimal administration route. We propose to implement three possible strategies to treat cancer as a function of disease type and state, while leveraging the advancement in materials design and in particular nanotechnology: (1) local primary tumor abrogation; (2) primary tumor re-programming to prevent metastasis; and (3) combination (local and systemic) therapy when metastasis has already transpired. Herein, we highlight potential means to bridge the gap between basic and translational research as related to metastasis therapy.

1. Introduction

Metastasis, cancer cell migration from the primary tumor, accounts for approximately 90% of cancer-related deaths. In fact, in most patients, by the time of cancer diagnosis metastases have already spread to secondary sites throughout the body.[1] Metastasis is a highly complex process which takes place via a series of sequential stepping-stones that include: invasion to boundary tissues, intravasation, circulation, imprisonment at a secondary site, tissue extravasation and growth to form a secondary tumor at a distant organ.[2] Each of these sequential stepping-stones involves rate-limiting processes that are regulated by non-malignant cells that patrol the Tumor Micro-Environment (TME). However, many of these cells become addicted to tumor-initiating alterations, such as mutations that offer unlimited proliferation properties or genetic defects that promote cell division and cell-autonomous utilities.[2] These faults represent excellent opportunities for therapeutic intervention with nanomedicines (i.e., bio- and nanomaterials) capable of targeting specific pathways that control the "metastatic cascade" (see **Figure 1**), or enhancing the regulation of tumor suppressors while impairing the expression of oncogenes and oncogenic transformation. Nevertheless, there is a visible gap between the discovery of therapeutic targets and the translational application of vehicles capable of targeting cancer cells throughout the metastatic process, not only during primary tumor proliferation or metastatic sites colonization (Figure 1). While systemic administration of nanomaterials that were designed to inhibit primary tumor proliferation or treat metastasis that has already colonized other organs was reported,[3,4] developing precision therapies to intercept pre-metastatic processes including intravasation, circulating cells and extravasation is of outmost importance (see Figure 1 for the different stages of the "metastatic clock").

The treatment of metastatic tumors is currently a frustrating challenge for clinicians due to poor clinical outcomes following conventional therapies. Systemic chemotherapy and radiotherapy are the main conventional therapies used to treat cancer. However, their use imparts limited improvement in survival following metastasis occurrence, due to inadequate drug bioavailability, selectivity and development of multidrug resistance.[5] Moreover, none of the conventional therapeutic modalities available for treating metastasis such as chemo-therapy, surgery and radiation provide adequate efficiency, quality-of-life or palliative care for cancer patients. In fact, the most commonly used drugs, such as taxanes, alkylating agents, antimetabolites, anthracyclines, aromatase and topoisomerase inhibitors or corticosteroids are associated with adverse effects such

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as hematologic toxicities, constipation and pneumonitis, as well as hepatotoxicity, hepatic fibrosis or osteonecrosis.[6,7]

In the past decade, novel biomaterials and nanomedicines have emerged,[8–12] prompting cancer researchers to call the status quo treatment regimen into question. It is here that Nanomedicine enters the fray in influencing therapeutic efficacy throughout the metastatic course.[13] Although there is a growing number of FDA approved monoclonal antibodies and small molecules targeting specific types of cancer,[5] their delivery is still challenging. In fact, numerous studies show that the relative bioavailability of encapsulated drugs is greater than that of free drugs. Chemotherapy results show better or equivalent clearance of encapsulated drug-administered groups (weekly) than with free drugs (daily). Nanomedicine can overcome some of these challenges by offering a wealth of tools able to (I) avoid side and off-target effects by homing to the site of interest; (II) reduce toxicity to healthy cells; (III) enhance intracellular uptake in cancer and metastatic cells; (IV) impart controlled payload pharmacokinetics and pharmacodynamics; and (V) protect the encapsulated payload from degradation or clearance.

