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ABSTRACTS SELECTED FOR POSTER PRESENTATIONS

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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, $Klf4^{flox/flox}$;*Villin-*Cre^{+}, were generated by crossing $Klf4^{flox/flox}$ and *Villin-*Cre^{+} mice, both of which were on the C57BL/6 genetic background. Beginning at 5 weeks of age, $Klf4^{flox/flox}$;*Villin-*Cre^{+} (n=29) and $Klf4^{flox/flox}$;*Villin-*Cre^{-} (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 $Klf4^{flox/flox}$;*Villin-*Cre^{+} and $Klf4^{flox/flox}$;*Villin-*Cre^{-} 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 $Klf4^{flox/flox}$;*Villin-*Cre^{+} and $Klf4^{flox/flox}$;*Villin-*Cre^{-} mice at 50 weeks of age. However, in the MNU-treated mice, significantly more of the $Klf4^{flox/flox}$;*Villin-*Cre^{+} mice (93.1%=27/29) than the $Klf4^{flox/flox}$;*Villin-*Cre^{-} mice (38.8%=14/36) developed gastric tumors (P<0.01). MNU-treated $Klf4^{flox/flox}$;*Villin-*Cre^{+} mice also had a greater number of induced tumors (multiplicity) than MNU-treated $Klf4^{flox/flox}$;*Villin-*Cre^{-} 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.