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EDITORIAL

E-Cadherin: An Enigma in Pancreatic Diseases

E-cadherin, one of the most studied proteins with regard to epithelial-mesenchymal transition (EMT), is a member of the classic family of cadherins. This calcium-dependent, transmembrane cell adhesion protein is expressed on the surface of epithelial tissues and plays important roles in epithelial cell behavior, tissue formation, and tumor suppression.[1] Cadherins form adherens junctions by interacting with other intracellular components and provide mechanical attachments between adjacent cells. Besides its role in mediating contact inhibition of proliferation, the cytoplasmic tail of E-cadherin forms a dynamic complex with catenins and regulates several intracellular signal transduction pathways, including Wingless-related integration/β-catenin, phosphoinositide 3-kinase/Protein Kinase B, Rho guanosine triphosphatase, and nuclear factor-κB signaling.[2] In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Kaneta et al[3] have uncovered a previously understudied role of E-cadherin in maintaining tissue homeostasis and tumorigenesis in the pancreas.

Partial or complete loss of E-cadherin in epithelial cells has been associated with their progression toward malignancy in a number of cancers. The up-regulation of the transcriptional repressors Snail Family Transcriptional Repressor 1, Zinc finger E-box-binding homeobox 1, Snail Family Transcriptional Repressor 2, and Zinc finger E-box-binding homeobox 2, which target the E-cadherin promoter or its methylation, are the most common causes of E-cadherin expression loss in human tumors.[4] Down-regulation of E-cadherin results in less intercellular contact and reduced cell polarity, promoting EMT, cancer invasion, and metastasis.[5–7] In gastric cancer, function loss of the E-cadherin gene, *CDH1*, has been associated with diffuse gastric cancer susceptibility, and it is involved in the initiation and progression of both sporadic and hereditary forms of the disease.[8–10] Abnormal reduction or loss of E-cadherin expression have been observed in 42%–60% of human pancreatic cancer specimens, especially in undifferentiated, noncohesive pancreatic tumors, which was associated with a poor patient outcome.[11] However, the exact role of E-cadherin loss in EMT induction and pancreatic cancer development remains unknown.

In the study by Kaneta et al,[3] they investigated the physiologic and pathologic roles of E-cadherin in a pancreas-specific conditional knockout mouse model. In the Ptf1a-Cre; $Cdh1^{flox/flox}$ mice (PC mice), they observed a reduction of acinar cells with increased levels of serum amylase, inflammatory cytokines, and CD45-positive cell infiltration. This suggested a pancreatitis-like phenotype. The PC mice started dying by postnatal day 12, and by postnatal day 28, none of the PC mice were alive. Furthermore, at the earlier time points (postnatal day 6) there was extensive acinar-ductal metaplasia, indicating an acinar collapse. However, there was no observable pancreatic intraepithelial neoplasia formation. This was supported by previous studies that showed that upon induction of acute pancreatitis, there was a disassembly of the adherens junctions, which was followed by up-regulation of E-cadherin expression.[12] In chronic pancreatitis, however, there was minimal expression of E-cadherin.[13] This is not surprising because in chronic pancreatitis there is extensive tissue damage, leading to fibrosis. Loss of E-cadherin and EMT has been shown to drive fibrosis in a number of other fibrotic diseases.[14]

To study the loss of E-cadherin in the context of oncogenic K-Ras activation, Kaneta et al[3] next generated the $Kras^{G12D/+}$ Ptf1a-Cre; LSL-$Kras^{G12D/+}$; $Cdh1^{f/f}$ mice. Interestingly, these mice showed both acinar-ductal metaplasia and pancreatic intraepithelial neoplasia formation. In addition, the tissues showed abundant desmoplasia resembling aggressive tumors in the early postnatal stage. The presence of desmoplasia and stromal architecture could be reflective of EMT-driven fibrosis that results from loss of E-cadherin. In addition, there was an increased expression level of stem cell markers (Cluster of Differentiation 44, Kruppel Like Factor 4, Kruppel Like Factor 5, and Cluster of Differentiation 133) in the $Kras^{G12D/+}$ Ptf1a-Cre; LSL-$Kras^{G12D/+}$; $Cdh1^{f/f}$ tumor tissues.

An intriguing question that arises from this study is why tumor formation is accelerated in mice lacking E-cadherin? Kaneta et al[3] speculated that deletion of E-cadherin can confer tumorigenic activity, leading to tumor initiation. It also is possible that there is a compensatory proliferation that is triggered as a result of E-cadherin loss. Furthermore, deletion of E cadherin in the models in this study led to an undifferentiated pancreatic cancer type as well as increased invasiveness in cells, indicating an EMT phenotype. However, the authors did not see any metastasis in their in vivo models.

In summary, the role of E-cadherin in pancreatic diseases remains an enigma. Although Kaneta et al[3] definitively showed that E-cadherin maintains cellular homeostasis in the pancreas under physiologic conditions and promotes tumor development in the presence of oncogenic mutations such as KRAS, a lot remains to be determined to conclusively understand the role of this protein in pancreatic biology.

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Conflicts of interest
This author discloses the following: Sulagna Banerjee is a consultant with Minneamrita Therapeutics LLC. The remaining author discloses no conflicts.

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