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Penetrable Nanoplatform for "Cold" Tumor Immune Microenvironment Reeducation

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Abstract: Lack of tumor-infiltration lymphocytes (TILs) and resistances by overexpressed immunosuppressive cells (principally, myeloid-derived suppressor cells (MDSCs)) in tumor milieu are two major challenges hindering the effectiveness of immunotherapy for "immune-cold" tumors. In addition, the natural physical barrier existing in solid cancer also limits deeper delivery of drugs. Here, a tumor-targeting and light-responsive-penetrable nanoplatform (Apt/PDGs-s@pMOF) is developed to elicit intratumoral infiltration of cytotoxic T cells (CTLs) and reeducate immunosuppressive microenvironment simultaneously. In particular, porphyrinic metal–organic framework (pMOF)–based photodynamic therapy (PDT) induces tumor immunogenic cell death (ICD) to promote CTLs intratumoral infiltration and hot "immune-cold" tumor. Upon being triggered by PDT, the nearly 10 nm adsorbed drug-loaded dendrimer de-shields from the nanoplatform and spreads into the deeper tumor, eliminating MDSCs and reversing immunosuppression, eventually reinforcing immune response. Meanwhile, the designed nanoplatform also has a systemic MDSC inhibition effect and moderate improvement of overall antitumor immune responses, resulting in effective suppression of distal tumors within less significant immune-related adverse effects (irAEs) induced.

1. Introduction

Triple-negative breast cancer (TNBC) is a highly aggressive subtype of breast cancers with poor prognosis and no approved targeted therapy available other than conventional chemotherapy.[1] Immunotherapy, an established new pillar of treatments for other cancers, has shown an impressive treatment outcome in partial TNBC patients.[2] However, nearly 80% of TNBC patients are diagnosed with low or no infiltration of cytotoxic T cells (CTLs) in tumor lesions, also called "cold" tumor, making the checkpoint inhibitors-based therapies invalid.[3] Cancer vaccine has been regarded as an effective agent for systemic antitumor immune enhancement and tumor-infiltration of CTL in the past decades.[4] However, mentioned in recent reviews, the immune-related adverse effects (irAEs) and resistances by existing immunosuppressive cells (likes myeloid-derived suppressor cells (MDSCs)) in tumor milieu made most cancer vaccines failing to accomplish an objective antitumor activity.[5] Thus, therapeutic approach to elicit intratumoral infiltration of CTLs and simultaneously reverse the resistances by immunosuppressive cells, as well as reduced irAEs, may be beneficial for effective anti-TNBC immunotherapy.

Immunogenic cell death (ICD) is a special type of cell death that can convert residual cellular pieces into a regional intensive vaccine to reinforce antitumor CTL infiltration.[6] Particularly, surface-translocated calreticulin (CRT) serves as an "eat me" signal for dendritic cell (DC) phagocytosis, milieu-released high mobility group protein B1 (HMGB1) promotes DC maturation and antigen-presentation to CTLs, as well as secreted ATP stimulates the intratumoral CTLs infiltration.[7] It is now accepted that the micro-invasive photodynamic therapy (PDT) had exhibited a superior capacity of reactive oxygen species (ROS)-related ICD induction.[8] However, most of frequently used

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