Multiple facet of cellular senescence in cancer treatment

Jae-Seon Lee

Department of Molecular Medicine, Inha University College of Medicine,

Incheon 22212, Korea

ABSTRACT

PART I: Cellular senescence is considered as an important tumor-suppressive mechanism. Here, we demonstrated that heparan sulfate (HS) prevents cellular senescence by fine-tuning of the fibroblast growth factor receptor (FGFR) signaling pathway. We found that depletion of PAPSS2, a synthetic enzyme of the sulfur donor PAPS, led to premature cell senescence in various cancer cells and in a xenograft tumor mouse model. Sodium chlorate, a metabolic inhibitor of HS sulfation also induced a cellular senescence phenotype. p53 and p21 accumulation was essential for PAPSS2-mediated cellular senescence. Such senescence phenotypes were closely correlated with cell surface HS levels in both cancer cells and human diploid fibroblasts. The determination of the activation of receptors such as FGFR1, Met, and insulin growth factor 1 receptor (IGF1R) β indicated that the augmented FGFR1/AKT signaling was specifically involved in premature senescence in a HS-dependent manner. Thus, blockade of either FGFR1 or AKT prohibited p53 and p21 accumulation and cell fate switched from cellular senescence to apoptosis. In particular, desulfation at the 2-*O* position in the HS chain contributed to the premature senescence via the augmented FGFR1 signaling. Taken together, we reveal, for the first time, that the proper status of heparan sulfation is essential for the prevention of cellular senescence. These observations allowed us to hypothesize that the FGF/FGFR signaling system could initiate novel tumor defenses through regulating premature senescence.

PART II: RNA-binding proteins (RBPs) are involved in mRNA splicing, maturation, transport, translation, storage, and turnover. Here, we identified *ACOT7* mRNA as a novel target of human WIG1. *ACOT7* mRNA decay was triggered by the microRNA miR-9 in a WIG1-dependent manner via classic recruitment of Argonaute 2 (AGO2). Interestingly, AGO2 was also recruited to *ACOT7* mRNA in a WIG1-dependent manner in the absence of miR-9, which indicates an alternative model whereby WIG1 controls AGO2-mediated gene silencing. The WIG1-AGO2 complex attenuated translation initiation via an interaction with translation initiation factor 5B (eIF5B). These results were confirmed using a WIG1 tethering system based on the MS2 bacteriophage coat protein and a reporter construct containing an MS2-binding site, and by immunoprecipitation of WIG1 and detection of WIG1-associated proteins using liquid chromatography-tandem mass spectrometry. We also identified WIG1-binding motifs using photoactivatable ribonucleoside-enhanced crosslinking and immunoprecipitation (PAR-CLIP) analyses. Altogether, our data indicate that WIG1 governs the miRNA-dependent and the miRNA-independent recruitment of AGO2 to lower the stability of and suppress the translation of *ACOT7* mRNA.