Comprehensive signaling network of regulated cell death: comparison of cell death modes in Alzheimer's neurodegenerative disease and cancer

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Based on experimental data retrieved from literature, an integrated signalling network of Regulated Cell Death (RCD map) has been constructed. The RCD map is composed of three layers; the "Initiation" layer covers biochemical triggers, input signals and mechanisms that initiate RCD. The "Signalling" layer, recipient of inputs, is the level where the decision about cell death mode is made choosing among Apoptosis, Necroprosis, Ferroptosis and Parthanatos and Pyroptosis. The "Execution" layer depicts the mechanisms activated by one of the five signalling RCD modes and represents the decomposition and degradation mechanisms of the cell. The RCD map is divided into 27 functional modules that can be visualized in the context of the whole map or as individual diagrams. The map contains above 1200 proteins and genes, 2020 biochemical reactions and is based on 600 scientific papers. The map is an open source platform facilitated by the NaviCell web-tool (https://navicell.curie.fr/pages/maps_rcd.html). The RCD map was applied to explore and interpret the differences in cell death regulation between Alzheimer's disease and lung cancer, diseases that have been suggested to have inverse comorbidity. Enrichment analysis of RCD map modules using gene expression data from each disease was performed using the ROMA algorithm; deregulated molecular functions as well as the main players were compared. Mostly, the activation of stress response and metabolic functional modules was observed in lung cancer; whereas the modules of cell death initiation, especially ligand-receptor pathways leading to apoptosis and necroptosis were less active. Alzheimer's disease data analysis revealed that the majority of regulated cell death modes are actually not completely present, except of pyroptosis, in agreement with previous studies showing an active pyroptosis key player in the beta-amyloid plaque development. We observed that metabolism-related modules are less active in the Alzheimer's disease, in opposite to lung cancer. We concluded that the inverse comorbidity between these diseases implicates rather metabolic pathways.