APPLIED SCIENCES AND ENGINEERING

Autonomous metal-organic framework nanorobots for active mitochondria-targeted cancer therapy

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Nanorobotic manipulation to access subcellular organelles remains unmet due to the challenge in achieving intracellular controlled propulsion. Intracellular organelles, such as mitochondria, are an emerging therapeutic target with selective targeting and curative efficacy. We report an autonomous nanorobot capable of active mitochondria-targeted drug delivery, prepared by facilely encapsulating mitochondriotropic doxorubicin-triphenylphosphonium (DOX-TPP) inside zeolitic imidazolate framework-67 (ZIF-67) nanoparticles. The catalytic ZIF-67 body can decompose bioavailable hydrogen peroxide overexpressed inside tumor cells to generate effective intracellular mitochondriotropic movement in the presence of TPP cation. This nanorobot-enhanced targeted drug delivery induces mitochondria-mediated apoptosis and mitochondrial dysregulation to improve the in vitro anticancer effect and suppression of cancer cell metastasis, further verified by in vivo evaluations in the subcutaneous tumor model and orthotopic breast tumor model. This nanorobot unlocks a fresh field of nanorobot operation with intracellular organelle access, thereby introducing the next generation of robotic medical devices with organelle-level resolution for precision therapy.

INTRODUCTION

Micro-/nanorobots have offered remarkable revolutions for biomedical applications benefiting from their autonomous movement (*1*, *2*). These tiny machines can harness local energy [e.g., magnetic (*3*, *4*), chemical (*5*, *6*), acoustic (*7*–*9*), and light (*10*, *11*)] to generate propulsive force, enabling effective movement within confined spaces and successful transport to hard-to-reach sites, such as blood vessels (*12*), the vitreous (*13*), and the lungs (*14*). Given that cellular dysfunction directly alters the homeostasis of living organisms to give rise to diverse diseases, recent efforts have extended the operation scope of medical robots from the organ level down to the cellular level, allowing precise operations to therapeutically regulate cellular dynamics. Pioneer works have reported various intracellular applications of nanorobots, such as motion within cells (*15*, *16*), rapid internalization for intracellular delivery [e.g., small interfering RNA (*17*), oxygen (*18*), enzyme (*19*)], intracellular sensing (*20*, *21*), and scavenging of reactive oxygen species (ROS) (*22*). In addition, nanorobots may help regulate cellular metabolism by targeting the subsystem of organelles involved, such as the nucleus, lysosome, mitochondrion, endoplasmic reticulum, and Golgi apparatus (*23*). The activity and chemical composition of these subcellular organelles alters cell metabolism, directly determining the homeostasis of living systems (*24*). Targeting these organelles shows great therapeutic potential to enhance drug delivery and treatment efficacy of prevalent pathologies (*25*–*27*). However, the subcellular manipulation of nanorobots to access the specific organelles within the cytoplasm remains a bottleneck. The lack of directed mobility and manipulation within the cell has limited the development and translation of nanorobots for cellular modulation.

Herein, we present a self-powered metal-organic framework (MOF)–based nanorobot capable of active and targeted drug delivery to mitochondria for cancer eradication and metastasis inhibition (Fig. 1A). Mitochondria are used as the therapeutic target due to their pivotal role in adenosine triphosphate (ATP) production, calcium regulation, cellular metabolism, and apoptosis in eukaryotic cells (*28*). Mitochondrial dysfunction has been demonstrated to contribute to various common pathologies, such as cancer growth and metastasis, inflammation, and neurodegeneration (*29*). Zeolitic imidazolate framework-67 (ZIF-67) capable of hydrogen peroxide (H_2O_2) catalysis was selected as the material foundation of the nanorobot, serving as the power engine (*30*). The chemotherapeutic drug, doxorubicin (DOX), conjugated with mitochondriotropic triphenylphosphonium (TPP^+) cation (denoted as DOX-TPP), was chosen to enhance the binding of nanorobots with mitochondria (*31*). The lipophilic TPP cation leverages the high mitochondrial membrane potential to passively target the mitochondria (*26*, *32*).

In this work, the self-propelled nanorobots were facilely fabricated by encapsulating DOX-TPP inside ZIF-67 nanoparticles (NPs) (denoted as ZIF-67@DOX-TPP) (Fig. 1A). The catalytic decomposition of ZIF-67 in the presence of H_2O_2, which is overproduced inside tumor cells, generates sufficient force to propel internalized ZIF-67@DOX-TPP nanorobots in the cytosol. Meanwhile, the encapsulated mitochondriotropic TPP^+ leads to mitochondria-targeted movement of untethered nanorobots, yielding a targeted accumulation of nanorobots and subsequently higher local drug concentration at the mitochondria. The controlled access to the mitochondria allows the regulation of mitochondrial dynamics for cancer therapy benefiting from the key role of mitochondria in modulating cancer growth and metastasis. The mitochondria-targeted propulsion of nanorobots could induce mitochondria-

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