CSI RESEARCH SEMINAR

CSI SINGAPORE
CANCER SCIENCE INSTITUTE OF SINGAPORE
National University of Singapore

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DNA Damage Response and Cellular Senescence
IFOM ETS - the AIRC Institute of Molecular Oncology

"RNA-dependent DNA Damage Response Activation in Aging and Cancer"

ABSTRACT

We previously reported that DNA double-strand breaks (DSBs) trigger the synthesis by RNA polymerase II of damage-induced long non-coding RNA (dilncRNA) that can be processed into shorter DNA damage response RNAs (DDRNAs). Such transcripts are essential for full DDR activation, and their inhibition by antisense oligonucleotides (ASO) allows site-specific inhibition of DNA damage signalling and repair (Francia et al Nature 2012, Michelini et al Nature Cell Biology 2017, D'Alessandro et al Nature Communications 2018).

We recently discovered that such transcriptional events depend on the assembly of seemingly fully functional transcriptional promoters that include a complete RNA polymerase II preinitiation complex (PIC), MED1 and CDK9.

Importantly, dilncRNAs drive molecular crowding of DDR proteins, such as 53BP1, into globular structures that exhibit liquid–liquid phase-separation condensate properties (Pessina et al Nature Cell Biology 2019).

Telomeres, the ends of linear chromosomes, progressively accumulate DNA damage during physiological and pathological aging. We recapitulated the above-described events at damaged telomeres (Rossiello et al. Nature Communications 2017) and demonstrated that specific DDR inhibition at telomeres by ASO improves aging's detrimental phenotypes and extends lifespan (Aguado et al. Nature Communications 2019).

Telomere dysfunction in some cancers provide an additional vulnerability, as I will discuss.

BIOGRAPHY

I am a cell and molecular biologist that studies the involvement of the DNA damage response (DDR) pathways in mammals in physiologically relevant processes, mainly aging and cancer.

I demonstrated that replicative cellular senescence is the outcome of the direct recognition of critically-short telomeres by the DDR apparatus (Nature 2003). As an independent PI at IFOM, Milan, Italy, we demonstrated that oncogene activation is an intrinsically genotoxic event that causes DDR activation and cellular senescence (Nature 2006). We reported that genomes are not uniformly repairable and, due to evolutionary constrains, telomeres, if damaged, cannot be repaired, as demonstrated in cultured cells and in the brain of aging primates (Nature Cell Biol 2012).

We reported an unanticipated role of non-coding RNAs in the direct activation of the DDR (Nature 2012, Nature Cell Biol 2017, Nature Cell Biol 2019). These events occur also at dysfunctional telomeres (Nature communications 2017) and antisense oligonucleotides (ASO) against noncoding RNA generated at damaged sites, which allows DDR inhibition at individual lesions, including at telomeres. Such ASO inhibit cellular senescence and organismal aging in a mouse model of Hutchinson-Gilford Progeria Syndrome (HGPS) (Nature communications 2019).

I am an EMBO member and a twice ERC Advanced grant recipient.

FRIDAY, 14 OCTOBER 2022
4PM - 5PM
LT37, TAHIR FOUNDATION BUILDING, MD1 (LEVEL 3)
CHAIR: PROF. ASHOK VENKITARAMAN