中文題目：HOXAs基因在人類胃細胞進行由JDP2/Oct4所誘導細胞重整中的角色

英文題目：Role of HOXA genes in JDP2/Oct4-induced pluripotent stem-like cells from human gastric cell lines CSN and CS12

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Background/Aim: We have generated and characterized the induced pluripotent stem-like cells from human gastric cell line, KMU-CS12 (CS12) and from an immortal cell line, KMU-CSN (CSN), which were derived from putative human gastric stem cell/progenitor cell clone, KMU-GI2. CS12 expressed cancer cell phenotypes, i.e. the ability of anchorage-independent growth high frequency (44%) and to the expression of Oct4, a stemness marker and many types of cancer cells, and tumor development in immune deficient mice. SKY analysis indicated a characteristic duplication of the short arm of chromosome 7 to chromosome 12. Agilent Human 1A oligo-array analysis and qPCR revealed that homeobox genes like Hoxa9 (57.83 fold), Hoxa7 (32.01 fold), Hoxa4 (24.14 fold), Hoxa5 (7.24 fold) and Hoxa13 (6.14 fold) were highly expressed in CS12 cells. We also generated induced pluripotent stem-like cells by electroporation using AP1 transcription factor Jun Dimerization protein 2 (JDP2) and Oct4. JDP2 plays roles in cell cycle regulation, cellular senescence, nuclear reprogramming and oncogenesis through the epigenetic control involved in cascades of $p19^{Arf}$-Mdm2-p53-p21-cyclin/CDK or $p16^{Ink4a}$-cyclin/CDK-RB-E2F.

Methods: Cells were seeded to each well of 12-well plate, 37 ℃, O/N Lentivirus infection with MOI=2 or 5, centrifuge 2300 rpm, 37 ℃, 90 min, culture O/N, Repeat step 2. Change K-SFM medium every day Passage to mito-MEF with ES medium. Pick up, purify single colony and amplification.

Results: We found that JDP2 functioned through Wnt signal and reprogrammed CS12 and CSN to iPSCs with Oct4. The enhanced expression of Sox2 is critical for generation of CSN-iPSCs. Both iPSCs and parental cells expressed three standard stemness genes like Oct4, Sox2, Nanog with different levels, but parental CS12 and CSN did not show the alkaline phosphatase activity. We observed endoderm and mesoderm in CSN iPS-like cells, ectoderm and endoderm in CS12 iPS-like cells but not in CS12 and CSN. Moreover, we found that original CS12 induced the tumor formation but CS12 iPS-like cells did not induce the tumor progression in nude mice.

Conclusion: These results indicate that JDP2/Oct4 generated iPS-like cells have the tumor suppressor function in SCID mice-xenograft mouse model. We also observed the significant reduction of Hoxa 4, 5, 7 and 9 but enhanced expression of Hoxa13. Thus, the different regulation of Hoxa gene family was detected. We discuss the role of HOXA genes in nuclear reprogramming and cancer development in gastric cell line.