When considering metastasis treatment, in addition to targeting cancer cells that are circulating cells or cells that have colonized in distant organs, abrogating the main source for metastasis, the primary tumor, is critical. In that regard, giving priority to systemic treatments despite the benefits of local and sustained therapies for primary tumor abrogation turns out to be quite reductive when using nanomedicines. It is evident that systemic administration is typically associated with rapid clearance from the blood stream and non-specific accumulation in kidneys, spleen, liver and lymph nodes. Nevertheless, more than 95% of all the nanomaterials developed to date for treating metastasis rely only on systemic administration via intravenous injection (**Table 1**). Due to the non-specific accumulation associated with systemic administration, this route requires a high dose to abrogate the primary tumor, whereas the local administration delivers a higher 'effective' dose while minimizing systemic toxicity, side effects and clearance. Here we propose the applicability of three rules that represent a paradigm shift in the way we view and treat cancer and metastasis: 1) Local rather than systemic administration routes to treat the primary tumor; 2) Local primary tumor reprogramming to prevent metastasis; and 3) Combined local and systemic therapies to abrogate the primary tumor and metastasis when metastasis already occurred.

2. Primary Tumor Abrogation – Local versus Systemic Administration: Make or Break

Cancer is commonly viewed as a "systemic" disease that mandates systemic treatment. Nevertheless, while systemic treatment is necessary to eliminate metastasis, this approach is suboptimal for treating the primary tumor. In fact, a recent meta-analysis on the evaluation of nanoparticle delivery to tumors in the last 10 years revealed that only 0.7% of the administered nanoparticle dose accumulate in the solid tumor.[26] The passive delivery of free or encapsulated therapeutics through the Enhanced Permeability and Retention (EPR) effect characterizing the primary tumor results in cargo accumulation at the primary tumor site. However, rapid clearance of

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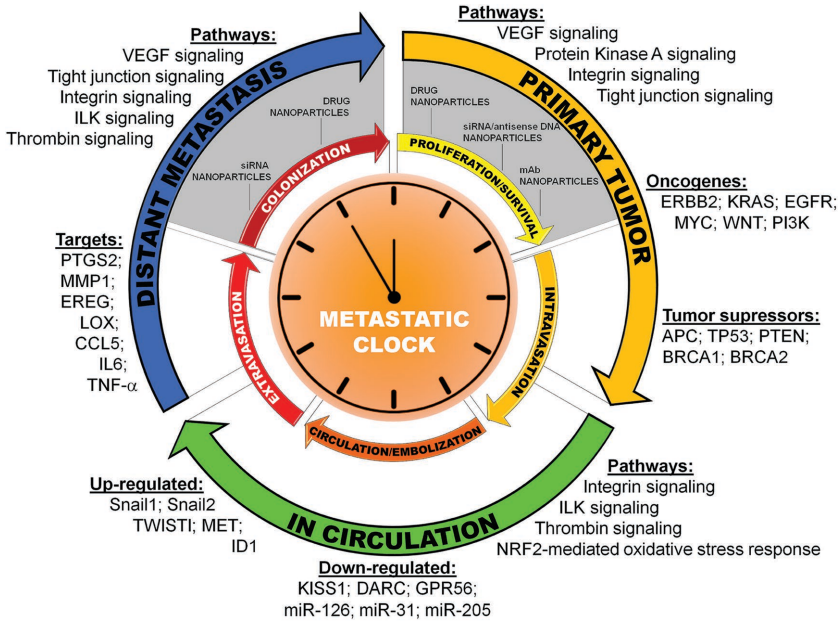

Figure 1. The "METASTATIC CLOCK": the steps of metastasis and targets/pathways for therapeutic modulation. The basic steps of metastasis that represent the progression of the primary tumor towards an invasive tumor include proliferation and survival, intravasation, survival in circulation and embolization in order to extravasate, infiltrate and colonize distant organs. Concisely, in order for metastatic cells to successfully colonize new organs and sites, they must break free from the primary tumor to enter the bloodstream. When in circulation, metastatic cells' distribution is determined by blood flow and the interactions between cancer cells, and the secondary organs determine their ability to colonize and disseminate. After harboring at the secondary site, cancer cells depart the bloodstream, proliferate and release pro-inflammatory compounds and proteinases that induce their neighboring cells to support them by releasing growth factors that further nourish the tumor. In each of these steps engineered nanomaterials can target specific signaling pathways or specific oncogenes, tumor suppressor genes, cellular markers or microRNAs (miRNAs) involved in the metastatic process: from the primary tumor to circulating tumor cells and distant metastasis. Nevertheless, nanomaterials have been mainly developed to target the first steps of primary tumor proliferation or the already formed metastatic sites. The marked gap between these stages of the disease calls for the design of specific nanomaterials able to target circulating cancer cells, as well as cells undergoing intravasation and extravasation.

