PancreasFest 2019

Pittsburgh, PA

Session III-C: Basic-Translational: Pancreatic Cancer Research

Modeling the Link between Pancreatitis and PC in Mice: GEMMS in Pancreatic Cancer Research

Thursday, July 24, 2019

10:30AM

Paul Grippo, PhD

The Gap between Pancreatitis and PC

Pancreatitis can promote PC

Pancreas
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Effects of Cerulein on the Normal Pancreas and on Experimental Pancreatic Carcinoma in the Syrian Golden Hamster

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Summary: The effects of cerulein on normal pancreas and on *N*-nitrobis (2-hydroxypropyl) amine (BHP)–induced experimental pancreatic carcinoma in Syrian golden hamsters were studied. Twenty hamsters received a subcutaneous injection of cerulein (20 μg/kg) twice daily for 10 days. The 10 control hamsters received normal saline (1 ml/kg). The results showed that when cerulein was injected subcutaneously for 10 days, pancreatic weight and amylase increased. DNA and the pancreatic weight/DNA ratio were also increased significantly in treated hamsters compared with controls ($p < 0.02$ versus $p < 0.01$). These results indicated that chronic cerulein injection had hypertrophic and hyperplastic effects. DNA synthesis, as measured by histoautoradiography of tritiated thymidine-labeled tissue, increased in pancreatic acinar cells ($p < 0.01$) and increased slightly in islet cells and in ductal cells. Tritiated thymidine uptake in the pancreas of the treated group indicated a rather selective exocrine gland incorporation by acinar rather than ductal cells. Sixty hamsters received a subcutaneous injection of BHP (500 mg/kg) once a week, while 63 hamsters received BHP (500 mg/kg) plus cerulein (20 μg/kg). Twenty-seven hamsters received cerulein (20 μg/kg) alone. All animals were killed from 8 to 27 weeks later, and no cancer-bearing hamsters were observed during the eighth and ninth week following administration. From the 10th to 14th weeks after administration of BHP and cerulein, 87.9% (13 of 15) had tumors compared with 18.7% (3 of 16) after BHP alone ($p < 0.01$). One of three and two of 13 tumors were adenoma. The earliest appearance of cancer, including carcinoma in situ and intraductal carcinoma, was at the 14th week after the administration of BHP alone and the 10th week after BHP and cerulein. During the 10th to the 14th weeks after administration of BHP and cerulein, cancer was found in 73.3%, which was statistically higher than after the administration of BHP alone (12.5%; $p < 0.01$). All tumors were of exocrine

CP for PC Induction

Cancer Cell
Article

Chronic Pancreatitis Is Essential for Induction of Pancreatic Ductal Adenocarcinoma by K-Ras Oncogenes in Adult Mice

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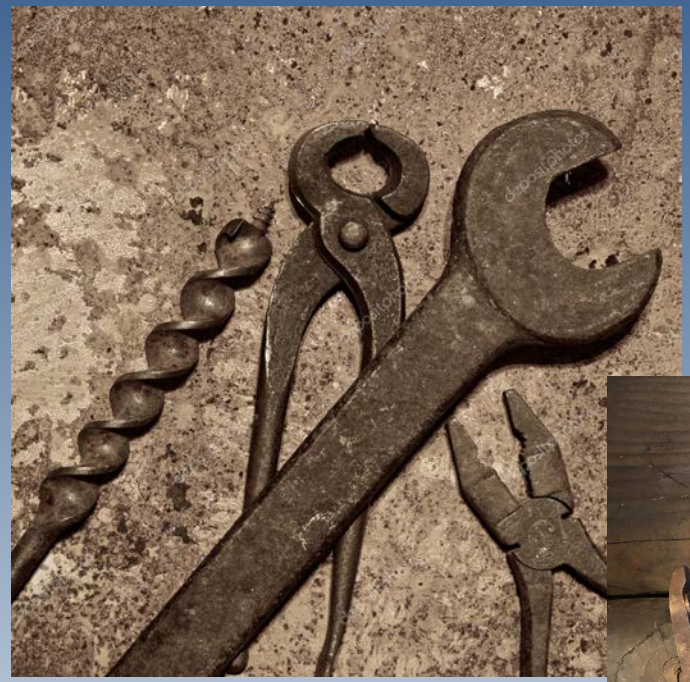
DOI 10.1016/j.ccr.2007.01.012

