Doctoral School of Information and Biomedical Technologies
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SUBJECT: Analysis of non-genetic sources of cell-to-cell heterogeneity as a potential cause of selective resistance of cancer cells

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DESCRIPTION: In a clonal population of cancer cells, individual cells have different sensitivities to compounds aimed at inducing cell death. The selective resistance of cancers does not result, therefore, from genetic heterogeneity alone but involves a tangible, non-genetic component[1]. The growing body of evidence recognizes the role of mitochondria as an important explanatory factor[2]. Changes in the amount of mitochondria can induce drastic alterations of a cell's gene expression program, which ultimately leads to cell-to-cell variability of protein concentrations. It means that genetically identical cancer cells with different numbers of mitochondria may have different propensity to die if exposed to the same drugs. It has particularly significant consequences for therapy responses of cancers whose proliferation and survival highly depends on the activity of a single or few proteins. For instance, the transcription factor signal transducer and activator of transcription 3 (STAT3) is constitutively active in a wide variety of tumors promoting their progression through deregulation of downstream target genes, and its inhibition leads to diminishing of cancer cells population[3].

We hypothesize that the cell-to-cell heterogeneity of STAT3 levels and uneven segregation of mitochondria with different functionality are the two major interrelated, non-genetic components responding to fractional killing in STAT3-dependent cancer cell lines.

The main goal of this project is to explore cell-to-cell variability in the level and activity of STAT3 along with the mitochondrial heterogeneity (abundance, activity, dynamics) as a potential source of the fractional killing in STAT3-dependent cancers and to evaluate the possibility of targeting these sources of non-genetic heterogeneity to reduce the number of drug-resistant cells.

The extended time-resolved automated microscopy and high content screening together with single-cell tracking analysis will be implemented to relate the phenotypic features of individual cancer cells exposed to drug treatment with their cellular fates (dividing, quiescent, senescent, and dead cells). The results obtained during the realization of this project will provide knowledge about the contribution of non-genetic sources of heterogeneity in fractional killing of cancer cells and may open novel research strategies into combinatorial targeting of the JAK/STAT pathway and mitochondrial functions to overcome the selective resistance of STAT3 dependent cancers.

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