Mutations of mitochondrial DNA are among the most common genetic events in all cancer; however, their impact on disease initiation and progression is not understood. Mitochondria perform numerous metabolic functions, relying on faithful expression and maintenance of mtDNA, a small, multi-copy genome separate from the nuclear DNA that is contained exclusively within mitochondria. Mutations of mtDNA and gross changes to mtDNA copy number can lead to profound metabolic alterations – one of the earliest identified hallmarks of cancer – and these changes are observed in >60% of tumours. In order to understand the possible links between mitochondrial genetics and metabolic dysfunction in cancer, our lab studies a range of cancer models using and developing cutting-edge mitochondrial genome engineering tools combined with genetic and metabolic analyses. By understanding the relationship between mtDNA and human cancer, we hope to identify new therapeutic targets for clinical application and to inform reallocation of existing treatments based on mtDNA genotype.

Defining the impacts of mtDNA mutations in cancer

Although current model systems for mtDNA mutations are limited in number, using model systems in hand we are addressing the effects of mtDNA mutations on cancer initiation, progression and behaviour across a range of established cellular, organoid and in vivo models of cancer.

Beyond experimental systems in the lab, using repurposed sequencing data from >40,000 tumours, we have shown that: i) mutations in mtDNA-encoded genes are among the most common pan-cancer mutational events, comprising 25% of the 30 most mutated genes in all cancer (Figure 1a), that mtDNA mutational status is unaffected by nuclear DNA mutation burden or microsatellite unstable (MSI) / microsatellite unstable (MSI) status (Figure 1b,c), that recurrent hotspots define the patterning of severe mtDNA mutations (Figure 1d) and that mtDNA mutation status affords major prognostic benefit in colorectal cancer (Figure 1e) (Gorelick et al., 2021, Nature Metabolism). These findings illustrate some of the major impacts of mitochondrial genetics in cancer for the first time, shining a light on a whole additional genetic system of potential therapeutic targets that have been overlooked in cancer research to date. Armed with this information, we will now seek to create models of disease-relevant mtDNA mutations for further study.

Control of mtDNA copy number

In the nucleus, well-described mechanisms that provide tight control of genome replication are poorly understood. Cancer cells, in a cancer-specific fashion, commonly demonstrate significant changes in mtDNA copy number, probably due to the metabolic requirements of their tissue lineage and primary site. By developing an understanding of mtDNA copy number regulation and identifying the molecular mechanisms underlying this process, we hope to design future therapeutic strategies underpinned by manipulation of mtDNA copy number.

Figure 1

a) Mutation rates (Mutations/Mb) of individual mtDNA-encoded genes (blue) and nuclear-encoded cancer-associated genes (grey). Inset plot: mutation rates among 504 genes with mtDNA genes highlighted. Outer plot: closeup of the most plot in the region containing all 37 mtDNA genes; commonly mutated cancer genes, there is no effect on mtDNA TMB. Moreover, mtDNA TMB is similar to (or exceeds) that of nuclear cancer-associated genes in both cancer types.

b) Circular mtDNA genome annotated with locations of homopolymer repeat loci ≥5bp in length. Dot width indicates the length of the repeat region (5-8bp). The 6 solid-colour homopolymer loci highlighted are statistically enriched hotspots for frameshift indels, and when combined are the site of ~40% of all mtDNA truncating mutations in cancer.

c) Controls showing the impact of mtDNA status on colorectal cancer patient survival. mitochondria with VUS status have a significantly worse survival than those with MSI-H or MSS.

d) Survival analysis of 344 stage I-III colorectal cancer patients from The Cancer Genome Atlas (TCGA), stratified by mtDNA status (Wild-type = 108; Truncating = 84; VUS = 152). Data from (Gorelick et al., 2021). VUS, variant of unknown significance (any other potential pathogenic mtDNA mutation that is not a truncating variant).