SUMMARY

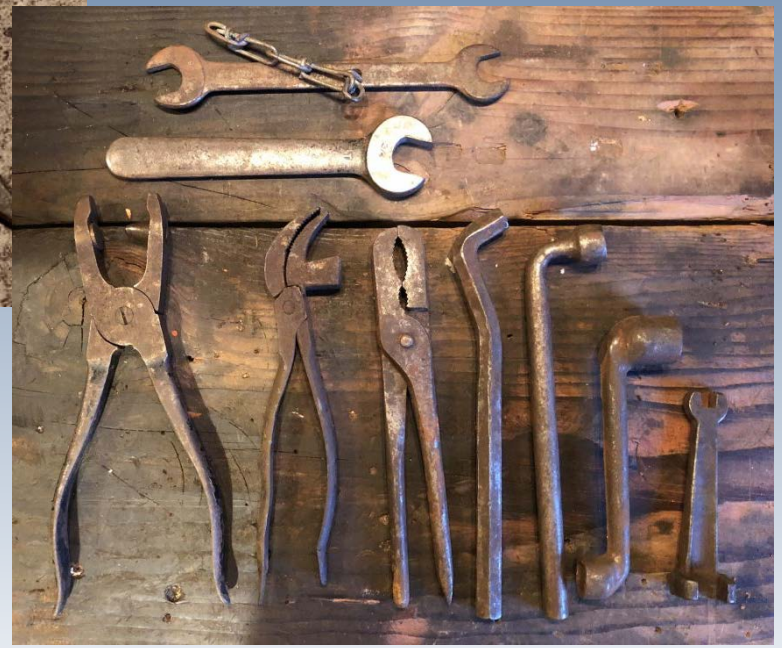
Pancreatic ductal adenocarcinoma (PDA), one of the deadliest human cancers, often involves somatic activation of K-*Ras* oncogenes. We report that selective expression of an endogenous K-*Ras*^{G12V} oncogene in embryonic cells of acinar/centroacinar lineage results in pancreatic intraepithelial neoplasias (PanINs) and invasive PDA, suggesting that PDA originates by differentiation of acinar/centroacinar cells or their precursors into ductal-like cells. Surprisingly, adult mice become refractory to K-*Ras*^{G12V}-induced PanINs and PDA. However, if these mice are challenged with a mild form of chronic pancreatitis, they develop the full spectrum of PanINs and invasive PDA. These observations suggest that, during adulthood, PDA stems from a combination of genetic (e.g., somatic K-*Ras* mutations) and nongenetic (e.g., tissue damage) events.

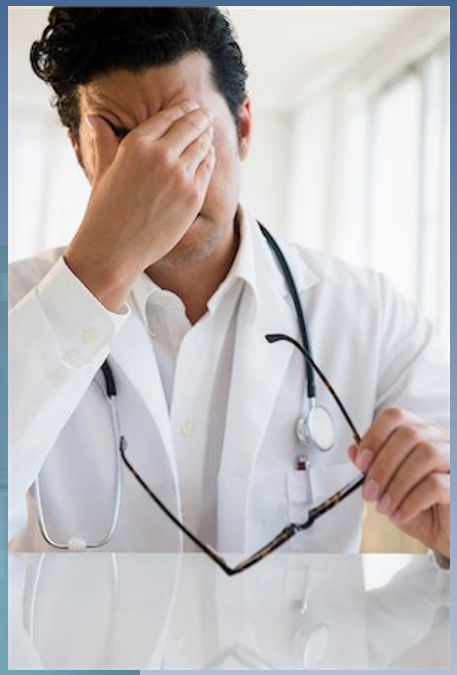
The GREAT Divide



Basic PC investigators use pancreatitis as a tool to induce what they want:

PC





Especially the mouse model community

Certain level of frustration for those doing clinical work and translational research in Pancreatitis

HB-EGF Tissue Recovery in Severe AP

ARTICLE IN PRESS

cmgh CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

ORIGINAL RESEARCH

Myeloid Cell-Derived HB-EGF Drives Tissue Recovery After Pancreatitis

Hui-Ju Wen,[1] Shan Gao,[2] Yin Wang,[3] Michael Ray,[4] Mark A. Magnuson,[5] Christopher V. E. Wright,[4] Marina Pasca Di Magliano,[6,7,8] Timothy L. Frankel,[6] and Howard C. Crawford[1,3,7]

