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A microfluidic oxygen sink to create a targeted cellular hypoxic microenvironment under ambient atmospheric conditions

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Abstract:

Physiological oxygen levels within the tissue microenvironment are usually lower than 14 %, in stem cell niches these levels can be as low as 0 – 1 %. In cell cultures, such low oxygen levels are usually mimicked by altering the global culture environment either by O_2 removal (vacuum or oxygen absorption) or by N_2 supplementation for O_2 replacement. To generate a targeted cellular hypoxic microenvironment under ambient atmospheric conditions, we characterised the ability of the dissolved oxygen-depleting sodium sulphite to generate an in-liquid oxygen sink. We utilised a microfluidic design to place the cultured cells in the vertical oxygen gradient and to physically separate the cells from the liquid.
We demonstrated generation of a chemical in-liquid oxygen sink that modifies the surrounding O_2 concentrations. O_2 level control in the sink-generated hypoxia gradient is achievable by varying the thickness of the polydimethylsiloxane membrane.
We show that intracellular hypoxia and hypoxia response element/dependent signalling is instigated in cells exposed to the microfluidic in-liquid O_2 sink/generated hypoxia gradient. Moreover, we show that microfluidic flow controls site-specific microenvironmental kinetics of the chemical O_2 sink reaction, which enables generation of intermittent hypoxia/re-oxygenation cycles.
The microfluidic O_2 sink chip targets hypoxia to the cell culture microenvironment exposed to the microfluidic channel architecture solely by depleting O_2 while other sites in the same culture well remain unaffected. Thus, responses of both hypoxic and bystander cells can be characterised. Moreover, control of microfluidic flow enables generation of intermittent hypoxia or hypoxia/re-oxygenation cycles.

Keywords: hypoxia, microenvironment, cell culture, microfluidic chip, oxygen depletion