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Mechanisms of pancreatic cancer associated with obesity or dietary fat

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Obesity is a risk factor for pancreatic adenocarcinoma (PAC), but the molecular mechanisms involved are unclear. Oncogenic mutation of K-Ras occurs early and nearly universally in this disease. However, genetic knock-in of oncogenic mutant K-Ras (K-RasG12V) into adult pancreatic acinar cels does not itself lead to pancreatic disease. It has been previously shown that this is because oncogenic Ras is not fully active without external stimulation. However, many stimulants can trigger an inflammation/Ras activity feed-forwed loop in cells expressing oncogenic K-Ras that leads to disease. Therefore, it was hypothesized that high-fat intake could act as an inflammatory stimulus to increase K-Ras activity and develop the feed-forward loop necessary for pathological responses. To test this hypothesis, LSL-K-Ras mice were crossed with elastase-CreER (acinar cell-specific) or Pdx1-Cre (pancreatic cell-specific) to "knock-in" expression of K-RasG12V. Additionally, acinar cell-specific K-RasG12V mice were crossed with Cox-2 conditional "knockout" mice. Mice were fed isocaloric diets with differential fat content for several weeks and pancreata were analyzed for Ras activity, p-ERK, inflammation, fibrosis, PanINs and PAC. It was found that consumption of a high-fat diet (HFD) increased each of these pathological parameters and reduced survival. Blocking the inflammation/Ras activity feed-forward loop by genetic deletion of Cox-2 in acinar cells or Celecoxib administration prevented the HFD-induced effects. These findings support a model in which a HFD stimulates activation of oncogenic K-Ras and initiates an inflammatory feed-forward loop that requires activity of Cox-2 leading to pancreatic inflammation, fibrosis, and tumorigenesis. This model may explain the PAC risks associated with consumption of a HFD.

Biography

Craig D Logsdon's is currently an Endowed Professor in the Department of Cancer Biology at the University of California San Francisco, the University of Michigan and at the University of Texas. His research on pancreatic *physiology* has been continuously funded by the NIH NIDDK for 30 years. He has been a member of numerous NIH, NCI and DOD Study Sections, serves as an Associate Editor of the *American Journal* of *Physiology*, and is a past president of the American Pancreatic Association. His goal is to make a difference to patients with pancreatic diseases.

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