DNA-repair Defects in Pancreatic Neuroendocrine Tumors and Potential Clinical Applications

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**Background:** While the role of DNA repair is not yet well understood in pancreatic neuroendocrine tumors (pNETs), the existing literature reveals important preliminary trends and targets in the genetic landscape of pNETs. Notably, pNETs have been shown to harbor defects in the direct reversal MGMT gene and the mismatch repair genes, suggesting that these genes may be strong candidates for further prospective studies.

**Methods:** PubMed searches were conducted for original studies assessing the DNA repair genes MGMT and MMR in pNETs, as well as for PTEN and MEN1, which are not directly DNA repair genes but are involved in DNA repair pathways. Searches were specific to pNETs, yielding five original studies on MGMT and four on MMR. Five original papers studied PTEN in pNETs. Three studied MEN1 in pNETs, and two others implicated MEN1 in DNA repair processes.

**Results:** The five studies on MGMT in pNETs found MGMT loss of between 24\% and 51\% by IHC staining and between 0\% and 40\% by promoter hypermethylation, revealing discrepancies in methods assessing MGMT expression as well as potential weaknesses in the correlation between MGMT IHC expression and promoter hypermethylation rates. Four studies on MMR in pNETs indicated similar ambiguities, as promoter hypermethylation of the MLH1 MMR gene ranged from 0\% to 31\% of pNETs. IHC staining revealed loss of MMR genes in between 0\% and 36\% of pNETs sampled. Studies also indicated that PTEN and MEN1 are commonly mutated genes in pNETs.

**Conclusion:** Further studies are essential in determining a more thorough repertoire of DNA repair defects in pNETs and the clinical significance of these defects. This literature review synthesizes the existing knowledge of relevant DNA repair pathways and studies of the specific genes that carry out these repair mechanisms in pNETs.