Stromal fibroblasts activated by tumor cells promote angiogenesis in mouse gastric cancer.

X Guo, H. Oshima and M. Oshima

Myofibroblasts constitute important niche for tumor development through the promotion of angiogenesis. However, the mechanism of stromal fibroblast activation in tumor tissues has not been fully understood. A gastric cancer mouse model (*Gan* mice) was recently constructed by simultaneous activation of PGE_2 and Wnt signaling in the gastric mucosa. Because both the PGE_2 and Wnt pathways play a role in human gastric tumorigenesis, *Gan* mouse model therefore, recapitulates the molecular etiology of human gastric cancer. Microvessel density increased significantly in *Gan* mouse tumors (Fig. 1). Moreover, the expression of vascular endothelial growth factor A (VEGFA) was predominantly induced in the stromal cells of gastric tumors. Immunohistochemistry suggested that VEGFA-expressing cells in the stroma were α-smooth muscle actin (SMA)-positive myofibroblasts (Fig. 1). Bone marrow transplantation experiments indicated that subset of gastric myofibroblasts were derived from bone marrow. Importantly, the α-SMA index in cultured fibroblasts increased significantly when stimulated with the conditioned medium (CM) of *Gan* mouse tumor cells, indicating that gastric tumor cells activate stromal fibroblasts. Furthermore, CM of *Gan* mouse tumor cells induced VEGFA expression both in embryonic and gastric fibroblasts, which further accelerated the tube formation of human umbilical vein endothelial cells *in vitro*. Notably, stimulation of fibroblasts with PGE_2 and/or Wnt1 did not induce VEGFA expression, thus suggesting that factors secondarily induced by PGE_2 and Wnt signaling in the tumor cells are responsible for activation of stromal fibroblasts. Such tumor cell-derived factors may therefore be an effective target for chemoprevention against gastric cancer.

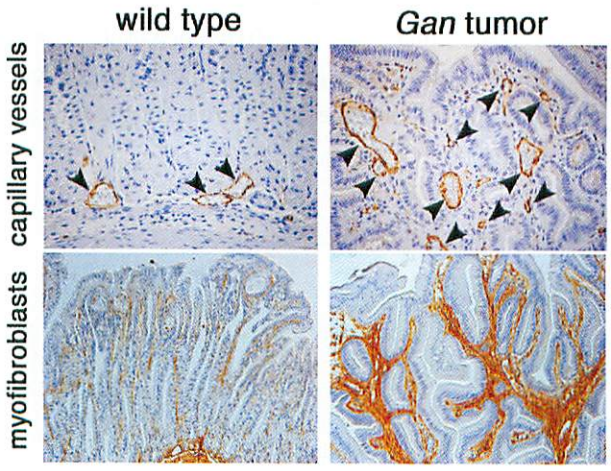

Fig. 1. Immunohistochemistry of wild-type mouse stomach (*left*) and *Gan* mouse gastric tumors (*right*) to show significantly increased capillary vessels (*top*) and myofibroblasts (*bottom*) in *Gan* tumor tissues.

Reference: Guo X, *et al.* J Biol Chem, 283: 19864, 2008.