circulating nanomaterials especially during systemic delivery is still a challenge along with non-specific accumulation in other organs including liver, kidneys and spleen.

One can leverage existing materials developed for tissue engineering[27] to locally deliver embedded nanotherapeutics to increase specificity and efficacy in abrogating the primary tumor. Understanding materials fate in vivo will then become critical to dictating and predicting the release kinetics of embedded therapeutics. The local tumor microenvironment will play a key role determining the fate of the materials as well as that of cancer and metastatic cells.[28,29] In addition, biomaterials route of administration will affect the delivery schedule of drugs from drug-doped materials. Hence, administration route must be carefully chosen and optimized in order to improve the efficacy of therapies based on nanomaterials.[30,31]

Antibody-drug conjugates, polymers or radioisotope-labelled antibodies are currently used in the clinic for cancer and metastasis targeting by systemic administration. Although some of these nanoproducts for the treatment of metastatic breast cancer are getting into clinical trials, such as protein nanoparticles encapsulating paclitaxel (Abraxane® from Abraxis BioScience), the final outcome is far from being effective. Complete or partial response to therapy rounds at only 20–30% of subjects and the treatment is associated with severe to moderate adverse events as gastrointestinal disorders, nausea, vomiting, metabolism and nutrition disorders or even hypertension and cerebrovascular ischemia.[32]

Other administration routes used to deliver nanoparticles are also associated with a systemic response. For example, non-cationic near-infrared (NIR) fluorescent nanoparticles were used to target lymph nodes after intratracheal instillation to the lungs.[33] These nanoparticles can traffic rapidly from the lungs to lymph nodes, to the bloodstream, and be subsequently cleared by the kidneys. Indeed, the majority of the studies reporting on systemically administered nanoparticles show non-specific accumulation in spleen, kidneys, liver, heart or lungs[16,34–36] or in body fluids, urine in particular.[33] In fact, the accumulation of nanoparticles administered systemically at the target tumor site rarely exceeds 1% of the administered dose.[26,37]

In contrast, reports about local cargo administration show marked improvement in therapeutic payload accumulation and uptake in cancer cells at a level higher than 90%. Local administration allows delivering much higher 'effective' dose while enhancing therapeutic molecules' stability, minimizing systemic toxicity and side effects as well as clearance. Local administration of smart scaffolds embedded with nanoconjugates for microRNA modulation[38] or gene therapy combined with chemotherapeutic drug delivery[39] has previously been reported with outstanding results for abrogating primary tumor locally, with approximately 90% reduction in tumor size.

Now it is imperative to leverage the local administration of composite scaffold/nanoparticles to create innovative platforms that locally abrogate the primary tumor as a neo-adjuvant therapy prior to tumor resection. Following primary tumor resection, biomaterials can be used in a washout procedure as a prophylactic scaffold to prevent cancer recurrence. Alternatively, the noninvasive application of this prophylactic patch may enable tumor remission, thus eliminating the need for surgery. Effective tumor shrinkage can be attained because of the sustained release of the therapeutic cargos from its supporting scaffold over weeks.[38,39]

3. Re-Programming the Primary Tumor: Preventing Metastasis

The metastatic cascade promotes programs that enable migration from primary to metastatic sites. These programs are

Table 1. Summary of nanomaterials for treating metastatic tumors.