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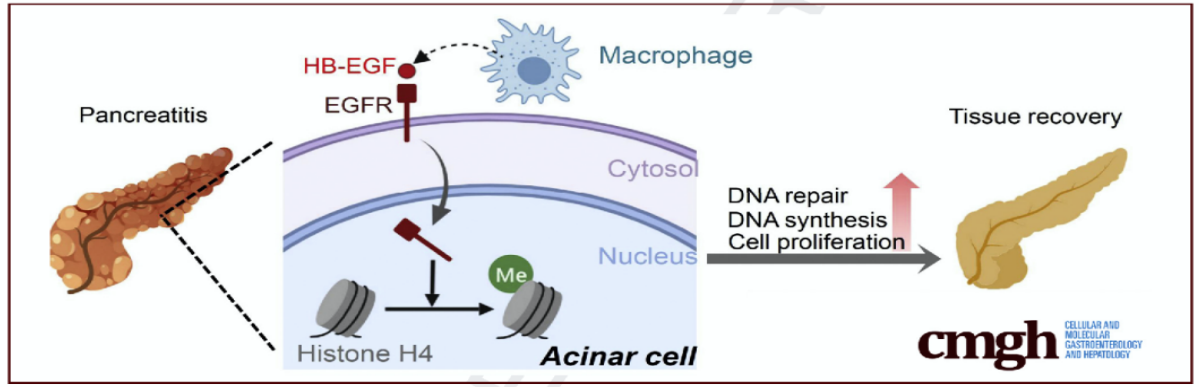


SUMMARY

Macrophages play a critical role in pancreatitis progression and pancreas regeneration. Heparin-binding epidermal growth factor receptor–like growth factor derived from myeloid cells is not involved in the initiation of pancreatitis, but contributes to pancreas recovery after pancreatitis by promoting DNA damage repair.

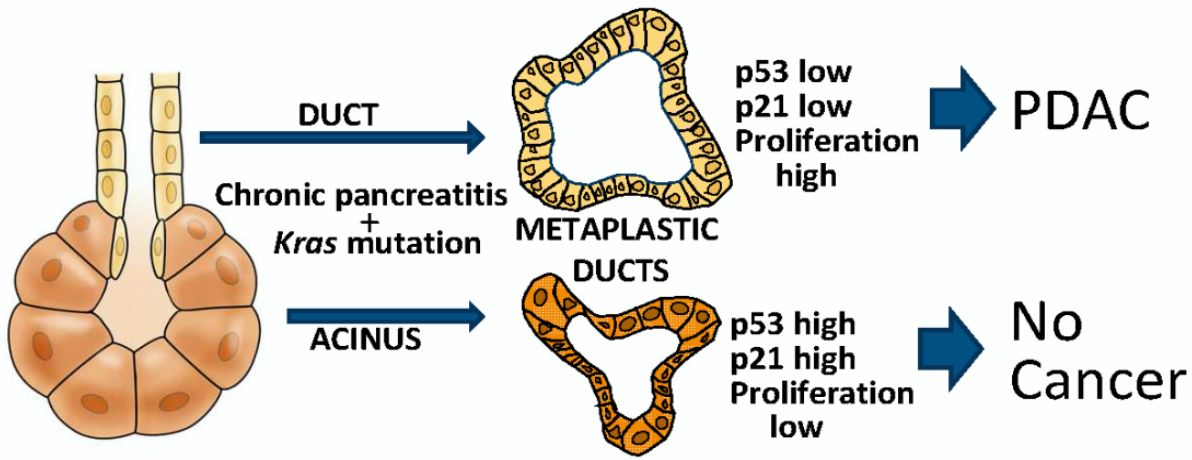
in $Egfr^{f/f};Ptf1a^{FlpO/+};FSF\text{-}Rosa26^{CAG\text{-}CreERT2}$ mice followed by tamoxifen treatment.

RESULTS: Macrophages infiltrating the pancreas in experimental pancreatitis make high levels of HB-EGF. Both depletion of myeloid cells and ablation of myeloid cell HB-EGF delayed recovery from experimental pancreatitis, resulting from a decrease in cell proliferation and an increase in apoptosis. Mechanistically, ablation of myeloid cell HB-EGF impaired epithelial cell DNA repair, ultimately leading to cell

Different response to Kras^{G12D} in Obstructive CP

Title: Differential cell susceptibilities to *Kras*^{G12D} in the setting of obstructive chronic pancreatitis.

