

Characterization of Tumor Suppressor PKP1 in Neoplastic Progression of Barrett's Esophagus

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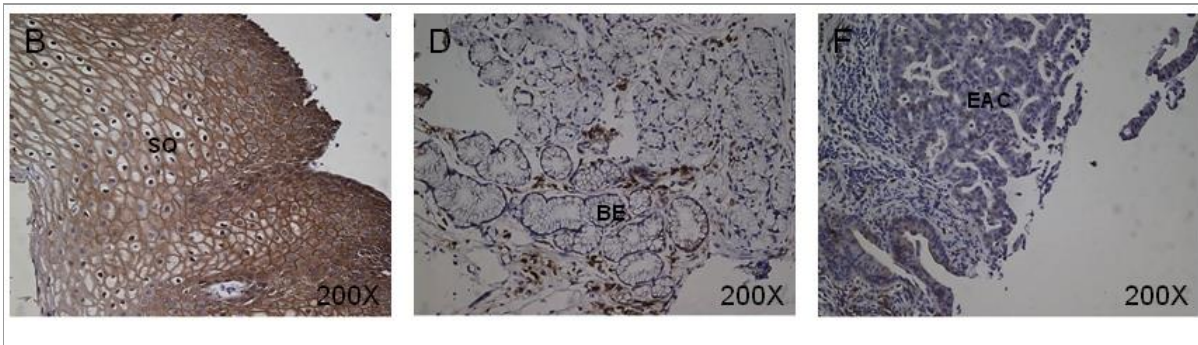
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In patients with Barrett's esophagus (BE), stomach acid chronically damages the esophagus, resulting in phenotypic and genetic changes in the tissue lining the esophagus. BE often occurs in individuals with gastroesophageal reflux disease, in which stomach acid leaks back into the esophagus, causing heartburn. Barrett's esophagus affects about one percent of adults in the United States. While progression to esophageal adenocarcinoma (EAC) is less common, the frequency of EAC is rapidly increasing. The progression of BE to EAC is characterized by a series of histologic, genetic and epigenetic changes in the esophageal epithelium. However, it remains unclear which of these events drive progression of BE to more deadly EAC.

To investigate the possible tumor suppressor role of a cell junction protein in EAC, Drs. Andrew Kaz and William Grady and colleagues in the Clinical Research Division report on the methylation, expression and role of *PKP1* in progression of BE to EAC. *PKP1* encodes a desmosomal protein that links cadherins to intermediate filaments within the cell. Thus, PKP1 plays a critical role in cell-cell adhesive junctions, including those found in normal esophageal epithelium. *PKP1* has also been implicated as a tumor suppressor in other epithelial cancers. RT-PCR and immunohistochemical staining showed significantly reduced expression of PKP1 in primary tissues from patients with BE, high-grade dysplasia or EAC relative to normal tissue. A significant increase in the CpG methylation of the promoter of *PKP1* was also observed in high-grade dysplasia and EAC relative to normal or Barrett's epithelium. Initial loss of *PKP1* expression in BE may be due to methylation at other sites in the *PKP1* locus or non-methylation factors. During the transition of BE to EAC, CpG methylation is likely to 'reinforce' this decreased expression of *PKP1*. Finally, siRNA-mediated knock-down of *PKP1* in two esophageal cell lines that normally express *PKP1* resulted in dramatic increases in cell motility.

Thus, factors that down-regulate *PKP1* expression, including CpG methylation, contribute to disrupted cell-cell adherence and BE progression. Further identification of the initial factors that down-regulate *PKP1* expression, as well as the molecular mechanisms behind increased motility will further our understanding of EAC development.

[Kaz AM, Luo Y, Dzieciatkowski S, Chak A, Willis JE, Upton MP, Leidner RS, Grady WM](#). Aberrantly methylated PKP1 in the progression of Barrett's esophagus to esophageal adenocarcinoma. *Genes, Chromosomes and Cancer*. DOI: 10.1002/gcc.21923.



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Immunohistochemical staining shows PKP1 localization at cell-cell interfaces of normal squamous esophageal tissues (SQ). Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) tissues have decreased or no PKP1 expression, and relocalization of PKP1 to the cytoplasm.