Drug delivery

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Rerouting nanoparticles to bone marrow via neutrophil hitchhiking

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Drug delivery to the bone marrow has limited efficiency, hitchhiking on bone marrow homing neutrophils offers a solution.

The treatment of bone disorders such as bone cancer, osteomyelitis, osteoporosis, and osteoarthritis has long been restricted because of the inefficient delivery of therapeutics to bone marrow[1]. Even though increasing the dose of therapeutics can improve drug concentrations in bone marrow, this leads to greater adverse off-target effects. To solve this dilemma, researchers have developed several strategies. For example, one study[2] found that nanoparticles with sizes smaller than ~170 nm can accumulate in bone marrow because of narrow intercellular clefts (~170 nm) between bone marrow endothelial cells. Improved paclitaxel delivery to bone marrow was achieved using 150 nm nanoparticles as carriers. Others have shown that decorating bone targeting modalities such as bisphosphonates[3], aptamers[4], and peptides[5] on nanoparticles can improve bone marrow delivery. Although these strategies have been encouraging, high drug accumulation in bone marrow for disease treatment remains marginal because of low blood perfusion in bone as well as blood-marrow barriers that significantly hamper the permeability of current delivery systems[6].

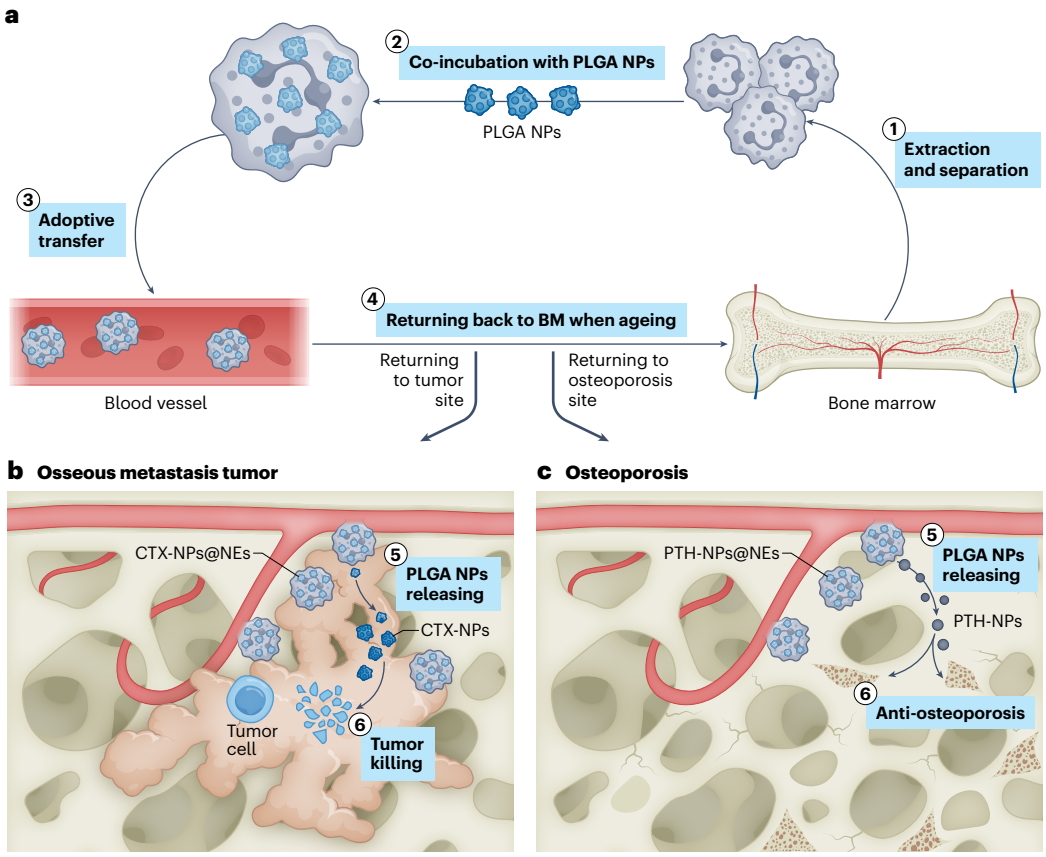

Fig. 1 | Rerouting nanoparticles to bone marrow via neutrophil hitchhicking. **a**, Schematic illustration of the mechanism of the bone-specific drug delivery system. Neutrophils were collected from mice and cultured in vitro for 6 h for aging (1). NEs were then incubated with PLGA nanoparticles (therapeutics can be loaded in the nanoparticles) to obtain nanoparticle-loaded NEs (2). After the cells were adoptively transferred to mice (3), aged neutrophils traffic to bone marrow and the therapeutics can thus be released to the bone marrow (4). **b**, The delivery system carrying a chemotherapeutic drug cabazitaxel (CTX) enhanced CTX delivery to bone marrow and improved osseous metastasis tumour treatment (see panel **b** (5,6)). **c**, When an anti-osteoporosis drug teriparatide (PTH) is delivered in NEs, PTH accumulation in the bone marrow can also be improved, which promoted osteoblasts growth and simultaneously inhibited osteoclasts growth to treat osteoporosis (see panel **c** (5,6)).

