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**Conditional Inactivation of *Klf4* Gene in Distinct Cell Population of Stomach Mucosa Renders Mice Susceptible to Gastric Carcinogenesis**

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**Background:** Previous studies have shown that Krüppel-like factor 4 (KLF4) is a putative tumor suppressor in human gastric cancer, and a distinct population of *Villin*-positive cells in gastric antrum has a significant role in gastric carcinogenesis. However, the functional significance of *Klf4* inactivation in those cells in gastric carcinogenesis is unknown.

**Methods:** Mice with genetic ablation of *Klf4* in villin-positive stomach mucosa cells, *Klf4*<sup>fllox/fllox</sup>; *Villin-Cre*<sup>+</sup>, were generated by crossing *Klf4*<sup>fllox/fllox</sup> and *Villin-Cre*<sup>+</sup> mice, both of which were on the C57BL/6 genetic background. Beginning at 5 weeks of age, *Klf4*<sup>fllox/fllox</sup>; *Villin-Cre*<sup>+</sup> (n=29) and *Klf4*<sup>fllox/fllox</sup>; *Villin-Cre*<sup>-</sup> (n=36) littermates were given drinking water containing 240 ppm N-methyl-N-nitrosourea (MNU) on alternate weeks for a total of 10 weeks. The MNU-treated and -untreated *Klf4*<sup>fllox/fllox</sup>; *Villin-Cre*<sup>+</sup> and *Klf4*<sup>fllox/fllox</sup>; *Villin-Cre*<sup>-</sup> mice were sacrificed at 50 weeks of age; gastric mucosae were collected and subject to histopathologic examinations.

**Results:** No gastric tumors were found in MNU-untreated *Klf4*<sup>fllox/fllox</sup>; *Villin-Cre*<sup>+</sup> and *Klf4*<sup>fllox/fllox</sup>; *Villin-Cre*<sup>-</sup> mice at 50 weeks of age. However, in the MNU-treated mice, significantly more of the *Klf4*<sup>fllox/fllox</sup>; *Villin-Cre*<sup>+</sup> mice (93.1%=27/29) than the *Klf4*<sup>fllox/fllox</sup>; *Villin-Cre*<sup>-</sup> mice (38.8%=14/36) developed gastric tumors (P<0.01). MNU-treated *Klf4*<sup>fllox/fllox</sup>; *Villin-Cre*<sup>+</sup> mice also had a greater number of induced tumors (multiplicity) than MNU-treated *Klf4*<sup>fllox/fllox</sup>; *Villin-Cre*<sup>-</sup> mice.

**Conclusions:** These data offer definitive evidence that conditional inactivation of the *Klf4* gene in a distinct cell population of stomach mucosa renders mice susceptible to gastric carcinogenesis. The

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combination of *Klf4* gene ablation and MNU exposure could be a useful model for the investigation of multi-stage gastric carcinogenesis.