3D sensing platform for single cell extracellular pH mapping in time and space: a pre-clinical model to study tumor microenvironment and drug screening

Stefania Forciniti[1], Valentina Onesto[1], Riccardo Rizzo[1], Anil Chandra[1] Saumya Prasad[1], Helena Iuele[1], Francesco Colella[1], Giuseppe Gigli[1,2], Loretta L. del Mercato[1]

[1]Institute of Nanotechnology, National Research Council (CNR-NANOTEC), c/o Campus Ecotekne, via Monteroni, 73100, Lecce, Italy;

[2]Department of Mathematics and Physics "Ennio De Giorgi", University of Salento, via Arnesano, 73100, Lecce, Italy.

Stefania.forciniti@nanotec.cnr.it

Abstract

Elevated hydrogen ion concentration accumulates in the tumor microenvironment as a result of metabolic reprogramming of cancer cells towards increased aerobic glycolysis and reduced mitochondrial oxidative phosphorylation, referred to as Warburg effect [1]. This results in spatially and temporally heterogenous acidic microenvironment which affects cancer initiation and progression as well as the efficacy of anti-cancer drug treatments [2, 3].

Therefore, monitoring the local pH metabolic fluctuations is crucial in understanding the basic biology of the tumors, and can also be used as a valid metabolic readout for cancer diagnosis and treatment [4].

Here, a method to embed silica-based ratiometric fluorescent pH sensors into a spherical 3D cell culture system, coupled with a computational method for pH spatio-temporal mapping, is presented (see figure 1) [5]. By using a confocal laser fluorescence microscopy, 3D time-lapse imaging of living cells was performed and the extracellular pH variations were monitored between 3D scaffolds with either mono or co-cultures of tumor and stroma pancreatic cells.

We obtained that the extracellular pH is cell line-specific and time-dependent. Indeed, differences in pH were detected between 3D monocultures compared to co-cultures, thus suggesting a metabolic crosstalk between tumor and stroma cells.

In conclusion, the 3D cell culture system has the potential of imaging complex 3D co-coltures in real time and of detecting their pH metabolic interplay under controlled experimental conditions, making it a suitable platform for drug screening and personalized medicine.

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References

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Figures

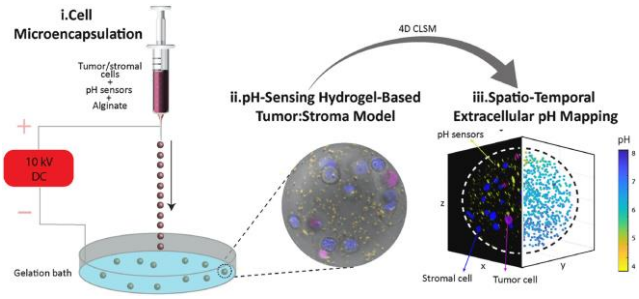

Figure 1. Schematic illustration of the method to embed silica-based fluorescent pH sensors into alginate 3D microgels tumor models. i) Tumor/stromal cells and sensors microencapsulation in alginate to form 3D microgels tumor models; ii) pH-sensing hydrogel-based tumor/stroma model; iii) Spatio-Temporal extracellular pH mapping obtained with a specific computational analysis.