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Tumor targeting via EPR: Strategies to enhance patient responses☆

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ABSTRACT

The tumor accumulation of nanomedicines relies on the enhanced permeability and retention (EPR) effect. In the last 5–10 years, it has been increasingly recognized that there is a large inter- and intra-individual heterogeneity in EPR-mediated tumor targeting, explaining the heterogeneous outcomes of clinical trials in which nanomedicine formulations have been evaluated. To address this heterogeneity, as in other areas of oncology drug development, we have to move away from a one-size-fits-all tumor targeting approach, towards methods that can be employed to individualize and improve nanomedicine treatments. To this end, efforts have to be invested in better understanding the nature, the complexity and the heterogeneity of the EPR effect, and in establishing systems and strategies to enhance, combine, bypass and image EPR-based tumor targeting. In the present manuscript, we summarize key studies in which these strategies are explored, and we discuss how these approaches can be employed to enhance patient responses.

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1. Introduction

Cancer is one of the major causes of death worldwide and its treatment remains to be very challenging [1]. First-line therapy of solid tumors is based on surgery, radiotherapy and/or chemotherapy. For

metastasized tumors, or for lesions, which cannot be removed surgically, chemotherapy is among the very few treatment options available. Unfortunately, however, the therapeutic potential of classical chemotherapeutic drugs is limited, and they generally cause severe side effects [2].

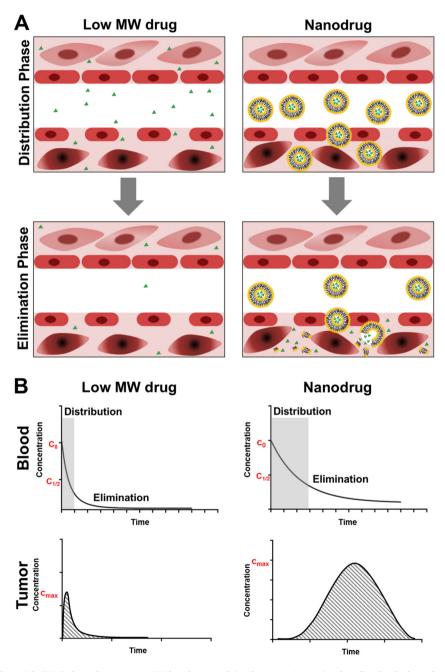


Fig. 1. Conventional low-molecular-weight (MW) chemotherapy versus EPR-based nanomedicine therapy. A: Conventional small molecule chemotherapeutic drugs show high levels of off-target accumulation in healthy tissues during the distribution and elimination phase (upper parts of the panels on the left) and low levels of tumor accumulation (lower parts of the panels on the left). Conversely, nanodrugs prevent chemotherapy accumulation in healthy tissues (upper parts of the panels on the right), and promote accumulation at pathological sites (lower parts of the panels on the right). B: Typical pharmacokinetic profiles of small molecule drugs (left) and nanodrugs (right) in blood and tumors, exemplifying prolonged circulation properties and enhanced tumor accumulation over time.

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