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Mutant p53 leads to enrichment of cancer stem cells that display ESC expression signature

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Abstract

Mutation in the p53 gene is a frequent alteration in human cancers which mostly leads to the acquiring of new oncogenic functions that promote tumorigenesis. In this study, we observed that bone marrow derived from mutant p53 mice exhibit higher ability to form tumors compared to WT-MSCs. Cultivation of tumors obtained from mutant p53 MSCs led to the selection of aggressive tumor-derived cell lines with an enhanced tumorigenic capacity as compared with their parental MSCs. The newly established tumor-derived cell lines were able to generate tumors following injection of as few as 100 cells, as well as displayed high expression of embryonic stem cell (ESC) signature. We were able to show that the enhanced tumor initiating capacity and the expression of ESC signature exhibited by the tumor-derived cell lines is mutant p53 dependent. In order to confirm our findings in human settings, we utilized datasets from The Cancer Genome Atlas (TCGA). Expression levels of genes belonging to the ESC signature expressed by mutant p53 derived tumor cell lines were examined in human tumors harboring p53 missense mutation. In agreement with data obtained from mouse models, we identified 41 genes that were significantly and exclusively upregulated in human tumors harboring p53 missense mutation. In conclusion, our results suggest that mutant p53 oncogenic GOF in MSCs leads to the acquirement of CSC features, including enhanced expression of ESC signature. This ESC signature might assist to design a more specific cancer stem-cells targeted therapy for Li-Fraumeni patients and cancer at large.

Mutations in the tumor suppressor p53 are the most frequent alterations in human cancer. These mutations include p53-inactivating mutations as well as oncogenic gain-of-function (GOF) mutations that endow p53 with capabilities to promote tumor progression. A primary challenge in cancer therapy is targeting stemness features and cancer stem cells (CSC) that account for tumor initiation, metastasis, and cancer relapse. Here we show that in vitro cultivation of tumors derived from mutant p53 murine bone marrow mesenchymal stem cells (MSC) gives rise to aggressive tumor lines (TL). These MSC-TLs exhibited CSC features as displayed by their augmented oncogenicity and high expression of CSC markers. Comparative analyses between MSC-TL with their parental mutant p53 MSC allowed for identification of the molecular events underlying their tumorigenic properties, including an embryonic stem cell (ESC) gene signature specifically expressed in MSC-TLs. Knockout of mutant p53 led to a reduction in tumor development and tumorigenic cell frequency, which was accompanied by reduced expression of CSC markers and the ESC MSC-TL signature. In human cancer, MSC-TL ESC signature-derived genes correlated with poor patient survival and were highly expressed in human tumors harboring p53 hotspot mutations. These data indicate that the ESC gene signature-derived genes may serve as new stemness-based prognostic biomarkers as well as novel cancer therapeutic targets.

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