Approach	Type of material	Surface modification	In vivo model	Metastatic model induction	Route of administration	Results	Ref.
Gene therapy	Polymeric NPs	PEI; siRNA anti-WT1	B16F10 melanoma mice	Intravenously (tail-vein)	Inhalation	WT1 silencing prolonged mice survival, by reducing lung metastasis from melanoma	[14]
	Lipid NPs	RGD, RAD peptides; siRNA anti-integrin β3	MDA-MB-231 breast cancer mice	Intravenously (tail-vein)	Systemic (intravenous injection)	Tumor resection at week 9 and total relapse of metastases	[15]
	Gold NPs – gold nanobeacons	Antisense DNA anti-Kras; PEG	MGC-803 gastric cancer mice	Subcutaneously	Systemic (intravenous injection)	~60% tumor size reduction and 90% reduction in tumor vascularization, preventing metastasis to lung (80% reduction), increasing mice survival in >85%.	[16]
	Liposome	DNA; siRNA anti-MDM2/c-Myc/VEGF	B16F10 melanoma mice	Intravenously (tail-vein)	Systemic (intravenous injection)	Significant reduction (~70–80%) of lung metastases and prolonged survival (30%)	[17]
	Polymeric NPs	p65 shRNA; PEI	MDA-MB-435 breast cancer mice	Intravenously (tail-vein)	Systemic (intravenous injection)	High accumulation in tumor and almost complete inhibition of metastasis	[18]
Chemotherapy	Polymeric NPs	DSPC; DOPE; DSPE; DOX cholesterol; cyclic RGD	Pancreatic and renal mice of spontaneous metastasis	Injection in the renal subcapsule	Systemic (intravenous injection)	Real-time targeting of NPs to tumor vessels and regions expressing integrin αvβ3, resulting in 15-fold increase of anti-metastatic activity	[19]
	Polymeric NPs	poly l-lysine; β-cyclodextrin; RIS drug	CHO ovarian cancer mice	Intravenously (tail-vein)	Systemic (intravenous injection)	Prevention of cancer-induced bone metastasis in animals	[20]
Phototherapy	Gold nanoshells	PEG	B16F10 melanoma mice	Intravenously (tail-vein)	Systemic (intravenous injection)	Combination of phototherapy and antitumor immune reactivity prevented primary tumor recurrence post-ablation and abrogated the outgrowth of lung metastases	[21]
	Polymeric NPs	DiR dye; (mPEG)-*b*-PDPA copolymer	4T1 breast cancer mice	Injection in the mammary fat pad	Systemic (intravenous injection)	Primary tumor and metastasis are entirely inhibited by a single treatment NPs with NIR irradiation	[22]
Chemotherapy + Phototherapy	Gold nanorods	calf thymus DNA; DOX	4T1 breast cancer mice	Injection in the mammary fat pad	Systemic (intratumoral injection)	Tumor growth inhibition and metastasis prevention attributed to NP's abilities to induce cellular apoptosis and necrosis to ablate intratumoral blood vessels	[23]
	Liposomes	Oligomannose; 5-FU	MKN28 and GCIY gastric cancer mice	Intraperitoneally	Systemic (intraperitonealinjection)	No apparent reduction was seen in tumor growth but significant control of cancer metastatic to milky spots	[24]
Chemotherapy + Gene therapy	Polymeric NPs emulsion	PEG; PLGA; EPL; surviving siRNA; DOX; TAX	B16F10 melanoma mice	Intravenously (tail-vein)	Systemic (intravenous injection)	Effective anti-tumor activity, with ability to target various sized tumors and overcome lung metastasis	[25]

5-FU- 5-fluorouracil; **c-Myc**- myelocytomatosis oncogene; **CTCs**- circulating tumor cells; **DiR**- 1,1-dioctadecyl-3,3,3,3-tetramethylindotricarbocyanine iodide; **DOPE**- dioleoylphosphatidylethanolamine; **DSPC**- distearoylphosphatidylcholine; **DSPE**- distearoylphosphatidylethanolamine; **DOX**- doxorubicin; **EPL**- co-polymer; **MDM2**- negative regulator of p53 tumor suppressor; **NPs**- nanoparticles; **PEG**- Poly(ethylene glycol); **PEI**- Polyethylenimine; **PLGA**- Poly(Lactide-co-Glycolide); **PPE**- poly(*para*-phenyleneethynylene); **RGD**- peptide Arg-Gly Asp; **RIS**- antitumor bisphosphonate drug risedronate; **TAX**- taxol (or paclitaxel – PTX); **VEGF**- Vascular endothelial growth factor; **WT1**- Wilms' tumor gene 1.

