

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

L. Cristobal Monraz Gomez¹, Jean-Marie Ravel^{2,3}, Emmanuel Barillot¹, Andrei Zinovyev¹ and Inna Kuperstein¹

Institut Curie, 26 rue d'Ulm, F-75005 Paris, France, PSL Research University, F-75005 Paris, France, Inserm, U900, F-75005, Paris France, Mines Paris Tech, F-77305 cedex Fontainebleau, France¹, Laboratoire de génétique, Centre Régional Hospitalier Universitaire de Nancy, Vandœuvre-lès-Nancy², INSERM UMR 954, Université de Lorraine, Vandœuvre-lès-Nancy³

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, Necroptosis, 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 26 functional modules that can be visualized in the context of the whole map or as individual diagrams. The map contains about 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 network map was applied for interpreting the functional differences in cell death regulation between Alzheimer's disease and non-small cell lung cancer based on gene expression data that allowed emphasizing the molecular mechanisms underlying the inverse comorbidity between the two pathologies. Furthermore, the map was employed for the analysis of genomic and transcriptomic data from ovarian cancer patients that provided RCD map-based signatures of four distinct tumor subtypes and highlighted the difference in regulations of cell death molecular mechanisms.