Short title: PDAC development in chronic pancreatitis



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Becoming aware of the AP or CP to PC paradigm

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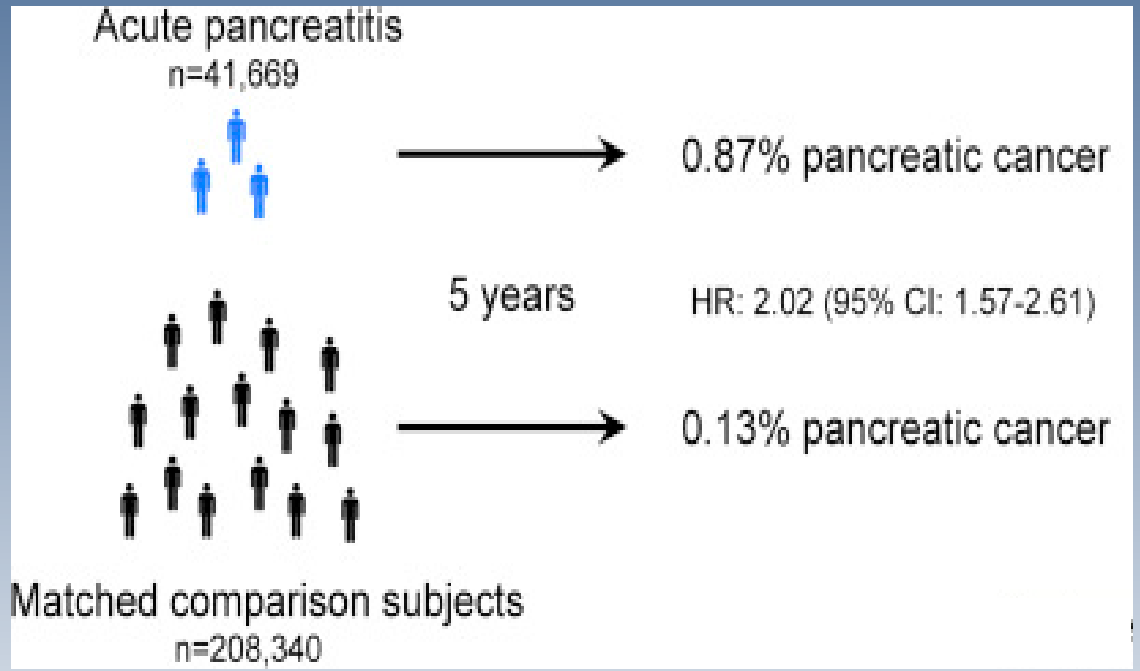
Acute Pancreatitis



Gastroenterology May 2018 154(6):1729-36

Chronic Pancreatitis

Study	ES (95% CI)
Subtotal (*I*-squared = 87.1%, *P* = 0.000)	7.96 (2.36, 26.86)
Subtotal (*I*-squared = 90.2%, *P* = 0.000)	6.09 (3.79, 9.79)
Subtotal (*I*-squared = 0.0%, *P* = 0.476)	16.16 (12.59, 20.73)
Subtotal (*I*-squared = 82.9%, *P* = 0.001)	7.90 (4.26, 14.66)
Subtotal (*I*-squared = 64.3%, *P* = 0.094)	3.53 (1.69, 7.38)