strongly adopted by the tumor cells and allow for multiple patterns of invasion,[40] posing strong barriers to the success of anti-metastatic therapy. In fact, it is well appreciated that targeting metastasis is far more difficult than targeting the primary tumor. However, unique moieties that are presented in both primary and secondary tumors represent a path to targeting metastasis in a specific and efficient manner. Metastatic cancer cells can upregulate certain cell-surface molecules (e.g., chemokine receptors, integrins, selectins) and secreted factors, that may originate from early embryonic cell development or may express unique endogenous surface proteins originating from the cells comprising the primary tumor.[41–43]

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New strategies must consider the binding affinity of the nanoparticles to the target cells and organs, as well as binding specificity and immunogenicity. Early primary tumor elimination prior to metastasis formation may afford metastasis prevention by eliminating the primary tumor that serves as the 'source' for metastasis. In addition, reprogramming the cancer cells to prevent their migration and invasion is another tool to blocking metastasis before its spread. For instance, Murphy et al. developed a liposome coated with a cyclic RGD to target αvβ3 integrin receptor to deliver a chemotherapeutic drug (Doxorubicin) and found that this system was able to target and disrupt the primary tumor vasculature, thus preventing metastasis from occurring in the hepatic hilar lymph node.[44]

The extracellular matrix (ECM) represents another barrier to metastasis formation,[40] where several cell-adhesion proteins and molecules are involved, especially the extracellular proteases such as Matrix Metallo-Proteinases (MMPs). MMPs are responsible for disintegrating the ECM and release growth factors and cytokines, such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) or tumor necrosis factor-α (TNF-α), influencing tumor cell survival, growth and proliferation.[40] Some nanomaterials (e.g., gadolinium metallofullerenol nanoparticles or superparamagnetic iron oxide nanoparticles) were developed to target and inhibit these proteinases, especially via decrease of MMP-2 and MMP-9 expression followed by the prevention of metastasis.[45,46]

Tumor associated immune cells are major contributors to metastasis formation and their levels correlate with patient prognosis.[31] Despite the key role immuno-modulation of the tumor microenvironment plays in controlling tumor growth and metastasis,[47] it is an underexplored field in materials science, in particular as related to local administration. The few studies that reported on the use of nanomaterials for immunotherapy describe the development of adjuvants that are systemically administered, which are often associated with insignificant tumor size reduction, non-specific accumulation in body organs and short half-lives.[48–50] As 99.9% of the tumor cells are recognized by our immune system, it is wise to further augment the immunity functions to inhibit metastasis.[51] Immunotherapy is thought to be a promising treatment for metastasis, either by stimulating or strengthening the immune system or by disabling the TME immune-suppressive processes.[31] Stephan et al. described a bioactive polymer implant capable of delivering, expanding and dispersing tumor-reactive T cells locally, reducing tumor relapse compared to conventional delivery modalities.[52] Several biomaterials have also been used to re-model and re-program tumor associated macrophages (TAMs) using STAT3 (triggers crosstalk between tumor cells and TAMs) or TNF-α inhibitors, monoclonal antibodies targeting cytokines and chemokines[53,54] (e.g., IL-2, IL-12, IL-10) for immunomodulation of the TME or anti-angiogenesis antibodies targeting EGFR or VEGF.[34,55] Fahmy and co-workers reported the use of nanoscale liposomal polymeric gels to deliver locally a transforming growth factor-β (TGF-β) and IL-2 in a melanoma mouse model. This system was designed to enhance systemic immunotherapy efficacy by the activation of $CD8^+$ T cells and natural killer (NK) cells, resulting in an increased survival and suppression of metastasis by approximately 50%.[54]

