Single Cell Biology
ISSN: 2168-9431

Jiang and Wang, Single Cell Biol 2017, 6:2
DOI: 10.4172/2168-9431.1000159

Commentary Open Access

Mir-195: Roadblock for Reprogramming Aged Cells

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Rec date: Mar 29, 2017; **Acc date:** Apr 11, 2017; **Pub date:** Apr 13, 2017

Commentary

Advanced age remains the greatest known risk factor for human diseases. According to a National Institute on Aging report, it is anticipated that people aged 65 or older will number nearly 1.5 billion by 2050, representing 16% of the world's population and a dramatic increase in the economic burden of providing care to patients with senile chronic diseases. Recent evidence strongly supports the current hypotheses that age-induced deterioration of tissue stem cells play an important role in initiation of several aging-associated disorders including heart failure, Alzheimer's disease, and Parkinson's disease [1].

Currently available somatic cell reprogramming technologies offer a promising strategy for patient-specific cardiac regenerative medicine, disease modelling, and drug discovery [2]. Induced pluripotent stem cells (iPSCs) are an ideal potential option as an autologous cell source (as compared to other stem/progenitor cells) because they can be propagated indefinitely and large number of functional target cells can be generated [3].

Techniques used for iPSC generation have already resulted in enormous progress for age-associated disease therapies. The efficiency of reprogramming is influenced by a variety of factors that include induction method and the age of cells [4]. One of the major pitfalls of iPSC generation from aged donors is that isolated somatic cells show increased cellular senescence and resistance to reprogramming as compared to younger cells [5]. Reprogramming of aged somatic cells therefore requires efficient approaches to rejuvenate cell senescence, erase age-associated feature, or enlighten the reversibility potential of aging. Extensive studies have shown that aging seems to be a critical 'roadblock' for somatic cell reprogramming [6], but the essential genes controlling this process have not been fully revealed.

MicroRNA (miR) microarray analysis has been used to identify miR-195 as a senescence-associated factor mediating aged mesenchymal stem cells [7]. Kondo et al. recently demonstrated that miR-195 acts as a barrier for reprogramming skeletal muscles (skMs) from old mice [8]. Expression levels of miR-195 were significantly upregulated in old skMs (2.3-fold at 24-months) as compared to cells from young mice (2-months) using RT-PCR and in situ hybridization. Proteins linked to the senescence pathways (i.e., P53, P21, and P16) were activated in SkMs obtained from old mice, and the characteristics of cellular senescence were demonstrated by β-galactosidase staining and telomere length reduction [8].

skMs also become resistant to reprogramming as they age, and miR-195 is significantly decreased in iPSCs derived from old skMs [8], indicating that miR-195 is a negative mediator of iPSC reprogramming. Kondo et al. used a lentiviral vector to knockdown the expression of miR-195 in old skMs to determine its role in iPSC generation. Inhibition of miR-195 was associated with downregulation of senescence-associated genes (i.e. *FOXO1* and *P53*) and elongation of the telomere [8]. Furthermore, blockage of miR-195 significantly (2.2 fold) increased the reprogramming efficiency of old skMs after transduction of Yamanaka factors (OKSM), as shown by alkaline phosphatase staining and expression of pluripotent genes (i.e. *SSEA1* and *Nanog*). The differentiation potential of iPSCs modified with miR-195 inhibitor was also confirmed by teratoma formation assay and staining of 3-germ layers. These results suggest that the iPSCs generated by this new approach possess properties similar to embryonic stem cells and are capable of differentiating into the functional cells of three germ layers.

MicroRNAs are post-transcriptional gene regulators in cells and can be manipulated to provide a better understanding of specific factors that alter aging signalling pathways during cellular reprogramming [9]. An online computational analysis by Kondo et al. identified Sirtuin (SIRT1) as a potential target of miR-195. Subsequently, the interactions between miR-195 and SIRT1 were demonstrated by luciferase assay and gene expression analysis [7]. TERT (telomerase reverse transcriptase) comprises the most important unit of the telomerase complex and prevents degradation of the chromosomal ends, and was also upregulated in old skMs after inhibition of miR-195 [10]. *SIRT1* has been shown as an important gene for telomere elongation and genomic stability of iPSCs [11]. These findings suggest that inhibition of miR-195 can increase telomere length in old skMs through restoration of the expression of telomerase genes.

In summary, Kondo et al. demonstrated that miR-195 serves as a target of cellular reprogramming and inhibition of miR-195 can be used as a tool to overcome genetic pitfalls associated with reprogramming aged cells into iPSCs. miR supplementation potentially facilitates iPSC generation approaches with high efficiency and quality. This novel approach could be of potential benefit for the development of effective stem cell therapies that treat age-associated diseases in the future.

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