Program: Biomedicínské vědy
Specializace: Biochemie a molekulární biologie
Forma studia: prezenční
Školitel: Nicola Silva, Ph.D.

Topic:
Identification and characterization of factors involved in meiotic DNA double strand breaks repair

Annotation:
Faithful repair of meiotic DNA double strand breaks (DSBs) is crucial to promote correct chromosome segregation in the gametes by allowing formation of physical connections (crossovers) between the parental chromosome (homologous chromosomes) and therefore to preserve fertility. Many genes drive this process and most of these factors are conserved throughout evolution, allowing dissection of complex pathways in simpler model organisms such as *Caenorhabditis elegans*, one of the most powerful systems to study chromosome dynamics during gametogenesis. We have recently shown that *C. elegans* ortholog of mammalian breast and ovarian cancer susceptibility gene *BRCA1*, *brc-1*, localizes to meiotic chromosomes in a dynamic way throughout meiotic prophase I and is enriched at the crossover sites (Janisiw et al.; 2018 PLoS Genet.). BRCA1/BRC-1 is an essential protein for repair of both endogenous and exogenous DSBs and we found that in *C. elegans* meiotic cells it promotes the stabilization of recombinase RAD-51 at the sites of damage allowing homologous recombination-mediated repair, which was previously unknown. Furthermore, we have identified the poly(ADP-ribose) glycohydrolase PARG/PARG-1 to be essential in promoting homologous recombination during meiotic progression, as well as displaying a genetic and physical interaction with BRC-1 (manuscript in preparation).

Two Ph.D. student positions will be available, to carry on the characterization of the meiotic roles exerted by *C. elegans* BRC-1 in promoting DNA repair, with particular emphasis on unravelling how post-translational modifications regulate the activity of this protein. Moreover, we identified a completely uncharacterized BRC-1 paralog which might shed new light on the mode of function of BRC-1.
Further, functional analysis of the PARG-1-BRC-1 interaction will also be performed, possibly in a shared effort between the two Ph.D. students.
Moreover, study of PARG-1 functions during meiosis also holds a crucial interest in the lab, and we have identified an important and completely unknown involvement of this protein during gametogenesis. Deep characterization of its mode of action and identification of both interactors and putative substrates will be performed.

Requirements:
- Strong background in Genetics, Molecular Biology and Biochemistry
- Solid experience with Western Blot, PCR and Immunofluorescence is highly desirable
- Excellent communication in English, Curiosity and enthusiasm about science are all essential skills

Information on the supervisor:
Dr. Silva is a newly appointed Junior Group Leader at the Department of Biology. His experience with the C. elegans model in the context of DNA repair in the germline spans over a decade. Throughout his career, Dr. Silva has made important contributions to the DNA repair and recombination field by shedding new light on the molecular functions of several repair factors during gametogenesis; he identified a previously unknown role for crossover-promoting factors in stimulating DNA-damage dependent apoptosis in the germline, as well as found that a family of protein localizing along the meiotic chromosome axes exerts a regulative role on coordinating establishment of synapsis and meiotic progression with a similar mechanism observed for Mad1-Mad2 in regulating the function of mitotic spindle checkpoint.
A comprehensive list of Dr. Silva publications can be found here: https://www.ncbi.nlm.nih.gov/pubmed/?term=silva+n+elegans