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TITLE

Microgels for *In Vitro* Three-Dimensional Cancer Models

HYPOTHESIS:

Most of the current understanding of cellular functions comes from research performed in two dimensions (2D), as it is straightforward and easy to interact with, image, and assay. While 2D studies have led to important pharmacological discoveries it is important to understand that within the human body cancer cells grow in a three dimensional (3D) context, very differently from monolayers attached to polystyrene surfaces as found in standard tissue culture. Mouse models are a powerful method for pharmacological drug screening but widespread application is hindered by high cost, long engraftment periods, low engraftment rates, and limitations when controlling parameters such as oxygen levels or nutrient gradients.

BACKGROUND/AIMS:

Developing 3D culture methods will bring greater understanding of the effects of drugs in a more physiologically relevant manner and can effectively bridge the gap in between the patient and the dish. While promising, drawbacks to many current 3D culture methods include: several methods are not possible with all types of cells, spheroids can be hard to control in size and shape, the number of cells required is large and primary biopsies may not be able to supply enough cells, and there are many types of cells that need to be cultured in specific environments and it is possible that they will not be able to aggregate into spheroids using current techniques.

METHODS:

We have developed a method that alleviates these limitations. Jammed granular microgels or liquid-like solids are a class of material that has a designed transition between solid and fluid state. Below their yield stress, these jammed microgels perform like a solid, but when this yield stress is exceeded, they flow like a liquid. The ability of microgels to switch between solid and liquid phases makes them a prime candidate for 3D printing. By 3D printing cancer cells into a liquid-like solid support material we enable the cells to interact with one another in 3D. This method enables mass culture of tumoroids, and provides an opportunity for co-culture and *in vitro* imaging. With the precise control offered by the 3D printer arrays of identical shapes can be produced over a variety of sizes and geometries.

RESULTS & CONCLUSIONS

In this study, primary Osteosarcoma cells are 3D printed into 1.5 mm diameter spheres. These spheres are imaged using fluorescence confocal microscopy in order to observe cell viability and morphology. After printing the cells are removed from the gel and embedded for histological sectioning and H&E staining. The cells are also treated with doxorubicin to monitor drug resistance. Cells in 3D sphere culture show an increased resistance to doxorubicin relative to cells that are cultured in 2D monolayer. Additionally, cells can be printed with matrix (i.e. matrigel) and multiple cell types can be printed together. Osteosarcoma and HUVEC cells are printed in a co-culture sphere to observe cell organization *in vitro*.