



PROGETTO

Supervisore:: Davide Mazza

Titolo/Title: The dynamic landscape of p53 interactions and their role in cancer cell fate determination

Curriculum: CMB

Link alla pagina <https://www.unisr.it/en/docenti/m/davide-mazza> personale del sito web di Ateneo o del polo ospedaliero di riferimento:

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

The fundamental role of the tumor suppressor p53 in determining the cellular response to genotoxic stress such as the one induced by many chemotherapies is well known (1). The canonical function of p53 is the one of a sequence-specific inducible transcription factor: upon detection of DNA damage, p53 is phosphorylated and tetramerize. Tetrameric p53 can bind the promoters and enhancers of target genes involved in the response to DNA damage to regulate their expression (2).

Despite being one of the most studied tumor suppressor, the development of drugs targeting p53 to enhance response to chemotherapies had shown limited success so far, possibly because p53 can regulate both pro-survival and pro-apoptotic pathways, in a stimulus and context-specific fashion. Notably – aside from its role as transcriptional activator – p53 also interacts with membraneless compartments in the nucleus, such as DNA damage foci (3), PML bodies (4) and nuclear speckles (5), with increasing evidence pointing at functional roles of these interactions. The dynamics of p53 interactions at DNA damage – for example – have recently shown to control the recruitment of the repair machinery (3), potentially modulating the efficacy of DNA repair and the cell fate of cancer cells exposed to chemotherapies (6).

Rationale and hypothesis

Our hypothesis for the proposed project is that by modulating p53 recruitment to nuclear organelles we can control the cellular response to genotoxic therapies.

Objectives and specific aims

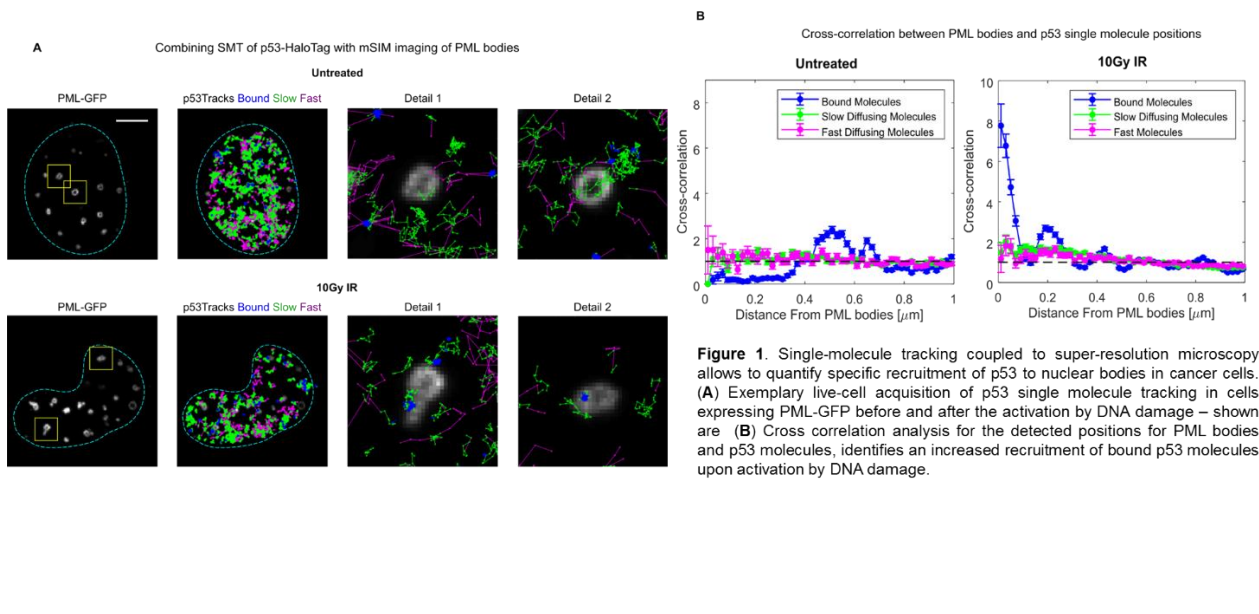


The goal of the project will be therefore to define the dynamics of p53 recruitment to DNA damage foci, PML bodies and nuclear speckles and the mechanisms underlying such recruitment, and its connection to the fate of cancer cells exposed to genotoxic chemotherapies.

To achieve this goal the PhD student will make use of an innovative and original microscopy technology (Figure 1) that we have developed to monitor the interaction of TFs with the nuclear environment with super-resolution and single molecule sensitivity in live cells (7,8,9,10).

Expected outcomes

The finding of the student will be fundamental to characterize non-canonical functions of the tumor suppressor p53 and identify novel therapeutic strategies to control cellular response to genotoxic chemotherapy in p53-wt cancers.



Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

The PhD student involved in our project will have the opportunity to be trained in a stimulating multidisciplinary environment on cutting-edge approaches in cellular and molecular biology, quantitative biology and advanced microscopy, including intranuclear single molecule tracking microscopy, a method that our laboratory has pioneered. The student will also use gene editing approaches such as CRISPR/Cas9 to label nuclear compartments with fluorescent tags and quantitative analysis tools, including those based on machine learning/artificial intelligence.

Bibliografia (max. 15)



- (1) Hafner A, Bulyk ML, Jambhekar A, Lahav G. The multiple mechanisms that regulate p53 activity and cell fate. *Nat Rev Mol Cell Biol.* 2019 Apr;20(4):199–210.
- (2) Panatta E, Zampieri C, Melino G, Amelio I. Understanding p53 tumour suppressor network. *Biology Direct.* 2021;16:14.
- (3) Wang Y-H, Ho TLF, Hariharan A, Goh HC, Wong YL, Verkaik NS, et al. Rapid recruitment of p53 to DNA damage sites directs DNA repair choice and integrity. *Proc Natl Acad Sci U S A.* 2022;119:e2113233119.
- (4) Fogal V, Gostissa M, Sandy P, Zacchi P, Sternsdorf T, Jensen K, et al. Regulation of p53 activity in nuclear bodies by a specific PML isoform. *The EMBO Journal.* 2000;19:6185–95.
- (5) Alexander KA, Coté A, Nguyen SC, Zhang L, Gholamalamdari O, Agudelo-Garcia P, et al. p53 mediates target gene association with nuclear speckles for amplified RNA expression. *Mol Cell.* 2021;81:1666.
- (6) Heltberg MS, Lucchetti A, Hsieh F-S, Minh Nguyen DP, Chen S, Jensen MH. Enhanced DNA repair through droplet formation and p53 oscillations. *Cell.* 2022;185:4394–4408.e10.
- (7) Mazza D, Mueller F, Stasevich TJ, McNally JG. Convergence of chromatin binding estimates in live cells. *Nature Methods.* 2013;10:691–2.
- (8) Loffreda A, Jacchetti E, Antunes S, Rainone P, Daniele T, Morisaki T, et al. Live-cell p53 single-molecule binding is modulated by C-terminal acetylation and correlates with transcriptional activity. *Nature Communications ;* 2017;8:313.
- (9) Mazzocca M, Fillot T, Loffreda A, Gnani D, Mazza D. The needle and the haystack: single molecule tracking to probe the transcription factor search in eukaryotes. *Biochem Soc Trans.* 2021;49:1121–32.
- (10) Mazzocca M, Loffreda A, Colombo E, Fillot T, Gnani D, Falletta P, et al. Chromatin organization drives the search mechanism of nuclear factors. *Nature Communications ;* 2023; 14:6433.