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A Biophysical Study of the Dynamic Properties of Glucagon Granules in α Cells by Imaging-Derived Mean Square Displacement and Single Particle Tracking Approaches

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Abstract : Insulin and glucagon are the two essential hormones for maintaining proper blood glucose homeostasis, which is disrupted in Diabetes. A constantly growing research interest has been focused on the study of the subcellular structures involved in hormone secretion, namely insulin- and glucagon-containing granules, and on the mechanisms regulating their behaviour. Yet, while several successful attempts were reported describing the dynamic properties of insulin granules, little is known about their counterparts in α cells, the glucagon-containing granules. To fill this gap, we used αTC1 clone 9 cells as a model of α cells and ZIGIR as a fluorescent Zinc chelator for granule labelling. We started by using spatiotemporal fluorescence correlation spectroscopy in the form of imaging-derived mean square displacement (iMSD) analysis. This afforded quantitative information on the average dynamical and structural properties of glucagon granules having insulin granules as a benchmark. Interestingly, the iMSD sensitivity to average granule size allowed us to confirm that glucagon granules are smaller than insulin ones (~1.4 folds, further validated by STORM imaging). To investigate possible heterogeneities in granule dynamic properties, we moved from correlation spectroscopy to single particle tracking (SPT). We developed a MATLAB script to localize and track single granules with high spatial resolution. This enabled us to classify the glucagon granules, based on their dynamic properties, as 'blocked' (i.e., trajectories corresponding to immobile granules), 'confined/diffusive' (i.e., trajectories corresponding to slowly moving granules in a defined region of the cell), or 'drifted' (i.e., trajectories corresponding to fast-moving granules). In cell-culturing control conditions, results show this average distribution: 32.9 ± 9.3% blocked, 59.6 ± 9.3% conf/diff, and 7.4 ± 3.2% drifted. This benchmarking provided us with a foundation for investigating selected experimental conditions of interest, such as the glucagon-granule relationship with the cytoskeleton. For instance, if Nocodazole (10 µM) is used for microtubule depolymerization, the percentage of drifted motion collapses to 3.5 ± 1.7% while immobile granules increase to 56.0 ± 10.7% (remaining 40.4 ± 10.2% of conf/diff). This result confirms the clear link between glucagon-granule motion and cytoskeleton structures, a first step towards understanding the intracellular behaviour of this subcellular compartment. The information collected might now serve to support future investigations on glucagon granules in physiology and disease. Acknowledgment: This work has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 866127, project CAPTUR3D).
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