PROJECT

Supervisor:	Davide Mazza
Title:	Control of transcription by p53 dynamics: from cell states to cell fates.
Curriculum:	CMB
Link to the personal page of the University or relevant hospital site website:	https://www.unisr.it/en/docenti/m/davide-mazza

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Predicting how tumor cells will react to therapy is a central problem in cancer biology. For the tumor suppressor p53 the activation dynamics following DNA damage have been shown to be predictive of cell fate outcomes, as for other transcription factors (*1*): oscillations are associated with DNA repair, while sustained responses lead to apoptosis or cell cycle arrest (*2*, *3*). Whether this is exerted through its canonical function as transcriptional activator (*2*) or through other functions (*4*, *5*) is unclear. Importantly, there is experimental evidence showing that cells coming from a division share a cell fate upon therapy (*6*); this opens the intriguing possibility that dynamic responses are determined by specific (epi)genetically transcriptional states, as we have shown for the dynamic transcription factor NF-kB (*7*).

Rationale and hypothesis

We hypothesize that p53 dynamics upon DNA damage produce specific gene expression patterns of sets of target genes that determine different cell fate decisions, particularly cell cycle arrest and different forms of cell death. Building on this, we further hypothesize that a snapshot of multiple target genes in a population might allow us to re-construct their past p53 dynamics. Finally, we consider that the same approach can be used to infer the variety of dynamics and cell fate decisions that might arise in a population of cancer cells.

Objectives and specific aims

1) To characterize how p53 responses to different genotoxic stresses (gamma irradiation or chemotherapy, respectively) lead to different patterns of target gene expression at single cell level.

2) To unveil how p53-dynamics mediated transcription determines cell cycle arrest or cell death using appropriate reporters (*8*, *9*).

3) To characterize transcriptionally the cell states that determine distinct p53 dynamics responses and cell fate decisions.

4) To apply these ideas to predict response to therapies in PDOs for colorectal cancer cultured in a high throughput system that we have contributed to develop (*10*).

Expected outcomes

At the end of this project, we will have provided mechanistic insights on how p53 can control cell fate decisions by specific control of target genes upon distinct genotoxic stresses. Furthermore we will have identified the determinants of distinct p53 responses to therapy. Taken together, our work will provide novel tools able to predict cancer cancer cell responses to therapy.

Skills that the student should acquire (max. 600 characters including spaces):

- Perform live cell imaging and use quantitative image analysis approaches and advanced data analysis.

- Generate models with reporters of cell death and cell cycle alongside p53 dynamics.

- To use the sequential single-molecule RNA-FISH technique autoFISH (*11*) and apply state of the art cell and molecular biology techniques (RT-PCR, Western Blots, Immunofluorescence)

- Work in a multidisciplinary environment, composed by biologists, biotechnologists and biophysicists.

References (max. 15)

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