J of Gastroenterology Sept 2017 112(9):1366-72

From Ignorance to Bliss: CP contributes to PC

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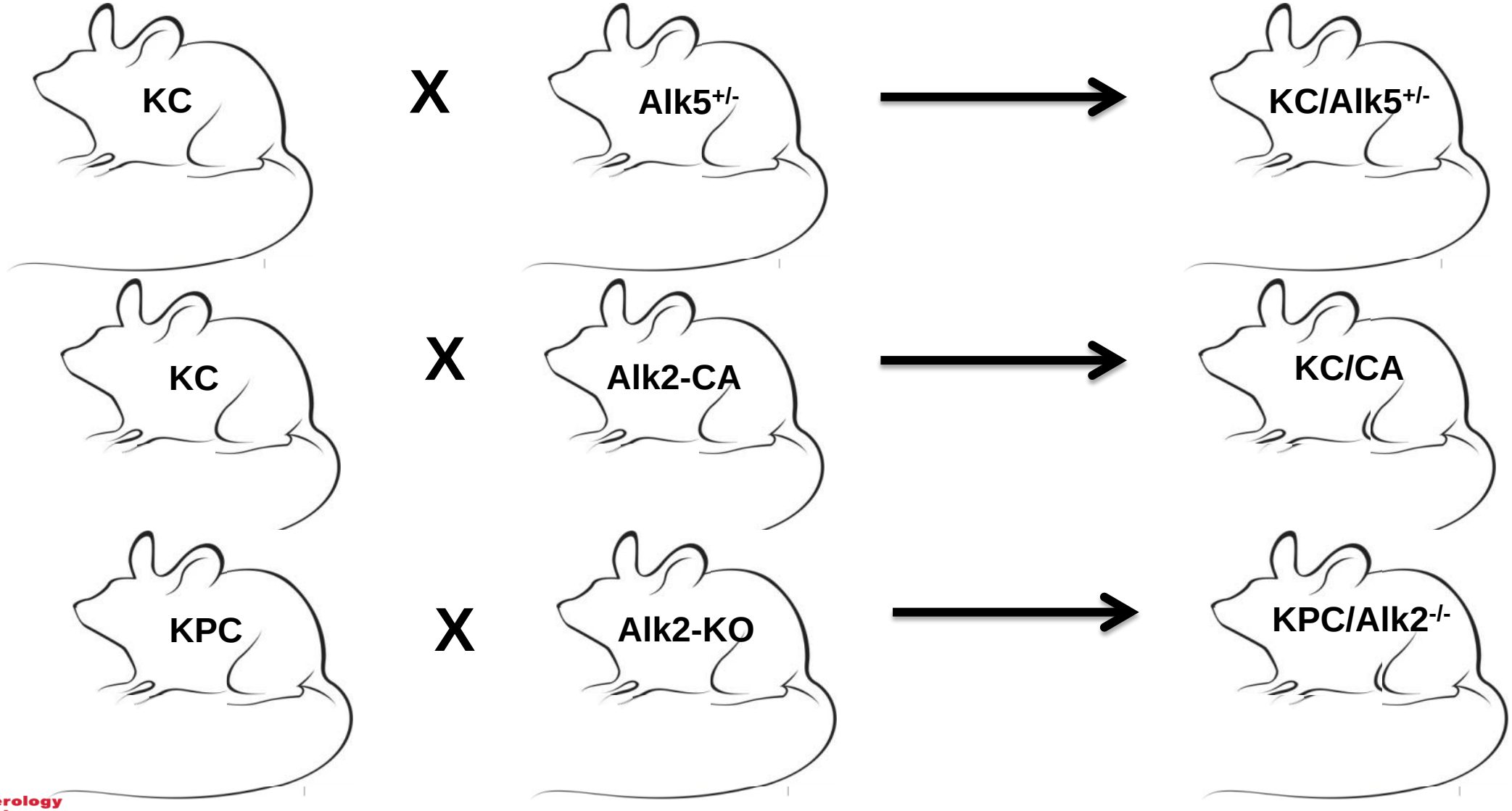
On multiple occasions, two independent pathologists have observed pancreatitis in KPC and KC mice with a second mutant gene - though penetrance has been low

We now have something else to consider – focal pancreatitis, how it develops, and the impact on developing PC

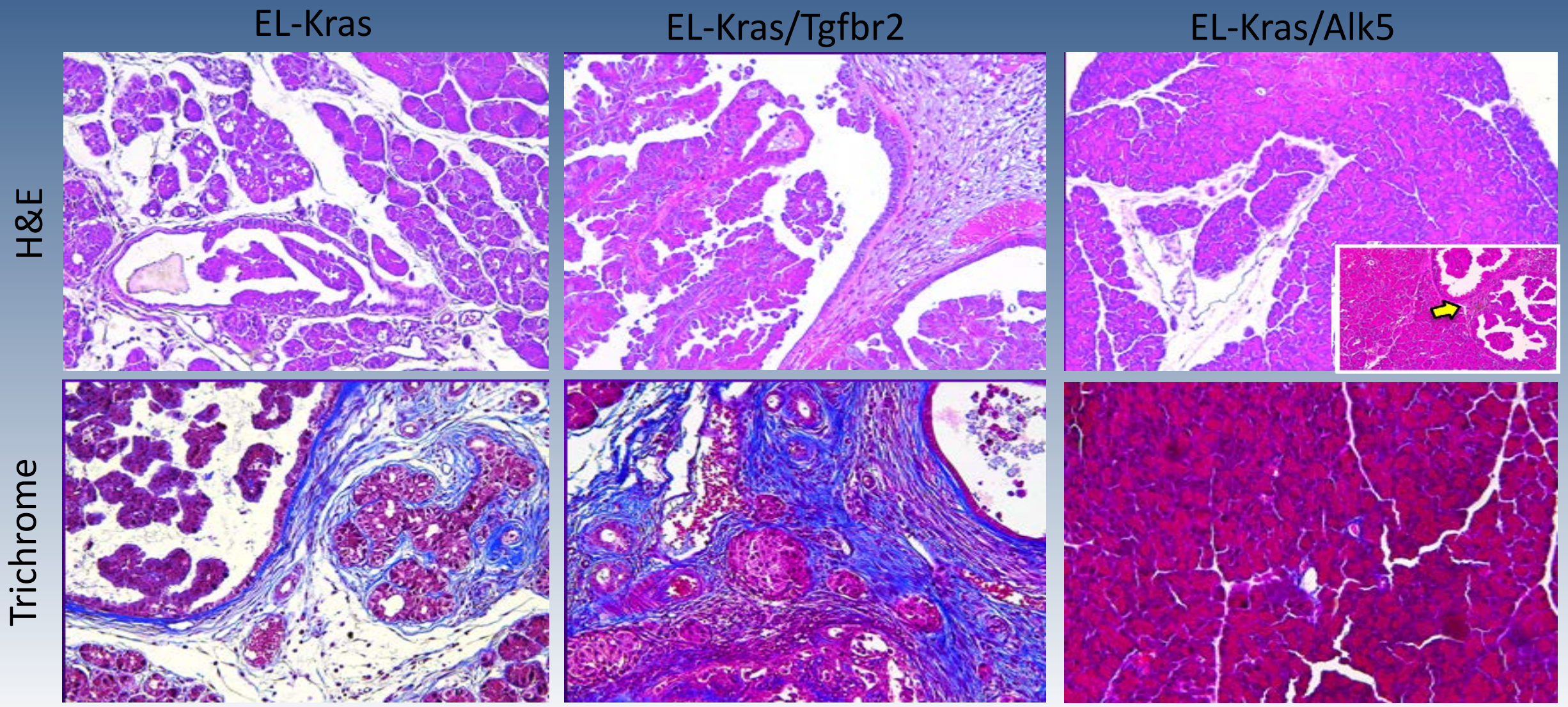
Based on these findings, we want to investigate:

