Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Characterization of splicing patterns in cells from carriers of *BRCA1* and *BRCA2* gene variants classified as VUS

Synopsis:

Heterozygous germline inactivating variants in *BRCA1* and *BRCA2* genes are associated to hereditary breast and ovarian cancer syndrome (HBOC) and to an increased risk for developing breast, ovarian, prostate and pancreatic cancer, or melanoma. About 10-30% of women diagnosed with triple negative breast cancer before the age of 60 will have a *BRCA1* or *BRCA2* gene inactivating variant and about 20% of ovarian cancer patients carry *BRCA1/2* deleterious variants. Germline line or cancer inactivating mutations on *BRCA1/2* genes are, currently, biomarkers for treatment of breast, ovarian or prostate cancer with PARP inhibitors, a new targeted cancer drug. Additionally, identification of these germline variants and screening of family members allows for preventive clinical measures.

BRCA1/2 predicted loss-of-function (LOF) variants, including nonsense variants, frame-shifting indels, and variants at the canonical splice sites are classified as pathogenic or likely pathogenic with the inherent clinical implications. However, a large fraction of genetic alterations found in these genes are classified as variants of uncertain significance (VUS), precluding an appropriate clinical management to patients and their relatives. However, studying the missplicing effect of some VUS at the transcript level can further inform on previously unpredicted loss-of-function outcome.

The aim of this study is to characterize splicing pattern and stability of mRNA transcripts in cells from carriers of *BRCA1/2* gene variants classified as VUS. The impact at the protein level will be addressed by a functional approach. An extensive molecular and functional description is expected to help us on reclassifying some of the VUS and enable patients to get access to personalized medicine and their relatives to preventive medical care.

Supervisor: *Célia Carvalho, Maria Carmo-Fonseca Lab, celiacarv@campus.ul.pt*
Webpage of the group