PROJECT

Supervisor:	Irene Franco
Title:	Lifestyle factors influencing somatic mutation in the kidneys
Curriculum:	CMB
Link to the personal page of the University or relevant hospital site website:	https://research.hsr.it/en/divisions/genetics-and-cell-biology/somatic-mutation-mechanisms.html

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Every cell of the body accumulates somatic mutations during a lifetime. This is relevant to human health, because rare cancer-driver mutations can initiate cancer. Our group has a long-lasting experience in detection and analysis of somatic genetic variants in multiple human tissues and experimental systems (Franco I, Johansson A *et al, Nature Communications*, 2018; Franco I, Helgadottir HT *et al, Genome Biology*, 2019; Margaria JP, Faienza S., Franco I, *Kidney International*). By analyzing normal cells from human kidneys, we have found that exposure to low oxygen (hypoxia) induces a mutational signature, i.e. a specific spectrum of somatic mutations. This hypoxia-related mutational signature is uniquely found in kidney tumors and in a rare subset of normal kidney cells, which become more frequent with aging.

Rationale and hypothesis

We think that episodes of micro-hypoxia occur in healthy kidneys with age and induce the mutational signature in a specific subset of kidney cells that are involved in tissue damage-repair. Micro-hypoxic episodes in the kidneys of healthy individuals might be caused by dietary habits that increase kidney workload.

Objectives and specific aims

We will use animal models to verify the causative link between hypoxia (induced by a surgically-induced ischemic insult) and appearance of aberrantly mutated cells in the kidneys. Moreover, we will test whether specific dietary treatments induce tissue changes similar to those observed after ischemia, i.e. kidney damage followed by the appearance of mutated cells.

AIM 1: Analysis of somatic mutations in kidney cells from mice exposed to ischemia/reperfusion

AIM 2: Analysis of somatic mutations in kidney cells from mice fed with high-protein diet

Expected outcomes

We expect that both treatments induce the specific mutational signature in selected kidney cells. This will be the first *in vivo* evidence of lifestyle factors that induce cancer-favoring mutation in the kidneys.

Skills that the student should acquire (max. 600 characters including spaces):

Mouse colony management, surgery model in mice, dietary treatments in mice, histology, immunohistochemistry, qPCR, FACS sorting, clonal culture of murine kidney cells,_DNA extraction and handling, genome sequencing, genomic analyses, bioinformatics.

References (max. 15)

Franco, I., et al., Whole genome DNA sequencing provides an atlas of somatic mutagenesis in healthy human cells and identifies a tumor-prone cell type. Genome Biol, 2019. 20(1): p. 285.

Franco, I., et al., Somatic mutagenesis in satellite cells associates with human skeletal muscle aging. Nature Communications, 2018. 9.

Margaria, J.P., Faienza S., and Franco I., Somatic mutations acquired during life: state of the art and implications for the kidney. Kidney International, 2025.