Dr. Tamas Gonda

Barrett's esophagus is a major risk factor for the development of esophagealcarcinoma. Exposure of the mucosa to chronic injury leads to accumulation of molecular changes and histologic progression to dysplasia and cancer. Epigenetic changes, heritable changes that are not due to DNA sequencealterations, are particularly important as these maybe some of the earliest hallmarks of progression and may be modifiable risk factors. Methylation isthe best-understood epigenetic change and both global loss of methylation and gene specific hypermethylation have important roles in cancer progression. Although methylation changes are nearly uniform in cancer certain aspects are expected to be unique in Barrett's. A better understanding of the accumulation of DNA methylation changes in stages of BE will likely improve our ability to define the best strategies for targeting epigenetic modifiers and to monitor these changes during BE progression. Closely linked to this issue is the need to define the epigenetic reference tissue that shares similarity with BE tissue. Since the description of field cancerization it has been suggested that a true risk modification would require reversal of epigenetic changes in adjacent normal mucosa. This is somewhat controversial in BE, given the ambiguity and difference between cardia and squamous tissue. Nonetheless, it is critical to understand which of these tissues shares epigenetic features as this would serve as reference tissue to evaluate reversal of epigenetic changes. The final aspect of this grant builds on pre-clinical data using an important epigenetic modifier or methyl donor: folate. Our results have shown that folate can modify DNA methylation status and cancer progression in a very similar gastric neoplasia model and the earlier it is introduced the greater its efficacy. We therefore propose a chemoprevention study with a goal to examine the epigenetic effect of folate supplementation on Barrett's tissue and adjacent normal tissues in patients with non-dysplastic Barrett's.