TGFβ Family of Signals in CP and PC in the same mouse

Building PC (& CP) Mouse Models



EL-Kras ± altered TGFβ signals



Tgfbr1$^{+/-}$ may increase T-cell Cytotoxicity

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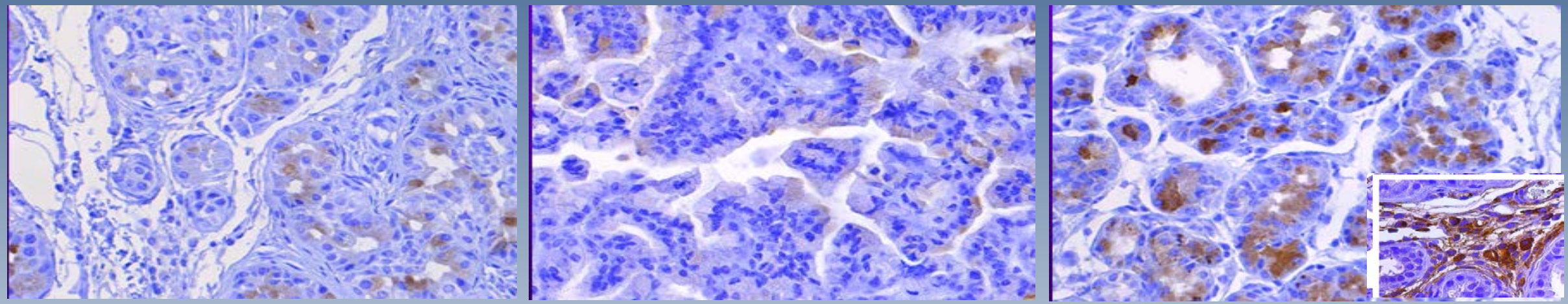
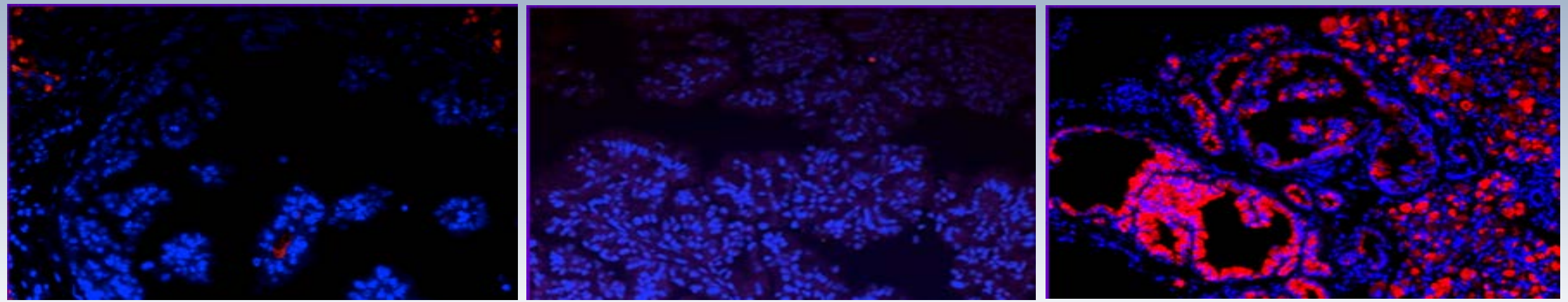
EL-Kras | EL-Kras/Tgfbr2 | EL-Kras/Alk5