Another enlightened study by *Chen* and co-workers revealed that hydrazinocurcumin encapsulated nanoparticles are able to re-educate TAMs and exhibit anti-tumor effects on metastatic breast cancer following in vivo STAT3 suppression.[56] The authors demonstrated that the re-polarization of the M1-like macrophages had an opposite effect to that of M2-like macrophages, especially as relates to the suppression of tumor growth, angiogenesis and metastasis in vivo.[56]

Nevertheless, no studies so far harnessed the combination of TME re-education with chemotherapy or phototherapy procedures to treat the primary tumor and prevent metastasis. The combined effect could impart more robust clinical outcomes particularly using nanoparticles with the capacity to encapsulate high payloads to be delivered locally. When metastasis already occurred, local application cannot be solely applied and systemic administration of nanoconjugates for gene and drug delivery should be used in conjunction with local therapy to eliminate metastasis.

4. Combination Therapy – Local and Systemic: Eliminating the Primary Tumor and Metastases

By the time of cancer diagnosis, many patients already present with metastasis. This prompts the use of a dual therapy approach that combines local therapy to efficiently treat the primary tumor with systemic therapy to abrogate metastasis, enabling to approach cancer from all sides (**Figure 2**). Nanomaterials can be engineered to carry multiple therapeutic payloads with different functions and co-deliver them both to the primary tumor and to the metastatic sites. Primary tumor re-education locally with nanomaterials to block the initiation of metastasis by repolarization of TAMs is one of the most common approaches.[57,58] Using anti-angiogenic agents such as nanomaterials carrying inhibitors or monoclonal antibodies (mAbs) against VEGF or EGFR were also explored to abrogate the primary tumor.[59,60] To target metastatic sites, the use of theranostic nanomaterials[61–63] and a dual targeting nanoparticle approach[51] to detect and intercept both circulating tumor cells (CTCs)[64–66] and already established metastatic tumors (which were colonized in an organ-specific manner, see Figure 2 for the percentages, which refer to the relative incidence of metastatic spread to a specific organ) may be used to co-deliver multiple drugs/genes.[67] In addition to local primary tumor abrogation, the majority of nanomaterials developed so far to treat metastasis systemically (Table 1) are based on gene therapy (~50%) or chemotherapy (~40%) alone. Treatment efficacy can be significantly improved by using combination therapies, such as immunotherapy, thermotherapy or photodynamic therapy to attain the desired therapeutic regimen.

In particular, an unexplored field in gene therapy is the local delivery of microRNAs (miRNAs) to the primary TME to control the primary tumor and leverage this platform for the treatment of early metastatic events. Being master regulators of gene expression, miRNAs constitute an attractive candidate to control metastasis progression via regulating cell motility. It is well known that miRNA signature characterizes primary tumors that metastasize.[69] In fact, in the last 5 years several miRNAs have been shown to activate metastasis by regulating

