Nitric oxide photodonor fine-tunes antitumor therapy

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Photoirradiation controls the release of molecules in the body that may inhibit tumor growth so therapy can be targeted to specific sites.

Some gaseous molecules can cause inflammation—and potentially disease—in the body. One example is reactive oxygen species (ROS), reactive, oxygen-related molecules that are central to the production of normal energy in a cell. Excessive ROS cause inflammation and can prompt the development of disease. Consequently, our aim is to regulate the levels of these molecules within the body using nanoparticle technology.

We can ‘scavenge’ excessively generated ROS using nanoparticles prepared from a reduction-oxidation (redox) polymer (such as polyethylene glycol, or PEG) that accumulate at the inflamed site and reduce ROS effectively. We cannot, however, place the nanoparticles within a cell’s mitochondria (where energy is produced) through the mitochondrial membrane. As a result, this method does not present any notable suppression in the production of adenosine triphosphate, the molecule that transports energy within cells. The redox nanoparticles work effectively against diseases of the cerebral and cardiovascular systems, as well as renal ischemia, in animal experiments.1,2

Excess quantities of bioactive gaseous molecules do not always promote the development of disease. Indeed, some can be beneficial in antitumor treatment, depending on their levels in the body. Spatiotemporal control to generate and eliminate bioactive gaseous molecules in vivo would, therefore, be valuable in antitumor treatment, and may help to fine-tune chemotherapy.3,4

To explore a new therapeutic system based on controlling these molecules, we considered nitric oxide (NO). NO is a free radical endogenously synthesized in the body and involved in vasodilation, angiogenesis, neurotransmission, and immune response. Depending on its concentration and localization, NO can both promote and inhibit tumor progression. Relatively high concentrations of NO stymie tumor growth by promoting apoptosis (programmed cell death). Consequently, a molecular system capable of site-specific delivery of NO should be useful in antitumor treatment.

Due to the poor bioavailability of NO, research has focused on developing a method for the controlled delivery of exogenous NO in living systems. We considered a photochemical process, in which we achieve spatiotemporal control by manipulating incident light. We have developed various NO-photogenerative compounds (NO photodonors) to study photocontrolled NO delivery, although we have yet to generate NO photodonors with ideal water solubility, biocompatibility, and tumor specificity.

Using our polymer therapeutic system, we designed a nanoparticle photo-NO-donor (see Figure 1). Our objective was to develop an NO release system controlled by photoirradiation after its accumulation at a target site. We tested phototriggered NO generation from the nanoparticles by electron spin resonance (ESR) spin trapping, using N-methyl-D-glucamine dithiocarbamate complex (MGD)_{2}\text{Fe}^{2+}). We mixed a freshly prepared (MGD)_{2}\text{Fe}^{2+} complex solution with the NO nanoparticles in a quartz cell, and irradiated the solution for one hour. Before irradiation, the mixed solution showed no significant peak in the ESR spectrum. But afterward it showed

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characteristic peaks corresponding to the formation of the paramagnetic (MGD)$_2$-Fe$^{2+}$-NO complex—see Figure 2 (left)—indicating that the irradiated nanoparticles had produced NO. Although NO is hydrophobic in character, it can be released from the nanoparticles through the PEG outer layer because of the high mobility of gaseous NO.

To assess the antitumor effect of the nanoparticles after photoinduced NO mediation, we performed in vitro examination using HeLa cancer cells. Figure 2 (right) shows the change in the viability of the cells as a function of the concentration of NO nanoparticles. Without UV light irradiation, the nanoparticles showed a relatively low toxic effect on cells (cytotoxicity). Upon UV light irradiation, cytotoxicity was enhanced with the increase in irradiation time, confirming a significant decrease in the nanoparticles’ half-maximal inhibitory concentration (IC$_{50}$) value. The fluence of the UV light in this experiment did not affect the viability of the cells in the absence of NO nanoparticles, indicating that the photoinduced enhancement of the nanoparticles’ cytotoxicity was caused by the photoproducts. Oxyl radical and its degradation products are known to exhibit no significant cytotoxicity, which strongly suggests that the liberated NO works against tumor cells in a photocontrolled manner.

We continue to study the physiological functions of gaseous molecules in the body, and the control of their generation and elimination. Photoirradiation is particularly suited to this function since it can diffuse low-molecular-weight gaseous molecules very rapidly. Our system uses only short-wavelength light at present, so it is limited in application to skin or eyes.

In future work, we aim to enable the use of long-wavelength light for treatment at other sites in the body.

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References