NANOMEDICINE

Swarming towards the target

A system comprising ‘signalling’ and ‘receiving’ modules — where the receiving module circulating in the bloodstream is directed to the tumour by a cascade triggered by the signalling module — improves the targeting effect of a nanomedicine.

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The power of nanomedicine — a subfield of nanotechnology that uses nanomaterials for the diagnosis and treatment of disease1 — stems from our ability to tailor the properties of materials. This can be achieved by engineering their compositions, structures, sizes and shapes, modifying their surfaces with ligands, and integrating different functions for multimodal imaging or theranostic applications. The full promise of nanomedicine is unlikely to arrive until we can selectively deliver nanomaterials to particular sites of interest, with minimal accumulation in off-target regions. Writing in Nature Materials, von Maltzahn et al. report a giant leap forward with their development of nanoparticles that can communicate to enhance cancer targeting.

In the case of cancer, nanomaterials can be directed to the tumour through both passive- and active-targeting mechanisms2. Passive targeting is based on the enhanced permeability and retention effect, which allows a nanomaterial to leak into tumour tissue because of permeable vasculature caused by rapid angiogenesis. Longer retention time of the nanomaterial in the interstitial space, attributed to decreased lymphatic drainage, also leads to a higher concentration in the tumour relative to surrounding tissues. The passive effect can be enhanced by coating the nanomaterial with poly(ethylene glycol) (PEG), which prevents the adsorption of blood serum proteins, and thus extends the circulation time and increases the probability of permeation into the tumour tissue. Active targeting takes advantage of the overexpression of certain receptors on the membrane surface of a tumour cell. Coating the nanomaterial with a ligand that binds specifically to a tumour-associated receptor causes a further increase of its retention in the tumour relative to passive targeting alone. Despite efforts devoted to the development of passive and active mechanisms, tumour-targeting efficiency is still undesirably low when compared with competing off-target and blood-clearance effects.

Von Maltzahn et al. propose a new strategy for improving tumour targeting based on an intelligent system containing ‘signalling’ and ‘receiving’ modules that communicate through endogenous signalling cascades (Fig. 1a). Just as military reconnaissance missions, deployed to gather information on enemy composition and location, can direct fighting troops to strategic locations during warfare, the dual-modular system aids in the accumulation of theranostic agents at the site of interest. Low numbers of scouting signalling particles pre-delivered to the cancerous lesion recruit masses of receiving particles, or fighting troops in our military analogy. Thanks to a cascade process, an enormous amplification occurs for the accumulation of receiving particles at the site of interest. Enhancement through communicative signal amplification is not a new biological phenomenon; well-known examples include insect swarming and human immune-cell trafficking3. In fact, the dual-modular system mimics the communication-dependent recruitment of inflammatory cells to regions of disease to improve in vivo tumour-targeting efficiency.

To test the approach, von Maltzahn et al. constructed two types of signalling modules, a PEG-modified gold nanorod and an engineered human protein, and two types of receiving modules, an iron oxide nanoworm and a drug-loaded liposome (Fig. 1b,c). They recruited the receiving module to the tumour site by taking advantage of the physiological coagulation cascade — a ubiquitous but complex process that occurs when a blood vessel is injured. Several proteins known as coagulation factors are

Figure 1 | The power of communication in tumour targeting. a, The signalling module (red) broadcasts the tumour location to the receiving module (blue) in circulation in the bloodstream. b, The two types of signalling modules: a gold nanorod that initiates coagulation on near-infrared laser irradiation and an engineered tumour-targeted human protein tissue factor that activates coagulation on binding to tumour receptors. c, The two types of receiving modules: an iron oxide nanoworm designed for magnetic resonance imaging and a drug-loaded liposome as an example of a therapeutic agent.
activated one by one in a cascade fashion, triggering platelet cells in the bloodstream to form a plug at the site of injury and thus terminate bleeding. The authors demonstrate a nanoscale signalling module based on gold nanorods, which is pre-delivered to a tumour site through passive targeting and then irradiated with a near-infrared laser to initiate the coagulation cascade via the photothermal effect. The heat released from the irradiated gold nanorods causes damage to blood vessels in the tumour, activating both the tissue-factor (extrinsic) and contact-activation (intrinsic) coagulation pathways. They also devised a molecular signalling module based on a truncated, tumour-targeted human protein tissue factor that activates the extrinsic coagulation pathway on binding to receptors on the surface of tumour cells. As revealed by fluorescence and thermal imaging, both signalling modules could indeed produce tumour-specific coagulation.

The coagulation signalling output is exploited using two receiving modules: iron oxide nanoworms as an imaging contrast agent (they are chain-like assemblies of iron oxide nanoparticles originally designed for magnetic resonance imaging), and drug-loaded liposomes as a therapeutic agent. By functionalizing their surfaces with peptides that target the coagulation cascade and serve either as direct targets for fibrin or as substrates for Factor XIII (a specific coagulation-cascade enzyme), the particles exhibited a tenfold increase in accumulation in tumours that were subjected to heat-induced coagulation.

Having developed signalling and receiving modules in isolation, von Maltzahn et al. then integrated both modules to enhance tumour targeting in vivo. In essence, the signalling module serves as an initiator for the coagulation cascade while the receiving module quickly responds to the output of the cascade. Impressively, the dual modular system could enhance the accumulation of doxorubicin (an anti-cancer drug) in tumours by 40 times when the drug is loaded within Factor XIII-covered liposomes instead of plain liposomes. When compared with an optimized, tumour-targeting liposome system lacking a signalling component, there was also a sixfold increase in accumulation for communication-enabled doxorubicin liposomes. When compared with an optimized, tumour-targeting liposome system lacking a signalling component, there was also a sixfold increase in accumulation for communication-enabled doxorubicin liposomes. These results clearly demonstrate enhancement of tumour targeting and drug delivery over conventional agents directly targeted to tumour receptors. Moreover, a single treatment with the dual modular system (gold nanorods coupled with Factor XIII-covered liposomes) showed a prolonged inhibition of the growth of mouse-implanted human carcinoma relative to non-communicating controls or components in isolation.

Although this study may motivate a shift towards systems nanomedicine, long-term studies are necessary before considering these systems for clinical applications.

Endogenous biological signalling cascades, such as that of coagulation, are complex and involve a myriad of biological players and targets. Exploitation of such cascades by synthetic nanosystems requires verification of non-toxicity and the absence of adverse side effects on a systemic level. Furthermore, a wider array of signalling and receiving toolkits as well as biological cascades will need to be carefully designed and tested to increase the applicability and usefulness of this communication system across a spread of human diseases. Despite necessary validation studies, the application of communication strategies to historically single-component nanosystems promises enormous potential in the improvement of targeted cancer diagnosis and therapy.

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References

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