Topic: Heart Failure (Basic), Molecular Cardiology**The Role of p53 Localised in Cytosol and Mitochondria During Reprogramming to iPS Cells**

Tomomi Akama,¹ Araya Tengkhattakorn,¹ Motoharu Yamasaki,¹ Yukihiro Harada,¹ Dai Ihara,¹ Tomoe Ueyama,¹ Takahiro Sogo,² Shu Nakao¹ and Teruhisa Kawamura¹

1. Department of Biomedical Science, Ritsumeikan University, Kyoto, Japan; 2. Global Innovation Research Organization, Ritsumeikan University, Kyoto, Japan

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Previous studies, including ours, suggest that tumour repressor p53 is activated during somatic cell reprogramming, and efficiency of induced pluripotent stem cell (iPSC) formation is limited through transactivation of p53 target genes leading to apoptosis and cell cycle arrest. Recent studies revealed non-transcriptional effects of p53 on mitochondria that directly trigger apoptosis. Thus, we attempted to examine the role of cytosolic and mitochondrial p53 in iPSCs.

We constructed plasmids to express EGFP fused with either p53 wild-type (WT) and its mutant K27R which is expected abundantly to localise to mitochondria. Then, we performed live cell imaging using mouse embryonic fibroblasts (MEFs) infected with retroviruses encoding p53 WT-EGFP or p53 K27R-EGFP. While EGFP-fused with K27R as well as WT was observed in both cytosol and nucleus at the

basal condition, nuclear expression was significantly enhanced after irradiation, suggesting nuclear translocation of p53 by DNA damage. Localisation of p53 K27R seemed similar to that of p53 WT under fluorescence microscopy. Inhibitory effects of p53 on cell proliferation were, however, not observed in K27R-expressing cells.

Since the results suggest the role of K27R except nucleus, we further tested whether K27R affects the efficiency of iPSC colony formation. We introduced combinations of the reprogramming factors, Oct4, Sox2, and Klf4 with or without c-Myc into MEFs, together with either p53 WT or p53 K27R. Interestingly, K27R mutant repressed iPSC formation to similar extent as p53 WT. These results above suggest that cytosolic p53 would be a potential negative regulator for somatic cell reprogramming in a transcription-independent manner. ■