Writing in *Nature Nanotechnology* Luo et al., inspired by aged neutrophil (NE) trafficking to bone marrow for apoptosis, report on a bone marrow-targeted nanoparticle drug delivery system[7] by hitchhiking aged NEs.

Using live cells as carriers to improve targeted therapeutic delivery holds great promise to overcome the above challenges, due to the potential of active targeted delivery over passive accumulation strategies. Cells carrying therapeutics are usually recognized as 'self' and tend to not be rapidly cleared by the body[8], which can prolong circulation time and increase therapeutic delivery to target tissues. Certain cells tend to traffic to the tissue or microenvironment of their origin, and some cells can migrate to specific physiological or pathological microenvironments upon sensing biological cues[8]. Therapeutics delivered by these cells can co-migrate with carrier cells and achieve site-specific delivery. Until now, many cell-based drug delivery platforms targeting the brain[9,10], lung[11], and tumour[12] have been designed by taking advantage of several tissue-tropic cell types[9–12]. However, using cells as carriers to deliver therapeutics to the bone marrow is challenging because of the lack of a bone marrow-specific delivery mechanism.

The human adult produces 100 billion neutrophils every day, and these cells have a short lifespan of ~5.4 days[13]. As neutrophils age, they express high levels of CXCR4, a protein that facilitates their cellular migration to bone marrow to undergo apoptosis[14]. Inspired by this, Luo et al. designed a bone marrow-targeted nanoparticle drug delivery system[7] by hitchhiking aged NEs. As illustrated in Fig. 1a, Poly(lactic-co-glycolic acid) nanoparticles encapsulating the fluorescent dye DiR (DiR-NPs) were phagocytosed by aged NEs to obtain DiR-NPs@NEs. In mice receiving intravenous injection of DiR-NPs@NEs, the researchers observed DiR-NP levels in bone marrow increased ~7-fold compared to treatment with free nanoparticles. Moreover, when delivering the chemotherapy drug cabazitaxel (CTX), CTX-NPs@NEs treatment leads to 5- to 20-fold increase in bone marrow drug concentration compared to CTX-NPs treatment. These results demonstrate that nanoparticles can actively enter bone marrow by hitchhiking on aged NEs and increase drug accumulation in the bone marrow.

Luo et al.[7] then constructed a mouse bone metastasis tumour model and tested if bone marrow-specific delivery of CTX PLGA NPs by aged NEs can improve the treatment of a bone metastatic 4T1 breast cancer (Fig. 1b). They found that CTX-NPs@NEs substantially inhibited bone tumour growth compared to CTX, CTX-NPs, and NE treatments. Further metastasis of tumour cells to the lung and subsequent lung-damaged associated dyspnea were observed in the CTX, CTX-NP, and NE treatment groups. However, in the mice treated with CTX-NPs@NEs, dyspnea was not detected. Remarkably, CTX-NPs@NEs treatment also led to 100% mice survival at day 21, whereas most mice in the other groups did not survive. In addition to testing the bone marrow-specific delivery system in the tumour model, an osteoporosis mouse model was constructed and used to investigate the anti-osteoporosis efficacy of NE-loaded PLGA nanoparticles encapsulating teriparatide (PTH-NPs@NEs) (Fig. 1c). PTH-NPs@NEs treatment greatly enhanced osteoblast proliferation and simultaneously inhibited osteoclast proliferation. Moreover, PTH-NPs@NEs improved trabecular bone mineral density, bone volume fraction, trabecular separation, and eventually cured osteoporosis in vivo. Given challenges with bone cancer and osteoporosis treatment, this work demonstrates a potential way to increase treatment efficacy.

This study is also of broader interest to the bone disease treatment field as aged neutrophils can potentially be harnessed to deliver a range of therapeutic cargos into the bone marrow microenvironment beyond chemotherapeutic and anti-osteoporosis drugs. For example, NEs carrying radiosensitizers accumulating in bone tumours could potentially enhance antitumour efficacy while reducing toxicity, while NEs carrying lipid nanoparticles encapsulating messenger RNA (mRNA) encoding cytokines or immune checkpoint blockades could induce tumour-specific immune responses for cancer immunotherapy. Additionally, NEs delivering imaging modalities could aid in the earlier diagnosis of various bone diseases. One of the key advantages of the hitchhiking aged NEs strategy described here is that they can improve the accumulation of cargos in the bone microenvironment due to their bone marrow-tropic trafficking. It will be interesting to observe how this NE-based delivery system compares to nanoparticles modified or functionalized with active targeting ligands, such as monoclonal antibodies. The advantages of this strategy for clinical translation includes: i) neutrophils are easy to obtain due to their high concentration in blood; ii) PLGA has been FDA-approved for a range of drug delivery applications. Future work should address whether the high number of aged NEs required to deliver drugs into bone marrow induce unwanted toxic immune responses, such as cytokine release syndrome, as has been reported in many adoptive T cell transfer therapies.

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Competing interests

The author declares no competing interests.