# The identification of cardio-vascular stem cells and clarification its differentiation mechanism

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Purpose: Ischemic disease is the main cause of death as well as cancer. To overcome it, we need to reveal the mechanism how cardio-vascular stem cells in tissue differentiate into cardiomyocytes or vascular cells. Furthermore, we would like to approach cancer stem cells, which have supposed as the cause of drug resistant cancer.

Results

1-1. In embryonic stage, vascular stem cells (VPCs) are originated from hematopoietic stem cells (HSCs) fraction and they differentiate into both ECs and SMCs (vascular cells) in vitro and in vivo.

1-2. HSCs($lin^-ckit^+CD45^+$), which differentiate into vascular cells, have tissue specific mechanism. HSCs in head region differentiate into vascular cells, but HSCs in fetal liver can not differentiate into vascular cells.

1-3. Tissue specificity in HSCs is due to the induction of Flk-1 expression by brain ECs.

1-4. In adult stage, especially in ischemic condition, vascular stem cells are exsited in monocyte/M-phage fraction, such as $CD45^+CD11b^+$ cells. Moreover, very interestingly, there are two populations, such as $CD45^+CD11b^{low+}$ and $CD45^+CD11b^{high+}$cells, and $CD45^+CD11b^{low+}$ cells mainly contribute to angiogenesis as vascular cells in both short term and long term.

2-1. We identified cardiac stem cells in brown adipose tissue. We named them BATCM (brown adipose tissue derived cardiomyocyte)

2-2. BATCMs expressed CD29, CD105, and CD133, such as mesenchymal stem cells marker, but not expressed linage marker, c-kit, and CD31, such as hematopoietic and endothelial cells marker.

2-3. In vitro, BATCMs differentiated into sarcomeric-actin, troponinT, MEF2C, and GATA-4 positive CMs, furthermore, they differentiated into CD31, VE-cadherin, Flk-1 positive ECs and SMA, PDGF-$\beta$ and desmin-positive SMCs.

2-4. In vivo infarction model, BATCMs contributed as CM, ECs and SMCs in ischemic border zone, and improved the function of heart and mortality.

3-1. Cancer cells interacted with hematopoietic cells and performed as cancer stem like cells in vivo.

Future plan

1. To detect vascular stem cells in other condition, such as in tumorangiogenesis and brain ischemia. To detect the inducible factor for Flk-1 expression in HSCs.

2. To detect the regulating factor from stem cells into CMs in adipose tissue.

3. To analyze the features of cancer stem cell like cells precisely in vitro and in vivo.

Publication

1. Yamada. Y et al (2003) Blood 101:1801-1809.

2. Yamada. Y et al (inpress) Biochem. Biophys. Res. Commun.