**2021 OddPols Meeting**

## Nucleolar Homeostasis Connects with Nuclear Organization

Chen Wang[1] Hanhui Ma[2,6] Samuel Sondalle[3] Susan Baserga[3,4,5] Thoru Pederson[2] andSui Huang[1]

[1] Department of Cell and Molecular Biology, Northwestern University Feinberg School ofMedicine, Chicago, IL; [2] Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA; [3] Department of Genetics,Yale School of Medicine, New Haven, CT; [4] Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, CT; [5] Department of Therapeutic Radiology,Yale School of Medicine; [6] School of Life Science and Technology, ShanghaiTech University, Shanghai, China

Beyond its classically established role in ribosome synthesis, the nucleolus is now known to be a multi-functional nuclear organelle. Although certain stressors and genotoxic encounters disrupt nucleolar integrity and ribosome synthesis, they can influence much more than just the nucleolus, making it difficult to selectively address thenucleolar function. For example, classical studies use low concentrations of acintomycinD to inhibit rDNA transcription and perturb the nucleolus. But the drug also inhibits topoisomerases I and II and intercalates DNA with selective affinity for G+C-rich sequences that abound throughout the genome. To more selectively tease out the potential unrecognized roles of the nucleolus, we disrupted rDNA transcription by siRNAknockdown of the RNA polymerase I largest subunit, RPA194, in HeLa cells, which reduced pre-rRNA synthesis and induced nucleolar segregation, similar to that observed in actinomycin D-treated cells. Nucleolar segregation induced by RP194 knockdown led to a repositioning of the centromeric regions of chromosomes normally situated in the nucleolar periphery. In addition, spatially distal Cajal bodies underwent morphological alterations and loss of certain components. Furthermore, certain genomicloci situated far from nucleoli displayed extensive repositioning. These widespread effects throughout the 3-D nucleome were not observed when the pre-ribosomal RNA processing factor UTP4 was knocked down, which also reduced ribosome synthesis, but does not induce nucleolar segregation, establishing that the RPA194 effects throughout the nucleus are not due to an inhibition of ribosome synthesis but rather a nucleolar reorganization. These findings point to an intranuclear commutative system that links the homeostasis of the nucleolus to the maintenance and localization of certain proximal and distal nuclear bodies and gene loci.