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Hiding in plain sight:

A common biomarker of pancreatic disease has a functional role in pathogenesis

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Pancreatic cancer remains one of the deadliest human malignancies. This is in part due to the lack of a reliable method of early detection, because late-stage disease is largely refractory to treatment. Biomarkers for early disease detection have remained elusive. However, the glycan carbohydrate antigen 19–9 (CA19–9), which is produced by pancreatic cancer cells, is increased in the serum of most patients (1). It is clinically useful as a biomarker of tumor burden during treatment, rather than for early detection, because serum CA19–9 is also increased in other diseases, including inflammation of the pancreas (pancreatitis), a risk factor for the development of pancreatic cancer. To date, there has been little understanding of CA19–9 function in pancreatic pathophysiology. On page 1156 of this issue, Engle *et al.* (2) report that CA19–9 drives the development of pancreatitis and accelerates pancreatic tumor progression.

CA19–9, also known as sialyl-Lewis^a, is a glycan moiety that modifies proteins, lipids, and other glycans. In humans, the expression of CA19–9 is dependent on Lewis (Le) blood type (3), a human blood group system based on the expression of two fucosyltransferase (FUT) enzymes, FUT2 and FUT3. Individuals with the blood type Le(a-b-) do not generate CA19–9 because they lack FUT3; mice also do not express this enzyme and therefore cannot produce CA19–9. Functionally, CA19–9 can promote cancer cell metastasis by binding to the adhesion protein E-selectin that is expressed on the surface of endothelial and mesothelial cells (4). This binding presumably enhances migration of metastatic cells through these cell layers. Additionally, CA19–9 expression in colon cancer cells replaces the structurally related disialyl Lewis^a expressed by normal colon epithelia (5). Disialyl Lewis^a produced by normal epithelium serves an immune inhibitory role by binding sialic acid–binding immunoglobulin-like lectins (siglecs) on resident macrophages, suppressing the expression of proinflammatory cyclooxygenase-2 (6). Accordingly, it is thought that the replacement of disialyl Lewis^a by CA19–9 during carcinogenesis relieves this immune suppression through its failure to engage siglecs, thereby promoting tumor progression. Apart from these generic functions, a pathophysiological function induced by CA19–9 modification of a specific protein has not been reported until now.

Pancreatic cancer cells nearly universally contain activating mutations in the *KRAS* oncogene. Expression of epidermal growth factor receptor (EGFR) is required for induction of *Kras*-driven tumorigenesis in the pancreas of mice (7, 8) by increasing total RAS activity above a minimal threshold that is required for transformation. Concomitantly, the EGFR–RAS–mitogen-activated protein kinase (MAPK) signaling axis in pancreatic epithelium increases the production of proinflammatory cytokines (9). These cytokines recruit immune cells, which are key drivers of pancreatitis and pancreatic tumor development and maintenance (10–12). The numerous reactive inflammatory and stromal cells are in turn a rich source of EGFR ligands (13, 14), invoking the involvement of a vicious cycle of chronic EGFR signaling and inflammation in benign pancreatic disease. In later stages of pancreatic cancer, EGFR is largely dispensable (7), and inhibiting it in pancreatic cancer patients provides minimal benefit (15).

Using genetic engineering, Engle *et al.* created a mouse model that expresses both FUT3 and the galactosyltransferase β 3GALT5, allowing the production of CA19–9. They find that CA19–9 synthesis promotes modification of the extracellular matrix protein fibulin-3, producing CA19–9: fibulin-3. This activates pancreatic EGFR signaling, inducing a pathology that is similar to pancreatitis, which is reversible either by shutting down the expression of the CA19–9 synthesis machinery or by targeting CA19–9 itself (see the figure). Thus, inhibiting this newly described function of CA19–9 presents an attractive potential target for the treatment of early-stage pancreatic cancer and pancreatitis patients.

The results of Engle *et al.* suggest that the canonical EGFR ligands produced by the pancreatic epithelium or the inflammatory and stromal cells (7, 12) are minimally involved in maintaining the disease state. One potential explanation for this is that CA19–9: fibulin-3 engages and activates EGFR with distinctive kinetics compared to other ligands. Alternatively, CA19–9: fibulin-3 is necessary but not sufficient to maintain the phenotype without collaborating with other CA19–9–modified molecules. This latter possibility seems more likely because, as shown by Engle *et al.*, blocking CA19–9 is more effective at reversing the pancreatitis phenotype than inhibiting EGFR itself, which causes severe pancreatic atrophy (wasting).

Although the discovery of a new function of CA19–9 is exciting, Engle *et al.* have also potentially revitalized a role for CA19–9 in the early detection of pancreatic cancer. A major issue for many putative early detection markers, including CA19–9, has been the limited ability to distinguish between chronic pancreatitis and pancreatic cancer. With their transgenic mouse model and the organoids (cells grown as three-dimensional cultures) derived from them, they have generated an optimal system with which to identify CA19–9–modified proteins that can distinguish the metaplastic epithelia found in pancreatitis from the cancerous epithelia of adenocarcinoma. Finding specific cancer-associated CA19–9–modified proteins in the circulation could greatly enhance the specificity of a biomarker compared to either CA19–9 or the unmodified protein alone.

To date, there are still no effective therapies or early detection methods for pancreatic cancer. This is arguably because of a lack of understanding of the biology underlying the disease, a void illustrated by the study of Engle *et al.*, which ascribes a critical function to the most

commonly used biomarker of the disease, first identified over 30 years ago (1). The translational potential of the findings of Engle *et al.* also reinforce the value of studying the events that precede and promote the formation of pancreatic cancer. These observations lend much needed insight into the understanding of pancreatic cancer and can inform new treatment strategies for the advanced stages in which it is usually diagnosed in patients.

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REFERENCES AND NOTES

1. Herlyn M, Sears HF, Steplewski Z, Koprowski H, J. Clin. Immunol 2, 135 (1982). [PubMed: 7068815]
2. Engle DD et al., Science 364, 1156 (2019). [PubMed: 31221853]
3. Tempero MA et al., Cancer Res 47, 5501 (1987). [PubMed: 3308077]
4. Gebauer F et al., Gut 62, 741 (2013). [PubMed: 22490524]
5. Miyazaki K et al., Cancer Res 64, 4498 (2004). [PubMed: 15231659]
6. Miyazaki K et al., J. Immunol 188, 4690 (2012). [PubMed: 22467657]
7. Ardito CM et al., Cancer Cell 22, 304 (2012). [PubMed: 22975374]
8. Navas C et al., Cancer Cell 22, 318 (2012). [PubMed: 22975375]
9. Halbrook CJ et al., Cell. Mol. Gastroenterol. Hepatol 3, 99 (2017). [PubMed: 28090569]
10. Guerra C et al., Cancer Cell 11, 291 (2007). [PubMed: 17349585]
11. Liou GY et al., Cancer Discov 5, 52 (2015). [PubMed: 25361845]
12. McAllister F et al., Cancer Cell 25, 621 (2014). [PubMed: 24823639]
13. Zhang Y et al., eLife 6, e27388 (2017). [PubMed: 28980940]
14. Ray KC et al., Oncogene 33, 823 (2014). [PubMed: 23376846]
15. Moore MJ et al.; National Cancer Institute of Canada Clinical Trials Group, J. Clin. Oncol 25, 1960 (2007). [PubMed: 17452677]

Signaling underlying pancreatic disease

Posttranslational modifications by CA19-9 can confer new functions to proteins. CA19-9: fibulin-3 can act as an EGFR ligand, thereby activating the downstream RAS-RAF-MEK-ERK signaling cascade.