Hidalgo-Sastre, Ana; Brodylo, Roxanne L; Lubeseder-Martellato, Clara; Sipos, Bence; Steiger, Katja; Lee, Marcel; von Figura, Guido; Grünwald, Barbara; Zhong, Suyang; Trajkovic-Arsic, Marija; Neff, Florian; Schmid, Roland M; Siveke, Jens T

Hes1 Controls Exocrine Cell Plasticity and Restricts Development of Pancreatic Ductal Adenocarcinoma in a Mouse Model.

Perturbation of pancreatic acinar cell state can lead to acinar-to-ductal metaplasia (ADM), a precursor lesion to the development of pancreatic ductal adenocarcinoma (PDAC). In the pancreas, Notch signaling is active both during development and in adult cellular differentiation processes. Hes1, a key downstream target of the Notch signaling pathway, is expressed in the centroacinar compartment of the adult pancreas as well as in both preneoplastic and malignant lesions. In this study, we used a murine genetic in vivo approach to ablate Hes1 in pancreatic progenitor cells (Ptf1a(+/Cre); Hes1(fl/fl)). Using this model, we studied the role of Hes1 in both acinar cell plasticity and pancreatic regeneration after caerulein-induced pancreatitis and in Kras(G12D)-driven PDAC development. We show that, although pancreatic development is not perturbed on the deletion of Hes1, terminal acinar differentiation in the adult pancreas is compromised. Moreover, the loss of Hes1 leads to the impaired regeneration of the exocrine compartment, accelerated fatty metaplasia, and persistent ADM after acute caerulein-induced pancreatitis. In Kras(G12D)-driven carcinogenesis, Hes1 ablation resulted in increased ADM, decreased...
formation of high-grade pancreatic intraepithelial neoplasias, and accelerated development of PDAC with shortened survival time. In conclusion, Hes1 plays a key role in acinar cell integrity and plasticity on cellular insults. Furthermore, Hes1 is an essential component of the pancreatic intraepithelial neoplasias-to-PDAC route in Kras(G12D)-driven mouse pancreatic carcinogenesis.

Zeitschriftentitel / Abkürzung:
Am J Pathol

Jahr:
2016

Band:
186

Heft / Issue:
11

Seiten:
2934-2944

Sprache:
eng

Volltext / DOI:
http://doi.org/10.1016/j.ajpath.2016.07.025

Pubmed:

Print-ISSN:
0002-9440

TUM Einrichtung:
II. Medizinische Klinik und Poliklinik; Institut für Allgemeine Pathologie und pathologische Anatomie; Institut für experimentelle Onkologie und Therapieforschung

Occurences:
- Hochschulbibliographie > 2016 > Fakultäten > Medizin > Institut für Allgemeine Pathologie und Pathologische Anatomie
- Hochschulbibliographie > 2016 > Fakultäten > Medizin > Institut für Experimentelle Onkologie und Therapieforschung
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Institut für Experimentelle Onkologie und Therapieforschung > 2016
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > II. Medizinische Klinik und Poliklinik (Gastroenterologie) > 2016
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Institut für Allgemeine Pathologie und Pathologische Anatomie > 2016

entries: