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Loss of MLH1 Regulates a Metabolic Phenotype in Endometrial Cancer

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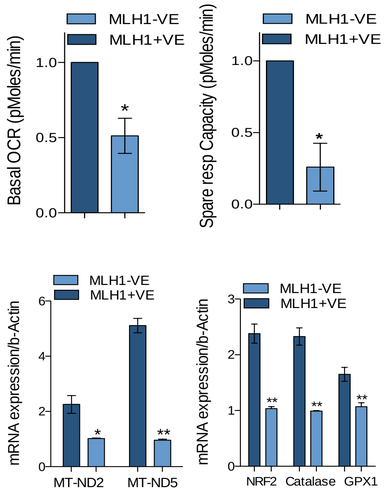
Endometrial cancer is the fourth most common cancer in women and the most common gynaecological malignancy in the developed world. No new systemic treatments for endometrial cancer have been developed in recent years and its incidence is expected to double over the next decade. As such, there is a need to gain a better understanding of key molecular pathways that are altered in the disease and could be targeted by novel treatments. The DNA mismatch repair (MMR) pathway is lost in approximately 30% of endometrial cancers. Recently, our lab has shown that MLH1-deficient cells demonstrate a mitochondrial phenotype characterised by reduced oxidative phosphorylation (OXPHOS), reduced mtDNA copy number and Complex I inhibition. OXPHOS-deficient cells have to adapt their metabolism to compensate for energy defects and the inability to efficiently use the tricarboxylic acid cycle to generate energy. We hypothesise that this altered metabolism is driving tumourigenesis by increasing the metastatic potential of the tumour cells. We have performed metabolomic analysis on a panel of MLH1-proficient and deficient paired endometrial cell lines and identified a metabolic map of alterations upon MLH1 loss. Ultimately, we aim to use this knowledge of altered metabolism upon MLH1 loss to identify more targeted treatments for MMR-deficient endometrial cancer patients.

1. MLH1 loss leads to a deregulated mitochondrial metabolism

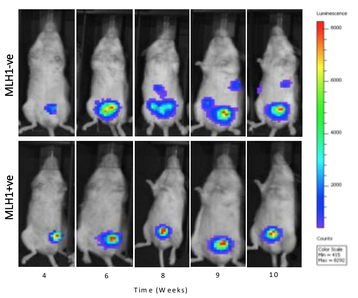


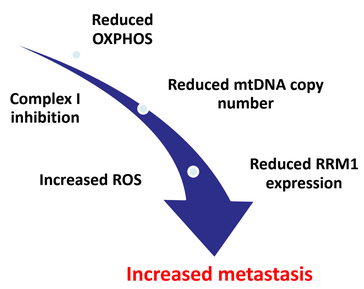
Loss of MLH1 results in a mitochondrial phenotype, characterised by reduced oxidative phosphorylation (OXPHOS) alongside a reduced activity in respiratory chain Complex I and mitochondrial DNA copy number.

As a functional consequence, MLH1-deficient cells have a reduced anti-oxidant response and increased induction of reactive oxidative species.

OXPHOS-deficient cells adapt their metabolism to compensate for energy defects and the inability to efficiently utilize the tricarboxylic acid (TCA) cycle. This typically affects intermediary cell metabolism, in particular the metabolism of amino acids that feed into the TCA cycle. The metabolic changes that occur to allow MLH1-deficient cells to survive are currently unknown.

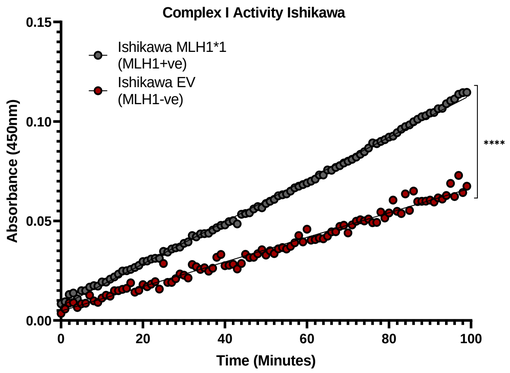
2. Working Hypothesis





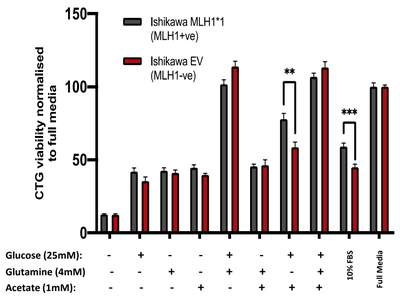
Loss of MMR is a key feature of tumour progression in EC – is MLH1 loss driving tumourigenesis in EC through deregulated mitochondrial metabolism?