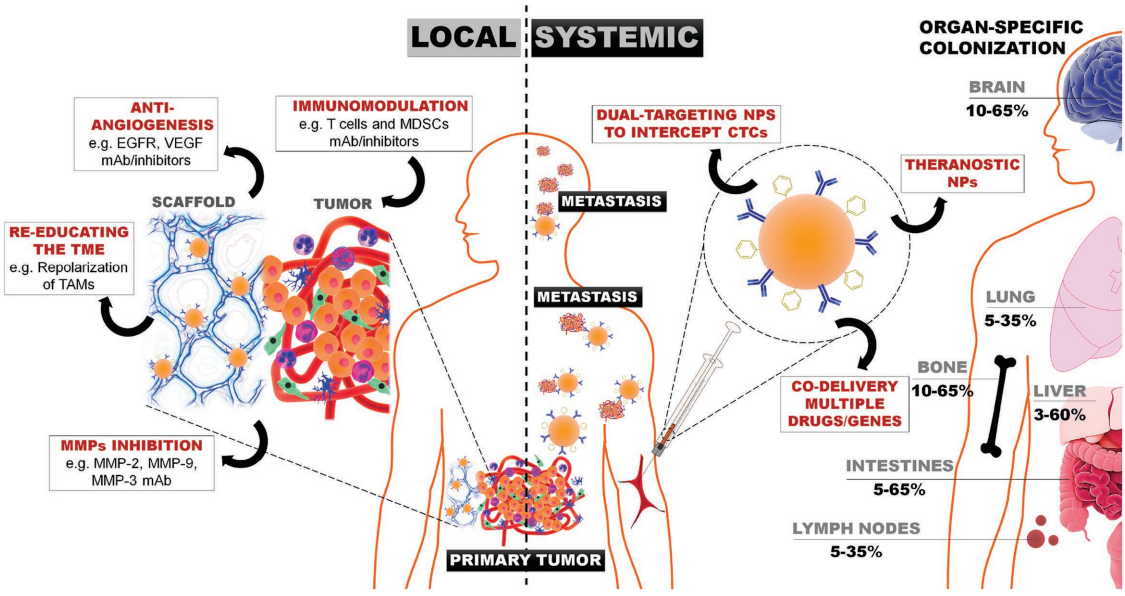

Figure 2. Exploiting the tumor microenvironment (TME) to prevent metastasis locally via the targeting and re-modelling of the primary TME and at the same time intercept circulating tumor cells (CTCs) and treat the already existing metastatic sites systemically. LEGEND: **EGFR**- epidermal growth factor receptor; **mAb**- monoclonal antibody; **MDSCs**- Myeloid-derived suppressor cells; **MMPs**- Matrix metalloproteinases; **TAMs**- tumor-associated macrophages; **VEGF**- Vascular endothelial growth factor. Organ specific colonization statistics adapted from.[13,68]

multiple signaling pathways, such as (I) migration, invasion and adhesion, (II) EMT modulation and stem cell-like processes, and (III) pathways involved in proliferation both at the primary tumor and at distant sites.[69] Therefore, the development of a strategy to impair the tumorigenic process using engineered biomaterials capable of targeting miRNAs that control both oncogenes and tumor suppressor genes simultaneously is highly promising.[70]

Further down the road, we anticipate that biomaterials delivering other non-coding RNAs, possibly transfer RNAs or small nuclear RNAs (which are key players involved in mRNA splicing) could manipulate the cell's systems to imbalance or rebalance natural events (such as translation or mRNA splicing). miRNAs in particular, besides their local effect, may have far-reaching implications on systemic events, as they are relatively stable in the blood.

5. The Future of Anti-Metastatic Nanomedicines

To date, most nanomaterials used for cancer therapy have largely focused on targeting the primary tumor, giving priority to systemic treatments, despite the promise and benefits of local and sustained therapies for primary tumor abrogation. A shift in cancer molecular treatment must take place now that early cancer detection and therapy may enable inhibiting the formation of metastasis, calling for a local approach to abrogating cancer and preventing metastasis at the same time. Treating cancer cells to prevent local motility and metastasis could represent a better alternative rather than systemic delivery of large doses of drugs. Although local treatment poses the risk of seeding metastases, there are many cases in particular in early tumor stages in which the sole treatment involves tumor resection without systemic chemotherapy. In that case, few remaining cancer cells at the resection site may facilitate cancer recurrence and formation of metastases and can benefit from local material application as a washout procedure to completely abrogate tumor recurrence following tumor resection. Local therapy is not sufficient when metastasis has already occurred; in that case systemic therapy should be used in conjunction with local therapy to eliminate metastasis. The combination of a local platform to treat and re-educate the primary tumor along with systemic administration to treat existing metastasis would impart highly efficacious translational therapeutic platforms with improved clinical outcomes. Progress in materials science, cancer biology and immunology calls for the adoption of new approaches and treatment modalities. We urge the scientific community together with clinicians to decide on standardized treatment plans while considering tumor type and state to impart the optimal therapeutic outcome. In order for nanomaterials to achieve a broad clinical implementation, they need to endure a delicate balance between ease of synthesis and manipulation while providing adequate safety and efficacy. Hence, the construction of standardized treatment for metastasis is imperative. A paradigm shift in the way we treat cancer and metastasis in particular will provide the scientific, pharmaceutical and clinical communities with unprecedented opportunities for the development of new clinically relevant cancer therapeutics.

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