Construction of transgenic mouse model for gastric cancer

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It has been demonstrated that nuclear translocation of β-catenin, a hallmark of Wnt activation, is found in human gastric cancer, suggesting the causal role of Wnt pathway in gastric carcinogenesis. We examined 80 cases of gastric cancer by immunohistochemistry, and found nuclear β-catenin in 54% (51% and 58% for intestinal- and diffuse types, respectively). Accordingly, it is conceivable that Wnt pathway activation is one of the major causes of gastric cancer development regardless of the histological type. To investigate the genetic mechanism further, we constructed transgenic mice (*K19-Wnt1*) expressing *Wnt1*, one of the ligands that activate the canonical Wnt signaling, in the gastric epithelial cells. Importantly, trefoil factor 2 (TFF2)-expressing cell population was expanded in the gastric gland of the *K19-Wnt1* mice. TFF2 is a marker for undifferentiated gastric epithelium which expresses in the small isthmal cells where β-catenin accumulated. Moreover, we found dysplastic preneoplastic lesions consisted of β-catenin-accumulated epithelial cells in the *K19-Wnt1* mice (Figure). These results, taken together, suggest that Wnt signaling keeps gastric stem cells and progenitors undifferentiated and that activation of Wnt pathway leads to development of preneoplastic lesions in the stomach. For gastric cancer development, activation of an additional pathway (e.g., COX-2) appears to be required. It is of important to investigate compound mutants of *K19-Wnt1* and *K19-C2mE*.