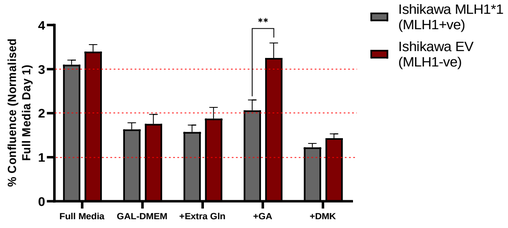
3. MLH1 loss leads to a reduced Complex I activity in Ishikawa EC cells



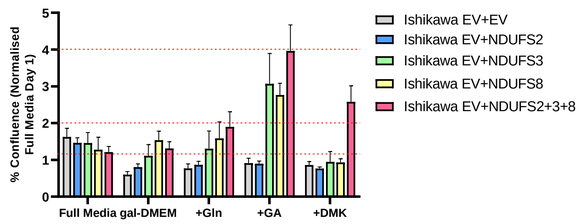
We observe a decrease in the activity of Complex I in the MLH1-deficient Ishikawa cells (Ishikawa EV), compared to the MLH1 proficient Ishikawa cells (Ishikawa MLH1*1). We hypothesise that a reduced Complex I Activity could impair OXPHOS in the MLH1-deficient cells, contributing to a more aggressive phenotype and consequently driving metastasis. We have seen that over-expression of Complex I subunits, NDUFS2, NDUFS3, NDUFS8 individually and in combination increases Complex I activity in MLH1-deficient Ishikawa cells (Ishikawa EV).

4. Metabolic rewiring in MLH1-deficient EC cells

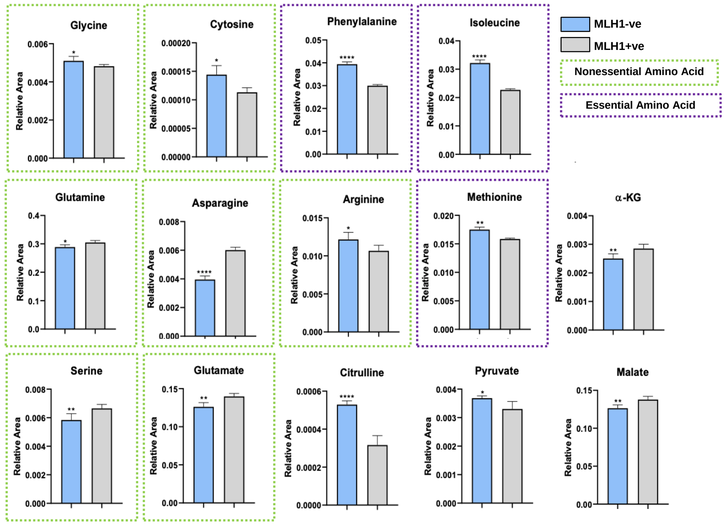




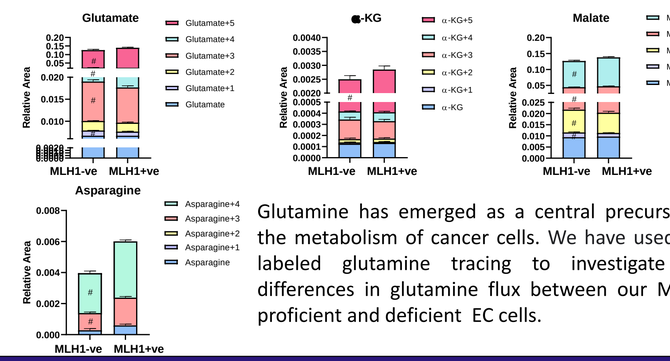
MLH1-deficient Ishikawa cells display a reduction in cell viability in the absence of glutamine. Studies have shown, mtDNA mutant cells with OXPHOS dysfunction are highly dependent on glutamine metabolism.



5. Altered amino acid metabolism in MLH1-deficient EC cells



Amino acids support cancer metabolism by serving as energy sources, biosynthetic molecules, and mediators of redox balance among other roles. MLH1–deficient EC cells display altered metabolic dependencies on both essential and nonessential amino acids.



Glutamine has emerged as a central precursor in the metabolism of cancer cells. We have used ^{13}C-labeled glutamine tracing to investigate the differences in glutamine flux between our MLH1-proficient and deficient EC cells.

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