

がん幹細胞ニッチの破綻とがん幹細胞の細胞死の誘導

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Regulation and molecular analysis of cancer stem cells in the tumor

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1. Kidoya H, Naito H, Takakura N. (2010)

Apelin induces enlarged and non-leaky blood vessels for functional recovery from ischemia.

Blood, 115: 3166-3174.

The efficacy of therapeutic angiogenesis for revascularization in ischemia using genes, proteins, and cells has been established. For further improvement, processes allowing enlargement of the luminal cavity to facilitate efficient blood flow need to be facilitated. Recently, we found that expression of APJ and its specific ligand, apelin, is seen in endothelial cells when angiogenesis is taking place during embryogenesis. Apelin-deficient mice are viable but have narrow intersomitic vessels during embryogenesis and narrow blood vessels in the trachea and skin after birth. Apelin induces the formation of larger cords of endothelial cells, mainly mediated by cell-cell aggregation, resulting in the generation of larger blood vessels. Here we report that transgenic overexpression of apelin in keratinocytes induces enlarged but not leaky blood vessels in the dermis. In the hind limb ischemia model, apelin together with vascular endothelial growth factor (VEGF) effectively induced functional vessels larger than with VEGF alone. Endogenous apelin is required for the suppression of VEGF-, histamine-, or inflammation-induced vascular hyperpermeability. Apelin inhibited the down-modulation of vascular endothelial-cadherin by VEGF, resulting in suppression of hyperpermeability. Our results suggest apelin efficacy for therapeutic angiogenesis.

2. Nagahama Y, Ueno M, Miyamoto S, Morii E, Minami T, Mochizuki N, Saya H, Takakura N. (2010)

PSF1, a DNA replication factor expressed widely in stem and progenitor cells, drives tumorigenic and metastatic properties.

Cancer Res, 70: 1215-1224.

PSF1 (partner of sld five 1) is an evolutionarily conserved DNA replication factor implicated in DNA replication in lower species that is strongly expressed in a wide range of normal stem cell populations and progenitor cell populations. Because stem and progenitor cells possess high proliferative capacity, we hypothesized that PSF1 may play an important role in tumor growth. To begin to investigate PSF1 function in cancer cells, we cloned the mouse PSF1 promoter and generated lung and colon carcinoma cells that stably express a PSF1 promoter-reporter gene. Reporter expression in cells correlated with endogenous PSF1 mRNA expression. In a tumor cell xenograft model, high levels of reporter expression correlated with high proliferative activity, serial transplantation potential, and metastatic capability. Notably, cancer cells expressing reporter levels localized to perivascular regions in tumors and displayed expression signatures related to embryonic stem cells. RNAi-mediated silencing of endogenous PSF1 inhibited cancer cell growth by disrupting DNA synthesis and chromosomal segregation. These findings implicate PSF1 in tumorigenesis and offer initial evidence of its potential as a theranostic target.

3. Ueno M, Itoh M, Sugihara K, Asano M, Takakura N. (2009)

Both alleles of PSF1 are required for maintenance of pool size of immature hematopoietic cells and acute bone marrow regeneration.

Blood, 113: 555-562.

Hematopoietic stem cells (HSCs) have a very low rate of cell division in the steady state; however, under conditions of hematopoietic stress, these cells can begin to proliferate at high rates, differentiate into mature hematopoietic cells, and rapidly reconstitute ablated bone marrow (BM). Previously, we isolated a novel evolutionarily conserved DNA replication factor, PSF1 (partner of SLD5-1), from an HSC-specific cDNA library. In the steady state, PSF1 is expressed predominantly in CD34(+)KSL (c-kit(+)/Sca-1(+)/Lineage(-)) cells and progenitors, whereas high levels of PSF1 expression are induced in KSL cells after BM ablation. In 1-year-old PSF1(+/-) mice, the pool size of

stem cells and progenitors is decreased. Whereas young PSF1(+/-) mutant mice develop normally, are fertile, and have no obvious differences in hematopoiesis in the steady state compared with wild-type mice, intravenous injection of 5-fluorouracil (5-FU) is lethal in PSF1(+/-) mice, resulting from a delay in induction of HSC proliferation during ablated BM reconstitution. Overexpression studies revealed that PSF1 regulates molecular stability of other GINS components, including SLD5, PSF2, and PSF3. Our data indicate that PSF1 is required for acute proliferation of HSCs in the BM of mice.

4. Kidoya H, Ueno M, Yamada Y, Mochizuki N, Nakata M, Yano T, Fujii R, Takakura N. (2008)

Spatial and temporal role of the apelin/APJ system in the caliber size regulation of blood vessels during angiogenesis.

EMBO J, 27: 522-534.

Blood vessels change their caliber to adapt to the demands of tissues or organs for oxygen and nutrients. This event is mainly organized at the capillary level and requires a size-sensing mechanism. However, the molecular regulatory mechanism involved in caliber size modification in blood vessels is not clear. Here we show that apelin, a protein secreted from endothelial cells under the activation of Tie2 receptor tyrosine kinase on endothelial cells, plays a role in the regulation of caliber size of blood vessel through its cognate receptor APJ, which is expressed on endothelial cells. During early embryogenesis, APJ is expressed on endothelial cells of the new blood vessels sprouted from the dorsal aorta, but not on pre-existing endothelial cells of the dorsal aorta. Apelin-deficient mice showed narrow blood vessels in intersomitic vessels during embryogenesis. Apelin enhanced endothelial cell proliferation in the presence of vascular endothelial growth factor and promoted cell-to-cell aggregation. These results indicated that the apelin/APJ system is involved in the regulation of blood vessel diameter during angiogenesis.

5. Huang X, Yamada Y, Kidoya H, Naito H, Nagahama Y, Kong L, Katoh SY, Li WL, Ueno M, Takakura N. (2007)

EphB4 overexpression on B16 melanoma cells affects arterial-venous patterning in tumor angiogenesis.

Cancer Res, 67: 9800-9808.

EphB4 receptor and its ligand ephrinB2 play an important role in vascular development during embryogenesis. In blood vessels, ephrinB2 is expressed in arterial endothelial cells (EC) and mesenchymal supporting cells, whereas EphB4 is only expressed in venous ECs. Previously, we reported that OP9 stromal cells, which support the development of both arterial and venous ECs, in which EphB4 was overexpressed, could inhibit ephrinB2-positive (ephrinB2+) EC development in an embryonic tissue organ culture system. Although the EphB4 receptor is expressed in a variety of tumor cells, its exact function in regulating tumor progression has not been clearly shown. Here we found that overexpression of EphB4 in B16 melanoma cells suppressed tumor growth in a s.c. transplantation tumor model. Histologic examination of these tumors revealed that EphB4 overexpression in B16 cells selectively suppressed arterial ephrinB2+ EC development. By coculturing ephrinB2-expressing SV40-transformed mouse ECs (SVEC) with EphB4-overexpressing B16 cells, we found that EphB4 induced the apoptosis of SVECs. However, ephrinB2 did not induce the apoptosis of EphB4-overexpressing B16 cells. Based on results from these experiments, we concluded that EphB4 overexpression in B16 tumor cells suppresses the survival of arterial ECs in tumors by a reverse signaling via ephrinB2.