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Development of innovative in vitro and in vivo patient-derived cancer models for translational studies in G1/G2 gastroenteropancreatic neuroendocrine tumors

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BACKGROUND

Well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs) grow slowly but are nonetheless lethal when advanced. Despite progress, effective systemic treatments for GEP-NETs remain limited. A key barrier is the scarcity of clinically relevant models that accurately reflect human GEP-NET biology. To address this important gap, we have conducted the following studies.

METHODS

Doxycycline (Dox)-inducible TP53R273H and SV40LT lentiviruses, marked with EGFP, were generated, and characterized. Cells digested from 21 surgically resected primary or metastatic tissues of G1/G2 GEP-NETs were transduced with these lentiviruses to produce Dox-inducible genetically modified PDOs (GM PDOs). GM PDOs from PanNETs transduced with luciferase lentivirus were injected into pancreata of NSG mice to generate orthotopic GM PDO-derived xenografts (GM PDXs). The genetic and biological signatures of GM PDOs were examined and compared to their original tumor cells through WGS and RNA-seq analyses. Cell growth rates of GM PDOs cultured with Dox-on, and Dox-off conditions were quantified by measuring EGFP fluorescence intensity. Tumor growth of GM PDXs was monitored through bioluminescence imaging. Expression of NET markers, Ki67, p53 (R273H), and SV40LT in GM PDOs with Dox-on and Dox-off conditions, their original tumors and GM PDXs was measured by IHC staining.

RESULTS

A total of 12 GM PDOs were successfully generated, including 6 out of 10 PanNETs (60%), 5 out of 10 intestinal NETs (50%), and 1 gastrinoma (100%), achieving an overall success rate of 57%. WGS results showed that these GM PDOs maintained chromosome copy number and structure variants, gene mutations and tumor mutational burdens, of their original tumors. Cell proliferation of GM PDOs accelerated with Dox treatment; Dox withdrawal stopped TP53R273H and SV40LT expression, slowed cell growth, decreased Ki67 expression, and restored CHGA, SYP and SSTR2 expression and cell signaling pathways, suggesting that the effects of Dox-inducible p53R273H and SV40LT proteins on biological changes in GM PDOs were reversible, demonstrating that GM PDOs in Dox-off condition were similar to the original tumors. Furthermore, one orthotopic GM PDX model from a G2 PanNET was successfully generated, in which luminescent density gradually but significantly increased from 2 to 8 weeks post-injection. Histologic examination and IHC staining results confirmed GM PDX lesions with strong expression of CHGA, SYP and SSTR2 proteins.

CONCLUSIONS

Innovative in vitro and in vivo patient-derived cancer models that could recapitulate the genomic and biological features of human G1/G2 GEP-NETs were successfully developed for the first time. These models yield unique materials enabling translational studies in GEP-NETs.

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