Abstract: P4500

**Cellular senescence of endothelial cells impairs angiogenesis by altering energy metabolism through p53-tigar axis**

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**Background:** Ischemic disease is prevalent in elderly population due to impaired angiogenesis. Endothelial cell (EC) generates energy largely via glycolysis, which is further activated when angiogenesis actively occurs. PFK-1 is one of the most important regulatory enzymes for glycolysis, which is activated by PFKFB3. On the other hand, TIGAR inhibits PFK-1 under the control of p53. Crucial roles of PFKFB3 in EC functions under physiological and pathological conditions have been reported; however, a role of TIGAR in EC angiogenic functions remains to be elucidated. Furthermore, it remains unknown whether and how cellular senescence affect the energy metabolism in EC.

**Purpose:** The purpose of this study is to investigate molecular mechanisms underlying EC dysfunction associated with ageing, especially by focusing on endothelial energy metabolism.

**Method and result:** Senescent EC showed reduced glucose consumption assessed by [U-13C]-glucose tracer assay in association with increased expression of p53 and TIGAR. Angiogenic capacity assessed by tube-formation assay was reduced in senescent EC. Of note, either silencing of TIGAR by siRNA or lentivirus-mediated overexpression of PFKFB3 improved angiogenic capacity in senescent EC. These results collectively suggest that senescence impairs glycolysis in EC by activating p53-TIGAR axis, which leads to senescence-associated endothelial dysfunction. To analyze an impact of EC senescence in angiogenesis in vivo, we generated EC-specific progeroid mice in which dominant negative form of telomere repeat-binding factor 2 (TRF2) was overexpressed in EC under the control of the TIE2 promoter. After confirming EC-specific senescence in these endothelial progeroid mice, we generated hind-limb ischemia model. Recovery of blood flow assessed by laser doppler velocimeter was significantly impaired in endothelial progeroid mice, indicating that EC senescence is directly and causally implicated in age-related angiogenic dysfunction. Of note, genetic inactivation of TIGAR completely rescued the impaired ischemia-induced neovessel formation in EC-specific progeroid mice.

**Conclusion:** Using unique endothelial progeroid mice, we revealed that EC senescence is a bona fide risk for ischemic disease, largely by reducing glycolysis in EC through p53-TIGAR axis. Our data suggest that endothelial energy metabolism is an attracting therapeutic target for the prevention and/or treatment of ischemic diseases, especially in elderly population.