Mitochondrial Depletion is a Novel Phenotype of Lynch Syndrome-Related Endometrial Cancer

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Lynch syndrome (LS), defined by mutations in DNA mismatch repair genes including MSH2, carries a 60% lifetime risk of developing endometrial cancer (EC). Mismatch repair deficiency (MMRd) causes hypermutability, which is assumed to be the main driver of LS-related EC development. However, incomplete penetrance of EC development in women with LS suggests that other modulators are at play. The broad hypothesis of this dissertation is that MMRd causes consequences beyond hypermutability to impact LS-related EC development. Recent studies utilizing our lab’s Msh2-deficient mouse model for LS-EC revealed mitochondrial dysfunction in EC pathogenesis. This new insight led to the central hypothesis of this dissertation: mitochondrial dysfunction is a novel carcinogenic phenotype of LS-related EC development.

My initial studies on transcriptional data from Msh2-deficient mice and human EC from The Cancer Genome Atlas (TCGA) indicated loss of mitochondrial complex II expression. Further studies in vitro revealed that global reductions in mitochondrial content underly the transcriptomic changes and cause mitochondrial functional aberrations. Human and mouse MSH2-deficient cell lines exhibit loss of mitochondrial content by mitochondrial DNA copy number measurements and by quantifications of mitochondrial staining using immunofluorescence. Immunohistochemical staining confirmed that mitochondrial content is reduced in LS-related EC compared to non-LS-related EC, and that mitochondrial content decreases during EC development in Msh2-deficient mice. In vitro, MSH2-deficient mouse and human EC cells exhibit mitochondrial DNA (mtDNA) damage and reduced mitochondrial function, which increases dependence on non-mitochondrial metabolic pathways, including glycolysis. Indeed, inhibiting glycolysis in vitro exposed greater vulnerability of MSH2-deficient mouse and human EC cells through reduced cell viability compared to MSH2-intact cells.
Together, these studies indicate that diminished mitochondrial content is a novel phenotype of LS-related EC and results in mitochondrial dysfunction, including reduced mitochondrial respiration and increased dependence on non-mitochondrial metabolic pathways. The mechanism for how MSH2 loss causes the mitochondrial phenotype is an important area for further study, yet the presence of mtDNA damage in MSH2-deficient EC cells suggests that MSH2 loss has increased susceptibility to mtDNA damage. Ultimately, these findings confirm our overall hypothesis that consequences of MMRd beyond hypermutability exist that contribute to EC development. Further, mitochondrial dysfunction and metabolic vulnerabilities could be leveraged as novel biomarkers for LS-related EC development and/or targeted for cancer preventive purposes, two arenas critically lacking for women with LS.

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