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Cancer-selective toxicity of gold nanoparticles: effects of synthesis time and charge

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Introduction

It is estimated that 50% of people born after 1960 in the UK will develop some form of cancer in their lifetime 1. Cancer treatments include surgery, radiotherapy and chemotherapy. Each of these methods carries a risk of damaging healthy tissues surrounding the tumour. Nanotechnology offers novel tools for cancer diagnosis, early detection and treatments 2. Gold nanoparticles show great promise in targeted cancer therapy due to their unique physicochemical properties. They offer the advantage of interaction with biomolecules both at the cell surface level and inside the cell 3,4. This interaction is highly dependent on their ligand composition.

Midatech's technology is based on carbohydrate-coated gold nanoparticles (GNPs). The particles used in this project consist of a gold core with an average diameter of ca. 2nm to which an organic layer of a thiolated α-Galactose derivative and thiol PEG amine are attached via gold-sulphur bonds (Figure 1). The highly water-soluble carbohydrate layer provides colloidal stability in aqueous solutions, while the thiol PEG amine creates positive charges which enable the particle to interact with biomolecules.

→ The key advantages are:
- Solubility
- Stability
- Releasability
- Excretability
- Scalability

A. Effects between the same 50:50 GNP synthesized for different times (1h, 2h, 5h, overnight)*.

B. GNPs accumulate in endosomes/lysosomes.

C. Does toxicity correlate with uptake?

Methodology

1. Synthesis of GNPs
- GNPs were synthesized by the reduction of HAuCl₄ with NaBH₄ in the presence of disulphide-containing ligands (Figure 2).

2. Clonogenic Assays
- Isolated human skin cancer (HSC-3) and normal (HaCaT) cells (300 cells/well) were exposed to different GNP concentrations for 3h and left to grow for 6 days to form colonies.
- At the end of day 6, cells were briefly rinsed with water, stained and fixed with 2% methylene blue in 50% ethanol.
- The staining/fixation solution was removed and plates were washed with distilled water and dried. Colonies with >50 cells were counted.

3. Silver Staining
- After acute exposure of cells to GNPs for 3h, cells were washed with PBS and fixed in 4% PFA for 15 min. The cell membrane was permeabilized with 0.05% Tx-100 in PBS.
- The silver staining developer and enhancer solutions were mixed at 50:50 ratio and applied to cells for 5-10 min in the dark. Cells were then washed 2x with PBS and samples were stored at 4°C for subsequent imaging. Samples were photographed by bright-field and phase contrast microscopy.

Preliminary Data

A notable cancer cell only selective toxicity occurs that depends upon the synthesis duration of the GNP, probably due to differences in ligand density. In this work, 2nm GNPs surface functionalised with a 50:50 ratio of a thiolated α-Galactose derivative and a thiol PEG amine were examined for their toxicity towards normal (HaCaT) and cancerous (HSC-3) human skin cell lines in vitro.

→ Using this simple ligand structure, GNPs are toxic to HSC-3 cells without affecting the normal cell line (HaCaT).

Conclusions / Future Directions

Future Directions: Batch standardisation for the optimum synthesis time. Elucidation of the mechanisms of selective uptake & toxicity in various cancer and normal cell lines.

In detail:
1. Explain differences between selective effect observed in cancer vs normal cell lines
2. GNPs for visualization assays and unravelling of internalization route
3. Comparison of GNP amount/cell for different cell types by ICPMS

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