Host inflammatory responses and gastrointestinal tumorigenesis

H. Oshima, A. Matsunaga*, M.M. Taketo* and M. Oshima
(*Department of Pharmacology, Kyoto University Graduate School of Medicine)

Cyclooxygenase-2 (COX-2), a rate-limiting enzyme for prostanoid biosynthesis, plays a key role in gastrointestinal carcinogenesis. Among various prostanoids, prostaglandin E_2 (PGE_2) appears to be most responsible for cancer development. It has been shown that *Helicobacter pylori* infection induces expression of COX-2 and microsomal prostaglandin E synthase (mPGES)-1 in the gastric mucosa, resulting in increased level of PGE_2 in the stomach. To investigate the role of PGE_2 in gastric tumorigenesis, we constructed transgenic mice (*K19-C2mE*) expressing COX-2 and mPGES-1 in the gastric mucosa. The transgenic mice developed hyperplastic gastric tumors associated with inflammatory responses. To further investigate the roles of PGE_2-dependent host inflammatory and immune responses in gastric tumorigenesis, we introduced knockout mutations for tumor necrosis factor (TNF)-α, interleukin (IL)-1 receptor α chain and Rag 2 genes, respectively, into *K19-C2mE* mice. Among the compound mutants, only TNF-α (–/–) *K19-C2mE* mice showed significant suppression of hyperplastic tumors with reduced epithelial cell proliferation (Figure). Importantly, spasmolytic polypeptide-expressing metaplasia (SPEM) in the *K19-C2mE* stomach was also suppressed in the TNF-α (–/–) *K19-C2mE* mice. Gastric metaplasia to the SPEM lineage has been considered as a preneoplastic lesion of gastric cancer. These results indicate that TNF-α-dependent inflammation caused by increased PGE_2 is responsible for development of hyperplastic tumors and SPEM (Figure). Therefore, it is possible that inhibition of TNF-α-dependent inflammation together with eradication of *Helicobacter* is an effective prevention strategy for gastric cancer.