How TP53 gene loss drives gastric cancer evolution

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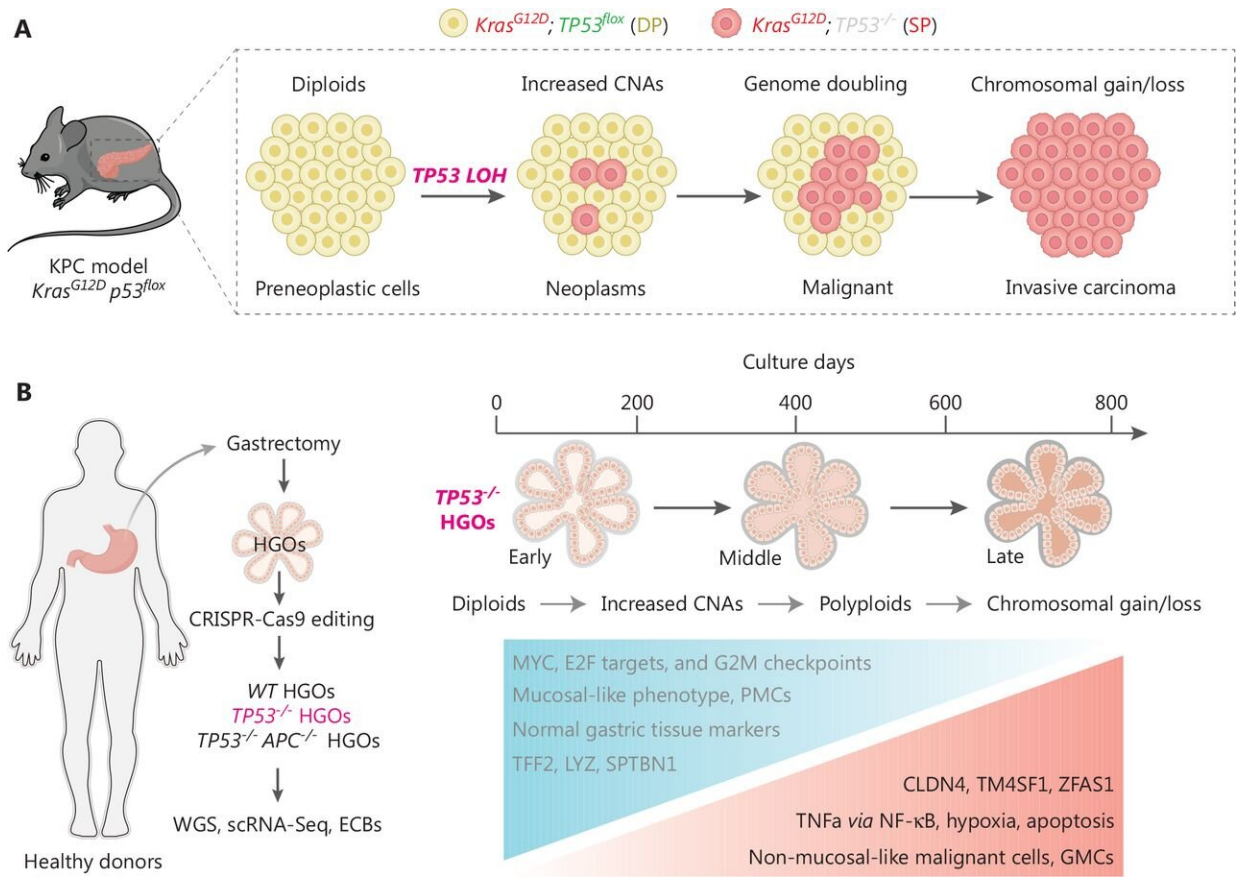

TP53 inactivation initiates ordered genomic evolution. (A) The Lowe et al. group applied the KPC^{LOH} reporter mouse model harboring both mutated Kras (mKate fluorescence) and intact Tp53 [GFP fluorescence, defined as DP cells (yellow)] and sporadic p53 inactivation resulted in the disappearance of GFP signal [defined as SP cells (red)]. This model allows for simultaneously monitoring TP53 status, genome evolution, and cellular phenotypes in vivo. Cartoon presentation is partially adopted[15]. (B) The Curtis's group utilized human gastric

organoids (HGOs) combined with CRISPR-Cas9 technology to generate TP53$^{-/-}$ HGOs (left panel) and temporally deciphered the genetic alterations with resultant transcriptional reprograms and phenotypes (right panel). Both studies revealed similar orders of genome evolutionary trajectories. TP53 loss progressively increases CNAs and structural variants, which followed by appearance of aneuploidy and loss/gain of genomic regions. Credit: *Cancer Biology & Medicine* (2024). DOI: 10.20892/j.issn.2095-3941.2023.0435

Gastric cancer (GC) ranks as the fifth-most common and fourth-deadliest cancer worldwide, presenting significant health challenges, particularly in China, where it is most prevalent and accounts for nearly half of newly diagnosed and death cases. In addition to somatic mutations, the complex pathology of GC is also determined by exposure to external factors like dietary and microorganisms such as Helicobacter pylori, Streptococcus anginosus, and Candida albicans.

Thus, a long-standing open question in this field is how the intrinsic genetic driver mutations such as loss of TP53 coordinate with extrinsic risk factors such as microbial infection to initiate gastric tumorigenesis.

An editorial contributed by Dr. Zhaocai Zhou, published in *Cancer Biology & Medicine*, has systemically digested work published by Lowe's and Curtis's groups in *Nature*, which sheds light on the critical role of TP53 loss, a gene known for its tumor-suppressing functions, in driving GC initiation. The new publication also discusses the limitations and future directions of this burgeoning research area.

Using innovative animal models and cutting-edge genomic technologies, the researchers were able to track cellular transformations in real time. Their key findings indicate that loss of TP53 gene function initially leads to an increase in chromosomal instability. This early instability, marked by widespread genetic rearrangements, increases the propensity for

aggressive cancer traits to develop.

As the disease progresses, specific gene alterations, including changes in gene copy numbers and structural variations, occur in a relatively defined but not random order, which is crucial for cancer to reach its full malignant potential. Importantly, the two groups identified distinct phases of genetic evolution, all linked to the worsening of the disease.

The initial phase involves subtle genomic changes, followed by more pronounced genetic alterations that solidify the cancer's growth and spread. This progression pattern offers potential markers for early detection and inspire preventive or therapeutic strategies aiming to interrupt this deadly evolution path.

"Understanding the role of TP53 loss in the roadmap of GC pathology opens new avenues for early detection and intervention of GC. By identifying the genetic trajectory of tumor evolution, clinicians can potentially devise strategies to intercept the road to cancer much earlier. Moreover, these findings support the use of personalized medicine approaches tailored to the genetic profile of individual tumors," said Dr. Zhou.

"In this regard, an immediate prominent issue is to evaluate how extrinsic factors influence TP53 loss-related evolution path during GC initiation and development; and future studies might rediscover the extrinsic factors in a second-hit paradigm."

More information: Liwei An et al, Road of no return—loss of TP53 paves a defined evolution path from gastric preneoplasia-to-cancer, *Cancer Biology & Medicine* (2024). DOI: 10.20892/j.issn.2095-3941.2023.0435

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