

## REPLICATION STRESS RESPONSE IN CSCs: MOLECULAR MECHANISMS AND THERAPEUTIC IMPLICATION

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**C**ancer stem cells (CSCs) are subpopulations of multipotent SCs responsible for the initiation, long-term clonal maintenance, growth and spreading of most human neoplasms, including colorectal cancer (CRC). CSCs reportedly share with embryonic and adult SCs a very robust DNA damage response (DDR), which favors their survival and drives the resistance to endogenous and exogenous genotoxins. Taking advantage of a panel of CRC patient-derived tumorspheres enriched for CSCs (CRC-SCs), we demonstrated that CSCs have high, although heterogeneous, levels of replication stress (RS). By performing genetic and cytogenetic analyses, we provided evidence that RS in CRC-SCs is boosted endogenously by p53 deficiency and the presence of supernumerary chromosomes. We also elucidated the tight, but plastic and multipronged RS response put in place by CSCs to set the threshold of and ensure tolerability to RS, which involves CHK1, PARP and some components of the homologous recombination repair. Of relevance for cancer therapy, we showed that such a robust and efficient response confers to replication-stressed CSCs elevated dependency on specific component(s) such as CHK1. Nonetheless, the redundancy and rewiring potential of RS response also favors the acquisition of resistance to RS-modulating and DNA-damaging regimens. Driven by this paradoxical evidence and based on the levels of RS at baseline, we designed dedicated RS response-targeting strategies with long-term CSC depleting effectiveness.

## BIOGRAPHY

Vitale Ilio has received his PhD in 2006 for Molecular Characterization of Mitotic Catastrophe. During his six-year Post-doctoral studies in France, he investigated the role of aneuploidy/tetraploidy in tumorigenesis uncovering surveillance mechanisms surveying cell ploidy (EMBOJ 2010, Science 2012). He currently is a Group Leader and Adjunct Professor in Neurobiology at the University of Rome "Tor Vergata" working on the link between CSCs, chromosomal instability, and tumor immunity. His group recently identified a novel strategy for the depletion of CSCs based on CHK1 inhibition (Gut 2017, Mol Cell 2017). He is the Executive Editor of Molecular and Cellular Oncology, Subject Editor in the Reference Module in Life Sciences and served as Editor for several books. He received the Young Scientist Award from the European Environmental Mutagenesis Society (2013). He is Author of >100 ISI papers (including Science, Nat Med, Nat Rev Mol Cell Biol., Nat Cell Biol). "h" index: 34.

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