Evolutionary perspective on irradiation resistance of stem cells

High irradiation doses cause double-stranded breaks in DNA double helix, which can evoke errors in DNA replication and cell divisions. To avoid the passage of double-stranded breaks to the next generation, the dividing cells engage the specific safety mechanism, the so-called cell cycle checkpoints, preventing the proliferation of cells with damaged DNA. In the first step, the cell attempts active repair of double-stranded breaks. If the repair mechanism fails (for instance, due to an excessive number of breaks), the signaling checkpoint molecules initiate apoptosis – a programmed suicidal death of the cell. As cell cycle checkpoints are only active in dividing cells, irradiation of the organisms leads to specific elimination of its proliferative cells. This mechanism is used as the basis for radiotherapy, in which uncontrollably dividing cancerous cells are specifically targeted with irradiation. On the other hand, this phenomenon is also responsible for acute irradiation sickness, in which irradiation leads to the total elimination of properly dividing tissue-specific stem cells, such as those present in bone marrow, and consequently to systemic depletion of new cells in an organism.

Although vertebrates, including ourselves, show low resistance to irradiation, some invertebrates can withstand relatively high doses of irradiation, exceeding doses lethal to humans by several orders of magnitude. In our project, we will study how (from a cell biology standpoint) and why (from an evolutionary perspective) those animals are resistant to irradiation. Importantly, some of the animals that can survive high irradiation doses, for instance, flatworms, rely on adult pluripotent stem cells for their development and cellular turnover. In contrast to vertebrates and insects, in which adult stem cells produce only some narrowly restricted tissues, stem cells of flatworms can give rise to every type of cell in their bodies. Hence, each stem cell of a flatworm can differentiate into ovaries and testes, giving rise to eggs and sperm, and its genetic material can be passed to the next generation. Flatworms should consequently experience stronger evolutionary pressure to protect the intact genotype of their stem cells when compared to animals with tissue-specific stem cells. It is, therefore, expected that flatworms should employ exceptionally efficient mechanisms of avoidance and repair of double-stranded DNA breaks to avoid the transfer of deleterious mutations to their progeny. On the other hand, extreme tolerance to irradiation was also reported in animals that don't harbor adult pluripotent stem cells, such as rotifers and tardigrades. These animals, like some flatworms, occur in temporary, shallow freshwater habitats, in which they are exposed to environmental factors that can cause double-stranded DNA breaks, such as UV and desiccation. In their case, avoidance and repair of double-stranded breaks could represent adaptation to those particular environmental conditions.

In our project, we will test whether the irradiation resistance of invertebrates results from the presence of adult pluripotent stem cells or, rather represents environmental adaptation. To achieve this goal, we will establish irradiation tolerance thresholds in diverse animals from multiple evolutionary lineages, occurring in various environments and employing different systems of stem cells. To establish if irradiation resistance is better explained by the type of stem cells or the species' environments, we will test for correlations between those three factors in a wide range of animals.

In addition, we will study a model flatworm species, *Stenostomum brevipharyngium*, that is particularly resistant to ionizing irradiation, even by flatworm standards. We will aim at resolving cellular and molecular mechanisms that provide this species with its unique ability to survive extremely high irradiation doses. By comparing those results with data on irradiation resistance in other animals, we will dissect universal mechanisms of irradiation resistance from those that evolve independently in particular groups of animals.