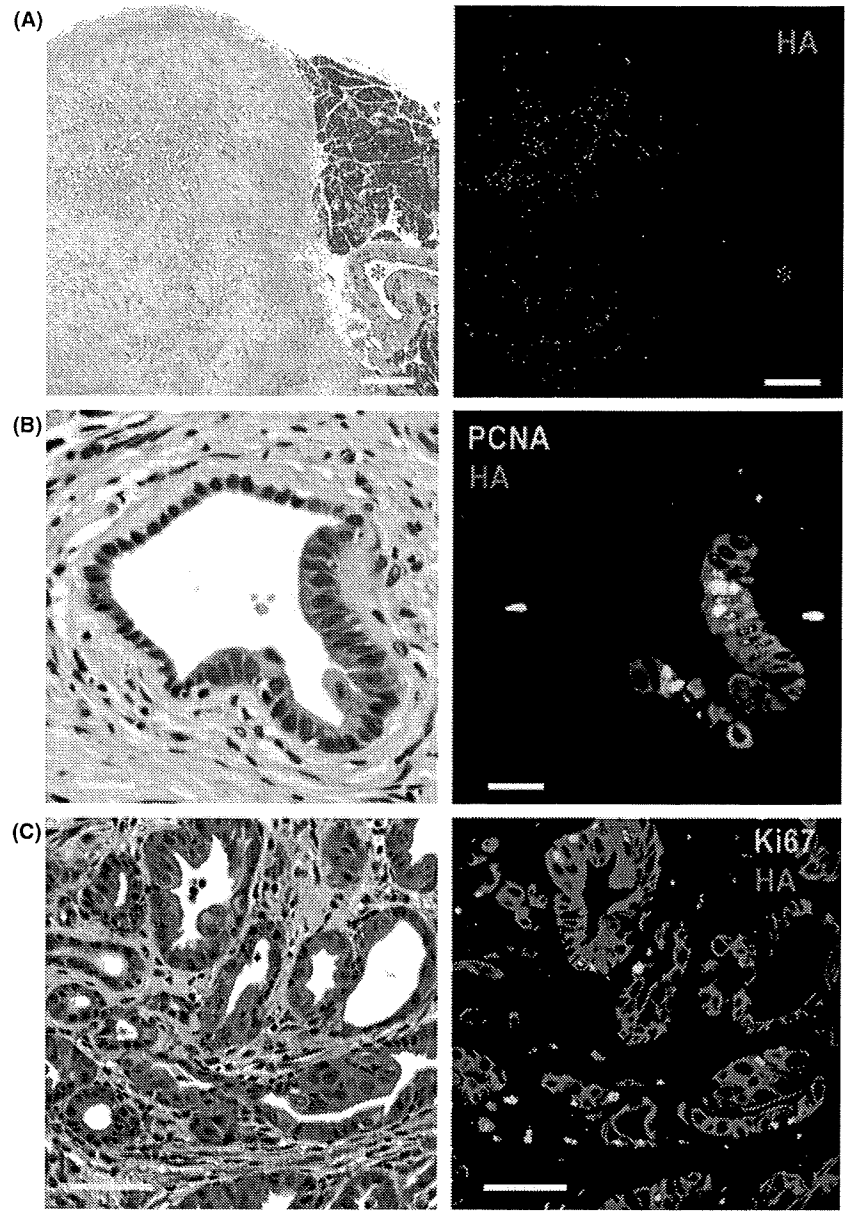


**Fig. 4.** Pancreatic ductal adenocarcinoma (PDA) induced by injection of Ad-CAG-Cre in Kras301/327 rats. (A) The expression of hemagglutinin (HA)-$Kras^{G12V}$ (red) was seen only in PDA lesions (on the left of photo), and not in stromal cells, acinar cells (on the right of photo), or normal pancreatic duct cells (*). Bar, 500 μm. (B) A pancreatic intraepithelial neoplasia (PanIN) lesion was surrounded by fibrous tissue with some infiltration of inflammatory cells. Expression of proliferating cell nuclear antigen (PCNA) (green) and HA protein (red) in a PanIN lesion in rats of the CAG-Cre group. PCNA is preferentially expressed in PanIN cells. Bar, 20 μm. (C) Expression of Ki67 (green) and HA protein (red) in PDA cells. Many PDA cells (red) are simultaneously positive for Ki67. Bar, 50 μm.

inflammation may play a role in PDA development in this model. However, interaction between the immune system and tumors is complex and whether inflammation actually promotes PDA development in this model remains to be examined.

A current study has demonstrated that the fibrous element accompanying inflammation can also play an important role in cancer development.[29] This aspect of PDA development in our model also remains to be examined.

In summary, while there are discrepancies between different animal models of pancreatic cancer, our results indicate that expression of oncogenic *ras* in fully mature acinar cells does not induce cell proliferation or result in development of any pancreatic lesions. Thus, we conclude that mature acinar cells are not the origin of PanIN or pancreatic neoplasia in this model.

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