Nanomedicine & Biotherapeutic Discovery

Extended Abstract

Imide Derived Carbon Dots Exhibit Promising Antitumoral Properties on Multiple In Vitro Experimental Designs

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Abstract

Cancer is still a leading cause of death worldwide. Multiple and heterogeneous intrinsic molecular defects account for malignancy aggressiveness features. Distorted and inappropriate control of fundamental cell biology programs, such as cell survival, cell suicide, cell differentiation and cell tissular architectural integration stand at the core of tumor development. Such factors activate Epithelial-toMesenchymal Transition (EMT) that allows tumor cells to acquire different characteristics enabling them to invade and increase survival to different type of treatments. Nanomaterial-based technologies offer new promising approaches to disease diagnostics and therapeutics. We investigate the potential antitumoral properties of one of the newest classes of carbon based nanomaterials, Carbon Dots. Two types of previously physico-chemically characterized Carbon-Dots have been assessed using in vitro models. Cell proliferation, apoptosis and vimentin as a marker of EMT have been investigated in cell cult ures models: 2D, 3D, mono-culture or co-culture. Imide derived C-Dots affect cancer cell survival in a graded way, with minimal impact on normal cells, indicating promising antitumoral effects for cancer treatment. Moreover, the presence of the imide derived C-Dots down regulates the expression of EMT-associated marker Vimentin. Tested Carbon-Dots possess selective antitumoral properties which may be defined by precursor type.

Carbon Dots (C-Dots) are a new class of nanostructured materials, which mainly consists of a carbonaceous core and surface located in various functional groups. As a result of their particular structure, C-dots present several remarkable features like excitation dependent tunable photoluminescence, facile preparation starting from a wide range of potential precursors, low toxicity, dispersibility in different solvents. Due to their unique features, they were thoroughly considered for applications ranging from optoelectronics and sensors to the biomedical field in recent 5 years.

Very recent studies report the use of C-Dots as efficient agents for drug delivery and antitumoral activity. The present paper assesses the potential antitumoral properties of two C-Dots types synthesized from imide precursors. One C-Dot type is prepared through thermal decomposition of N-hydroxyphthalimide (NHF) precursor in a controlled partial pyrolytic process as described in a previous paper. The second type of C-Dots was prepared from N-hydroxysuccinimide (NHS) according to a previously described method and tested in parallel with the first type. Tested C-Dots have been previously physicchemically characterized and the batches of C-Dots prepared for this study were morpho-structurally validated by FTIR, TEM, and DLS techniques. The NHF precursor has been proved to have antitumoral activity while NHS, routinely used as reagent for peptide synthesis has no reports in this respect.

Metastasis, meaning cancer cells that escape from the primary tumor, disseminate and engraf in distant organs, are responsible for 90% of cancer-related deaths. The Epithelial-to-Mesenchymal Transition is a complex molecular program where non-motile, polarized epithelial cells degrade their cell-cell junctions and convert to mesenchymal-like types, which facilitate cell invasion and metastasis, resistance to chemotherapy, resistance to radiation-induced DNA damage and increased cell survival. Defects in programmed cell death pathways including apoptosis play important roles in tumor pathogenesis, allowing neoplastic cells to survive. Apoptosis is a regulatory system for balancing the homeostasis situation during the growth, development, and differentiation among multi-cellular organisms. Caspases are a family of cysteine proteases that play key roles in programmed cell death and are the essential elements in the apoptosis process. It is known that apoptosis defects may allow epithelial cells to survive without attachment to extracellular matrix that later facilitates metastasis.

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The effect of C-Dots prepared through pyrolysis of N-hydroxyphthalimide or N-hydroxysuccinimide was investigated in different cellular microenvironments with notable antitumoral effects. Assessment of the antitumoral activity included sequential evaluation of the proliferation, survival, invasiveness and tissue scale interactions of several representative malignant cell lines. As expected, C-Dots prepared from NHF showed antitumoral activity, but surprisingly, the C-Dots prepared from NHS also displayed antitumoral activity on certain cell lines, with minimal toxic effects on normal cells. The fact that the tested C-Dots do not overlap entirely their antitumoral properties indicates that developing new C-Dots types may lead to the identification of new active molecules suitable for cancer treatment.

N-Hydroxyphthalimide (NHF) (97%) and N-hydroxysuccinimide (NHS) (98%) were purchased from Sigma-Aldrich. High purity Milli-Q water was used for C-Dots synthesis. Both types of C-Dots used in this study were prepared through pyrolytic processing of N-Hydroxysuccinimide (NHS) and N-Hydroxyphthalimide (NHF), respectively according to the experimental path described in previous papers. In each case, the resulted aqueous dispersion was centrifuged twice at 15000 rpm for 10 min. The resulted batches were morpho-structurally investigated using FT-IR, TEM, and DLS analysis, the results being in close agreement with the reported studies, as detailed in the Supplemental Information Section. MDA-MB-231, 4T1, (American Type Culture Collection, Rockville, MD ATCC) were cultured as described by Gjerdrum et al.. HMLE (ATCC) (a gift from Dr. J. Lorens) were maintained in MEBM media (Lonza) supplemented with MEGM bullet-kit (Lonza).

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