DESIGNING MULTIFUNCTIONAL AND BIODEGRADABLE GRAPHENE-BASED MATERIALS FOR CANCER THERAPY

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Graphene-based nanomaterials are considered unique systems for many applications in different fields including biomedicine [1]. They are offering the possibility of original chemical functionalization and design of complex multifunctional systems that allow further their exploitation in therapy, imaging and diagnosis [2]. In this presentation, I will describe the chemical strategies to functionalize graphene-based nanomaterials with appropriate functional groups and therapeutic molecules in view of their biomedical applications. I will present few examples of their use in cancer therapy and imaging. I will also describe how it is possible to enhance the biodegradability and tune the toxic effects of these different materials.

The last decade has seen an increase in the application of graphene oxide (GO) in the biomedical field. GO has been successfully exploited for its ability to deliver many kinds of drugs into target cells. However, GO toxicity assessment is still controversial. Several studies have demonstrated that GO protein coating is crucial to alleviate the material's toxicity. Besides, coronation leads to the formation of big agglomerates, reducing the cellular uptake of the material and thus its therapeutic efficiency. We have recently proposed a simple and efficient method based on rapid (ultraturrax, UT) mixing to control protein corona formation. Using the UT protocol, we were able to reduce GO agglomeration in the presence of proteins and obtain stable GO dispersions in cell culture media, allowing faster and more efficient internalization both in macrophages and HeLa cells without affecting cell viability [3].

Several studies have demonstrated the ability of GO to efficiently adsorb small-interfering RNA (siRNA) on its surface and to transport it into cells. However, studies on whether and how siRNA interacts with GO are still inconclusive. Understanding the interaction between GO and siRNA is fundamental to design new efficient gene silencing tools. The interactions between GO and siRNA molecules were systematically investigated [4]. We focused on how the GO size, oxygenated groups present on the surface and chemical functionalization affect the double helix siRNA structure. We found that the siRNA secondary structure was clearly altered by the interaction with GO flakes. We also demonstrated that GO functionalized with low molecular weight polyethyleneimine is able to protect siRNA from structural modifications.

In the cure of cancer, a major cause of today's mortality, chemotherapy is the most common treatment, though serious frequent challenges are encountered by current anticancer drugs. We discovered that few-layer graphene (FLG) dispersions have a specific killer action on monocytes, showing neither toxic nor activation effects on other immune cells [5]. We confirmed the therapeutic application of graphene on an aggressive type of cancer that is myelomonocytic leukemia, where the monocytes are in their malignant form. We demonstrated that graphene has the unique ability to target and boost specifically the necrosis of monocytic cancer cells.

Biodegradability of graphene is one of the fundamental parameters determining the fate of this material in vivo. Two types of aqueous dispersible graphene, corresponding to single-layer and few-layer graphene were subjected to biodegradation by human myeloperoxidase-mediated catalysis [6]. Graphene biodegradation was also studied in the presence of activated, degranulating human neutrophils, leading to the conclusion that highly dispersed pristine graphene is not biopersistent.

To enhance the biodegradability of graphene-based materials, we have proposed the design of surface-functionalized GO with the capacity to degrade more effectively compared to unmodified GO using horseradish peroxidase (HRP) [7]. We have functionalized the surface of GO with two well-known substrates of HRP namely coumarin and catechol. The results proved that GO functionalized with these moieties display a faster and more efficient biodegradation.

The design of multifunctional materials able to both selectively deliver a drug into cells in a targeted manner and display an enhanced propensity for biodegradation is an important goal. GO was functionalized with the chemotactic peptide N-Formyl-Methionyl-Leucyl-Phenylalanine (fMLP) known to interact with the formyl peptide receptor (FPR), which is expressed in different cancer cells, including HeLa cells [8]. This study highlights the ability of GOfMLP for targeted drug delivery and cancer cell killing and the subsequent degradation capacity of the hybrid. The results showed that GOfMLP is susceptible to a faster myeloperoxidase-mediated degradation. The hybrid material, but not GO, is capable of inducing neutrophil degranulation with subsequent degradation, being the first study showing inducible neutrophil degradation by the nanomaterial itself with no prior activation of the cells. In addition, GOfMLP is able to deliver the chemotherapeutic agent doxorubicin faster into cells, inducing higher levels of apoptosis, when compared to non-functionalized GO.

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