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Editorial

Photothermal Therapy Using Non-stoichiometric Copper Sulfide Nanoparticles

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Thermal therapy exploits local heating effect to kill cells. The oldest report on using thermal energy for therapeutic applications dates back to 3000 BC, and the modern era of thermal therapy started in the 1970s, where various forms of electromagnetic energy were used to kill cell directly under clinical settings with convincing outcomes [1]. However, this field has waned after nearly 20 years of development, due to difficulty of achieving efficient and selective cell killing effect as a direct consequence of heating without adverse side effect.

Thermal therapy can be an effective way to treat cancers, as tumors are generally poorly vascularized, making them more prone to heat damage compared to healthy cells as a result of local heat accumulation. The introduction of nanotechnology has spurred the renewed interests in thermal therapy [2]. In particular, nanoparticles that are capable of generating heat under laser illumination have attracted a lot of attention in the past decade. The employment of near infrared (NIR) light as the irradiation source minimizes the tissue self-heating effect, since there is minimal tissue absorption in this so called "biological window". Moreover, nanoparticles with sizes less than 100 nm in diameter have long circulating time in the bloodstream and can selectively target cancer cells with proper surface modifications, allowing effective nanoparticle accumulation in the tumor region only. Thus, the use of nanoparticle heaters with NIR light as external stimulus allows remote and localized heating effect, alleviating non-specific damage to healthy tissues.

Other than noble metal Au-based nanoheaters, which are under clinical trials [3], the recent discovery of semiconductor nanocrystals of non-stoichiometric copper chalcogenides which support localized surface plasmon resonances (LSPR) in the NIR has opened up a new regime in plasmonics and its related applications [4]. $Cu_{2-x}E$ ($0<x\leq1$, E = S, Se, Te) nanoparticles are p-doped due to copper deficiency, carrying a large amount of holes with high mobility. Since then, other heavily-doped semiconductor nanomaterials have also been developed and found to exhibit similar LSPR properties [5]. These semiconductor nanomaterials have attracted considerable attention as photothermal transducing agents in biomedical applications for their tunable and strong light absorption in NIR [6,7]. In addition, a very recent study demonstrates that CuS nanoparticles are biodegradable and highly biocompatible, meriting their usage for future clinical applications [8].

Using $Cu_{2-x}S$ nanomaterials as photothermal agents benefits from their low production cost, however, their lower free charge carrier density when compared to noble metal nanoparticles limits their light absorption strength [9]. Their absorption cross section is measured to be ~2 orders smaller than Au nanoshells and nanorods, albeit at smaller physical dimensions [10]. Besides the absolute optical cross section, the nanoparticles' ability to generate heat also depends on their photothermal transduction efficiency. Great efforts have been devoted to enhance these two factors, so that only low dose of nanomaterials as well as light irradiation are needed to generate enough local heating effect to induce cancer cell killing, without eliciting any side effect on healthy cells.

LSPR at noble metal nanoparticle surfaces generates highly enhanced near-field, which can extend beyond the resonant plasmon excitation energy [11,12], Utilizing enhanced local electromagnetic field to increase effective absorption cross sections has been demonstrated recently in Au-CuS [13] and Au-graphene oxide [14] nanocomposites, however, quantitative and detailed investigation of this enhancement effect is still lacking. In another report, self-assembly of CuS has been used to increase the extinction cross section and photothermal transduction efficiency of the nanostructures [15]. Moreover, crystalline phase engineering such as synthesizing $Cu_{7.2}S_4$ rather than Cu_9S_5 can also increase the photothermal conversion efficacy [16]. All of these different approaches have shown promising results, opening the doors for future material design with the aim of achieving optimal photothermal therapy.

Photothermal therapy can be used in conjunction with other therapeutic interventions methods such as photodynamic, radiation and chemo-therapies to achieve synergistic effects. Cellular metabolism rate, membrane permeability, and local oxygen concentration would all be increased for cells under hyperthermia treatment, which in turn would result enhanced drug uptake and more effective ROS generation. Hollow capsules made of CuS have been constructed to encapsulate hydrophobic drugs for thermo-chemotherapy, demonstrating better therapeutic effect than any of the single modality treatment combined [17].

For better therapeutic treatment outcome, it is essential to verify the tumor location and the accumulation of nanoheaters at the target site before photothermal therapy, which is also critical for monitoring the therapeutic effect after the treatment. This imaging guided therapy requires the nanoheaters used in the photothermal therapy can be imaged in vivo, preferably with common biomedical imaging modalities with good resolution and sensitivity. By grafting gadolinium-chelate [18] or iron oxide [19] on CuS nanoparticles surfaces, they can be used as MRI contrast enhancing agents simultaneously. Alternatively, by incorporating ^{64}Cu in CuS nanoparticles, PET imaging can be realized [20]. Another promising imaging modality is photoacoustic imaging (PAI), a non-invasive

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technique for quantifying acoustic signals generated after laser irradiation of tissues containing nanoheaters [21]. PAI offers good penetration depth and high spatial resolution. It can use incident light (from a pulsed laser) of the same wavelength for the photothermal treatment, making spatial registration of the nanoheaters simpler compared to other imaging modalities with different irradiation sources.

Finally, it is utterly important to be able to monitor spatial temperature distribution at real-time, since safety and efficacy of photothermal treatment depends on the local temperature as well as the heating duration. Currently, infrared thermal cameras are commonly used for monitoring tumor temperature profiles in small animal studies. However, these cameras measure only the surface temperatures, which could be substantially different from the actual intratumoral temperatures. By putting quantum dots nanothermometer in close proximity to the nanoheaters, local temperatures can be mapped by optical signal readout [22]. A more clinically relevant method would be magnetic resonance thermometry [23]. Moreover, PAI detects the acoustic wave generated by tissue volume expansion as a consequence of pulsed laser irradiation, whose pressure depends both on the volume expansion coefficient and the speed of sound. Since both parameters are temperature dependent, photoacoustic signals are then directly related to local temperatures. Thus, PAI can be used to image nanoheaters as well as to visualize temperature distributions [24]. Given that PAI combines imaging, photothermal therapy, local temperature monitoring all in one modality, it is expected that research work on PAI-related imaging would surge in the years to come, and hopefully by combining efficient photothermal agents and PAI modality, photothermal therapy can be translated into clinical settings in the near future.

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