REVIEW

Application of Near-Infrared Dyes for Tumor Imaging, Photothermal, and Photodynamic Therapies

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ABSTRACT: Near-infrared (NIR) dyes, small organic molecules that function in the NIR region, have received increasing attention in recent years as diagnostic and therapeutic agents in the field of tumor research. They have been demonstrated great successes in imaging and treating tumors both *in vitro* and *in vivo*. And their different applications in clinical practices have made rapid gains. This review primarily focuses on the progress of the application of NIR dyes in tumor imaging and therapy. In particular, advances in the use of different NIR dyes in tumor-specific imaging, photothermal, and photodynamic therapies are discussed. Limitations and prospects associated with NIR dyes in diagnostic and therapeutic application are also reviewed. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:6–28, 2013

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INTRODUCTION

Tumor has been a major public health problem around the world. Recently, about one in four deaths results from tumor. It is projected that about 577,190 patients in the United States will die from tumor in 2012.[1,2] The high incidence rate of tumor mortality is primarily because of several elements in tumor diagnosis and therapy. First, because of the lack of effective early tumor detection, many tumors are currently detected in advanced stages. According to statistics, up to 70% of ovarian tumors become metastatic or deteriorative before diagnosis.[3] Recently, several imaging modalities, such as magnetic resonance imaging, positron emission tomography, computerized tomography, X-ray radiography, and ultrasound, are widely being used for detecting the changes of function and structure in tumor areas. However, the major challenges for these conventional imaging modalities are difficult to achieve a high contrast over nearby normal tissues and distinguish malignant tumors from benign lesions.[4–6] It is mainly due to the poor tumor affinity of conventional contrast agents. In addition, to those whose cancers are at advanced or recurrent stage, conventional clinical treatments, such as chemotherapy and radiation, may appear to be inadequate. It is mainly due to tumor resistance and severe side effects.[7,8] Both therapeutic methods make use of cytotoxic drugs or radioactive rays to destroy tumor cells. But these two conventional treatments will damage or destroy healthy tissue or cells during tumor therapy because they lack of tumor specificity. Therefore, conventional chemotherapy and radiation will induce many local or systemic side effects such as severe marrow suppression and central nervous signs. Sometimes treatments have to be discontinued for these serious side effects. Additionally, some tumor cells will become resistant during chemotherapy or radiation process. After some cycles of chemotherapeutic drugs, upregulation of some transporters such as P-glycorprotein will eject cell-killing molecules to reduce drug concentration in tumor cells, which has been a major factor for the failure of chemotherapy. Besides chemotherapy, tumor tissue or cells will

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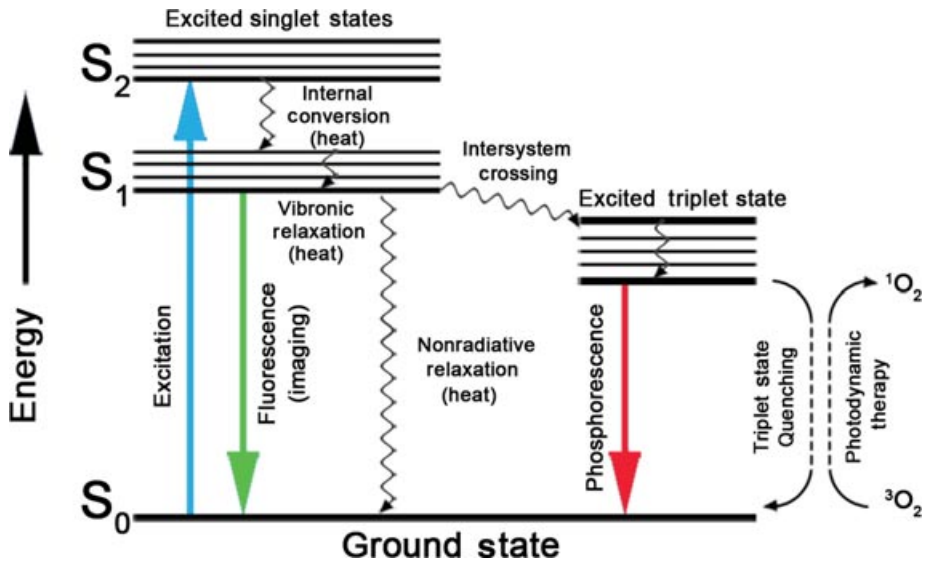

Figure 1. Energy level diagram for a photoluminescence system. Following absorption of a photon (blue arrow), several processes occur with varying probabilities. The first thing happens is relaxation to the lowest vibronic energy level of the first excited state (S1) through internal conversion or vibronic relaxation pathways (black wavy line). The excess energy is converted into heat. Then, relaxation from the lowest excited singlet state to ground state occurs, which is accompanied with emitting a photon. The process is known as fluorescence (green arrow). Some electrons in the excited singlet state can move to a lower energy excited triplet state via intersystem crossing. The latter event ultimately results in emitting a photon through phosphorescence (red arrow). Triplet oxygen, the ground state of oxygen molecule, is a very effective quencher for fluorophores in the excited triplet state. It can be excited to reactive singlet state (right-hand dotted line), producing phototoxic effect to living cells.

also become resistant to radiation. As reported, high-energy radioactive rays can destroy most of tumor cells. But some survived tumor cells will become cancer stem cells, which are insensitive to radiation therapy. And these cancer stem cells are considered as seeds for tumor recurrence.[9]

Near-infrared dyes, as promising imaging and therapeutic agents, have been of great interests in detecting and treating tumors recently. They can absorb NIR light with a specific wavelength to reach an excited singlet state. Part of the energy of the excited singlet state would be dissipated in the form of light with a longer wavelength, called fluorescence. Therefore, NIR dyes can be applied for *in vivo* tumor imaging effectively. And it has high specificity because targeted NIR molecules can distinguish the molecular changes between tumor and normal tissues. Furthermore, NIR imaging shows high sensitivity owing to extremely low absorption and autofluorescence from organic tissue in the NIR spectral range, which can minimize background interference and improve tissue penetration.[10]

In addition, some energy of the excited singlet state can be transited through vibronic relaxation or other nonradiative transitions pathways, which will be converted into heat. If the rate of heat production within the tissue can exceed that of tissue heat dissipation, the temperature of tissue would increase gradually. When temperature reaches up to 41.5°C, tumor cellular cytotoxicity occurs. And temperatures above 43°C can induce vascular destruction within tumor tissue. Therefore, NIR dyes can also be utilized as promising theranostic agents for photothermal therapy (PTT) while detecting tumors. Apart from the above-mentioned two kinds of energy transition way, the excited singlet state can move to a lower-energy-excited triplet state via intersystem crossing. In the excited triplet state, NIR dyes can induce reactive species generation, for example, free radical or reactive singlet oxygen. They induce oxidation reaction with nearby biomacromolecules and destruct organic tissues effectively. In which, generated singlet oxygen is more responsible for the destruction of targeted tissue. Thus, NIR dyes could also act as excellent photodynamic agents (Fig. 1). Compared with conventional methods, photothermal and photodynamic therapies have different therapeutic mechanism and modalities. First, targeted photothermal or photodynamic agents accumulate in tumor sites actively, and the tumor areas are imaged and located distinctly. Then, clear tumor imaging will guide laser treatment to the tumor site alone. And heat energy and singlet oxygen produced by therapeutic agents will destroy adjacent tumor cells in cancer areas.[11] Therefore, these