Activated macrophages promote Wnt signaling through TNF-α in gastric tumor cells.

K. Oguma, H. Oshima and M. Oshima

The canonical Wnt signaling pathway (Wnt/β-catenin pathway) operates by stabilizing β-catenin. The activation of Wnt/β-catenin signaling plays a key role in gastrointestinal tumorigenesis as well as in normal intestinal stem cells. It has been suggested that the promotion of Wnt/β-catenin activity beyond the threshold is important for carcinogenesis. We herein investigated the role of macrophages in promotion of Wnt/β-catenin activity in gastric tumorigenesis. We found β-catenin nuclear accumulation in macrophage infiltrated dysplastic mucosa of the *K19-Wnt1* mouse stomach. Moreover, macrophage depletion in $Apc^{\Delta 716}$ mice resulted in the suppression of intestinal tumorigenesis. These results suggested the role of macrophages in the activation of Wnt/β-catenin signaling, which thus leads to tumor development. Importantly, the conditioned medium of activated macrophages promoted Wnt/β-catenin signaling in gastric cancer cells, which was suppressed by the inhibition of tumor necrosis factor (TNF)-α (Fig. 1). Furthermore, treatment with TNF-α induces GSK3β phosphorylation, which resulted in the stabilization of β-catenin. We also found that *Helicobacter* infection in the *K19-Wnt1* mouse stomach caused mucosal macrophage infiltration and nuclear β-catenin accumulation. These results suggest that macrophage-derived TNF-α promotes Wnt/β-catenin signaling through inhibition of GSK3β, which may contribute to tumor development in the gastric mucosa. Accordingly, the present results suggest that suppression of macrophage infiltration and its activation by anti-inflammatory drugs or inhibitors for PGE_2 pathway is a possible strategy for chemoprevention against gastric cancer.

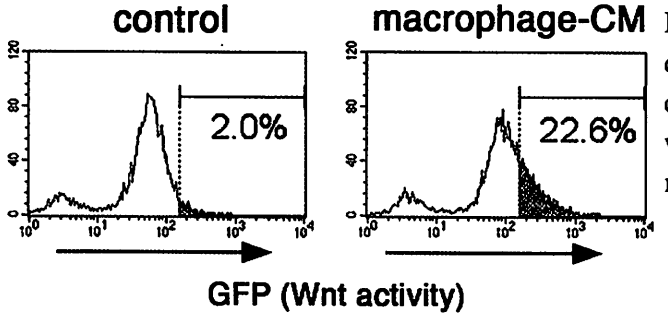

Fig. 1. FACS analyses of GFP intensity corresponding to Wnt activity of control gastric cancer cells (*left*) and stimulated cancer cells with conditioned medium derived from activated macrophages (*right*).

Reference: Oguma K, *et al.* EMBO J, 27: 1671, 2008.