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Molecular imaging of the bioeffects of β-amyloid and metal ions on live human neuroblastoma cells: internalization, subcellular localization and induction of ROS

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MOLECULAR IMAGING OF THE BIOEFFECTS OF β-AMYLOID AND METAL IONS ON LIVE HUMAN NEUROBLASTOMA CELLS: INTERNALIZATION, SUBCELLULAR LOCALIZATION AND INDUCTION OF ROS

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Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the deposition of extracellular amyloid-β(Aβ) plaques that are rich in metal ions such as zinc, copper and iron. The neurotoxic role of Aβ has been well established but the mechanism of action is still poorly understood. Recent in vitro evidence suggest that Aβ can interact with metal ions such as Zn(II), Cu(II) or Fe(II/III) which promote its aggregation and/or ROS production. However, it is unclear whether this is the case in cells and whether/how extracellular Aβ can get into cells. Our recently developed molecular imaging probes for iron, copper and ROS enable us to look at this in real time in live cells at subcellular resolution. First, we tagged the Aβ covalently with a fluorescent dye which allows its interactions with cells to be monitored under a microscope. Our laser confocal imaging experiments with human neuroblastoma cells revealed that Aβ accumulated at the cell surface first and subsequently entered the cells via endocytosis pathway over a period of a few hours and finally deposited into endosomes/lysosomes in the cells. The deposition of Aβ induced a marked production of oxygen free radicals in the mitochondria of the cells, as revealed by our oxygen free radical probe and colocalization experiments. Incubation of metal ions such as copper(II) increased the production of oxygen radicals significantly while zinc(II) appears to be protective against ROS production. Our data provided compelling and direct evidence on how amyloid-β(Aβ) entering the cells and its induction of oxygen free radicals as well as the effects of metal ions on the radical production at subcellular level.