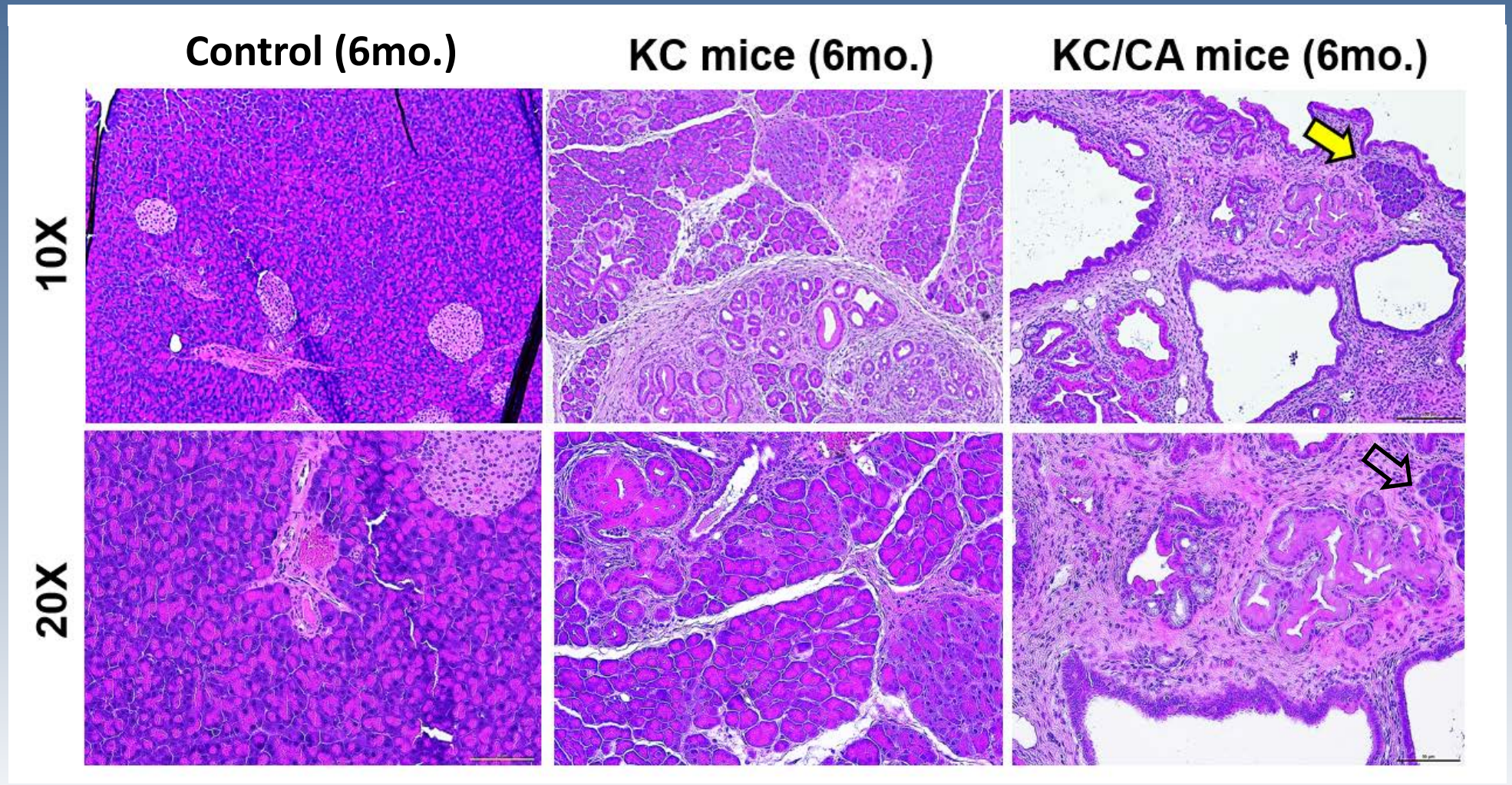
Cleaved Caspase-3



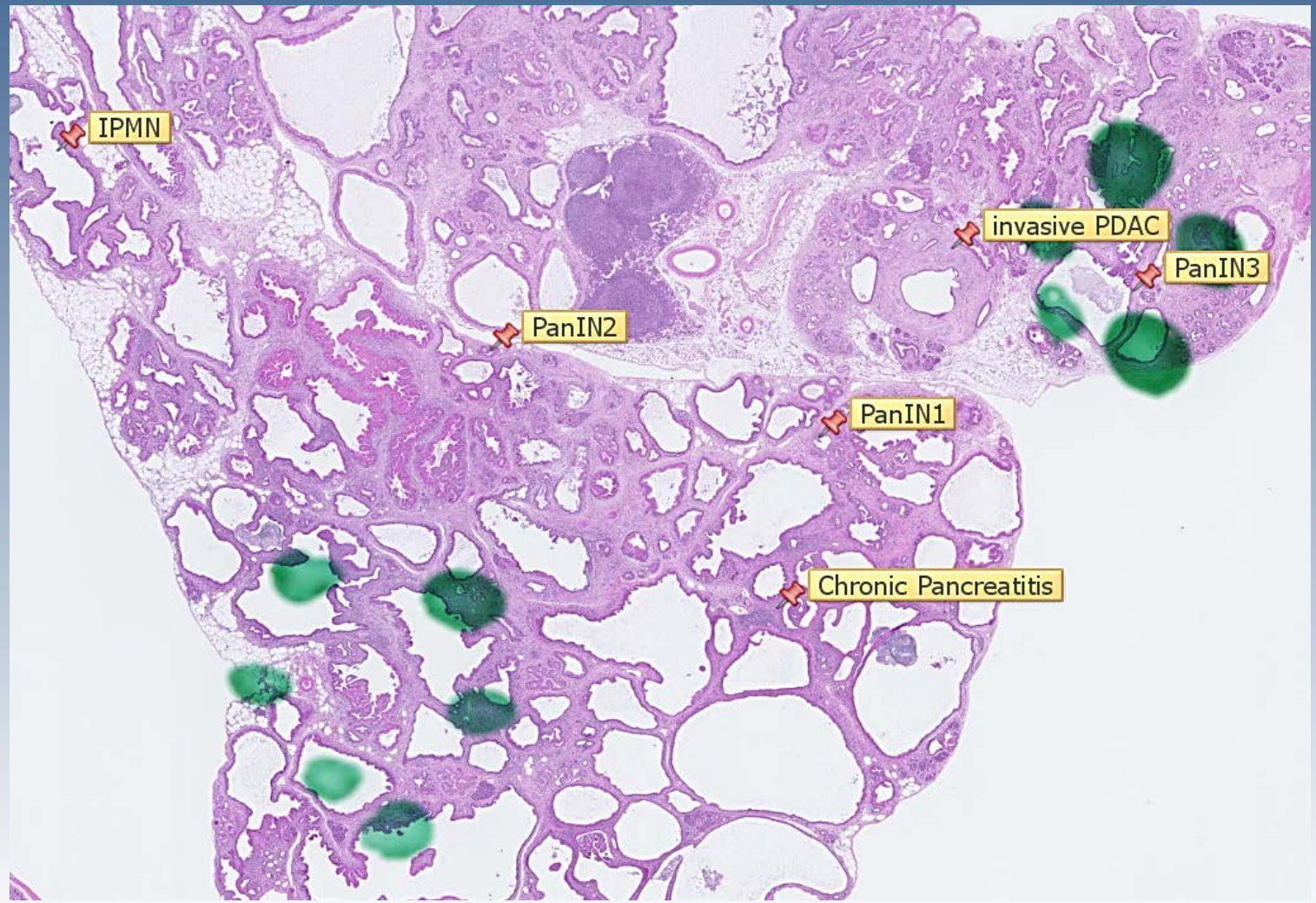
Granzyme B



Lesion Development in KC/Alk-CA mice



KC/CA mice can develop invasive disease



Implications

- Certain genetic changes may be relevant to both PC & CP
  - TGFβ Family signals appear to drive a variety of lesions/CP in the context of mtKras
- Parenchymal vs. mesenchymal pancreas compartments
  - Non-epithelial TGFβ signals can be more sinister – suppress targeted immunity
- Treatments that work for PC or CP may also work for the other
  - Blocking TGFβ Family ligands/receptors may serve as more efficacious therapies
- Focal CP may impact PC lesion development
  - Identifying protein expression near regional areas of CP and its potential impact on PC

Acknowledgements

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Dr. HG Munshi (NU)

Dr. David Bentrem (NU)

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