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Three-dimensional imaging and uptake of anticancer drugs in multicellular spheroids by light sheet fluorescence microscopy

Multicellular spheroids (MCS) are increasingly being used as tissue models by converting two-dimensional cell monolayers into three-dimensional cultures to mimic the physiology and functions of living tissues. Such natural cellular networks created through cell-cell contacts together with cell signalling enriched environments could be used in tumour biology for morphology and drug screening applications. MCS models are widely used in cancer research where cell signalling pathways, as for example the mammalian Target of Rapamycin (mTOR) pathway, responsible for the regulation of cell growth and proliferation, can be elucidated. Currently, some tumours have developed resistance to first generation mTOR inhibitors. AZD2014, a second generation mTOR inhibitor, is undergoing active clinical trials, but its mechanism of action within live cell environment is unknown. We report the study of the uptake of AZD2014 in Human Embryonic Kidney 293 (HEK293) MCS utilising the natural fluorescence of the drug by Light Sheet Fluorescence Microscopy (LSFM). LSFM was chosen for its capability of monitoring large volumes at high speed, as well as for its superior detection of fluorescence from MCS and lower phototoxicity compared to conventional microscopy. HEK293 MCS were cultured and transferred to agar wells in petri dishes. Different doses of AZD2014 were administrated while the MCS was imaged in real-time with a 10X/0.3 NA objective under excitation with a 405 nm laser. Z-stacks of 250 µm thickness were recorded every 15 s for at least 90 min. The uptake rate was determined for different depths inside the MCS and compared to that from monolayers. Volumetric changes difficult to observe in 2D cell cultures were also characterized. We observed an increase of 25% in the MCS size upon drug administration. Comparison with other drugs, including Combretastatin, was also performed. Altogether, this study highlights the significance of the combined use of MCS and LSFM for drug discovery.

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