Japanese medaka fish: A unique tool for investigating low dose radiation effects

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Introduction
- Research program focused on radiation in the environment
  - Investigate low dose radiation effects and the risk to human health
  - Evaluate acute toxicity and long term consequences of exposure
  - Describe vertebrate model used to assess the effects

Radiation in the Environment
- Naturally occurring
- Man-made
  - Global Fallout
  - Accidental Releases
  - Nuclear Facilities
  - Chernobyl Accident
- Dose is delivered chronically
  - Low dose-rates
  - Internal and external exposures
- Radionuclides typically occur in the environment along with other contaminants like metals

Biological Radiation Effects
- Passage of ionizing radiation through cells and tissue initiates a complex series of chemical reactions
  - Free radicals (electrons) - damage biological molecules both direct and indirect action
  - Reactive oxygen species (ROS)
- Production of DNA double strand breaks (DSBs) and complex lesions
- Un-repaired or Mis-repaired damage can lead to
  - Acute toxicity (cell killing – hours to days)
  - Long-term effects (cancer - years to decades)

Uncertainty at Low Dose Range
- Uncertainty about effects from Low Doses and Doses delivered at Low Dose-Rates because we don’t have a good understanding of the biological mechanisms.
- It is theorized that at high doses the cell microenvironment is essentially inactivated, but at low doses it is functional, maybe not optimal, and can affect processes such as:
  - DNA repair
  - Bystander effects
  - Adaptive Response
  - Genetic Mutations

Tools to determine low dose effects
- Sensitive markers to measure and observe the pathways for repair
- Markers and model systems that have characteristics relevant to humans and human health conditions
- Models that can yield good statistical power
Japanese Medaka Fish

- **Physical Characteristics**
  - 2-4 cm adult size
  - 8 week life cycle
  - 10-30 eggs/day
  - Organs of radiobiological interest
  - Life-span ~2-3 years
  - Hardy physiology
- **Sequenced genome**
- **Relatively inexpensive**

Embryo Development

- **Hatching Time**
  - 7-14 days
  - Temperature dependent
- **Characteristics**
  - Clear chorion
  - 45 described stages of development
  - Can be genetically manipulated

Medaka Genome

- Total genome is 700 Mb (~one-fifth of human genome)
- Of the 20,141 predicted medaka genes, 11,617 (57.7%) were shown to have human orthologues.
- Homology is between 60-80% for genes involved in processes such as DNA repair, Apoptosis, Stress Response, and Immune Response.


Medaka Strains

- **CAB Wild-type**
- **STII “See-Through”** (Drs. Wakamatsu and David Hinton)
- **T5 “Semi-See-Through”** (Dr. Hiroshi Mitani)
- **RicI-Olvas-GFP & Olvas-GFP** (Drs. Mitani and Hinton)
- **Gene Knockout Mutants** (Drs. Taniguchi, Takeda, and Todo)
  - P53 (-/-)
  - BLM (+/-)
  - ATM (+/-)
  - MsH2
  - Rb

1-month old T5 “Semi-See-Through” With visible internal organs

Research Collaboration with Medical College of Georgia

- Dr. William S. Dynan’s Lab in the Institute of Molecular Medicine and Genetics
- Development of transgenic fish with recombinant reporter to investigate DNA damage in somatic cells.
- Experiments utilizing transgenic and mutant strains (MCG & LoDIF) will lend insights into long-term consequences of exposure.

Investigation of Long-term Consequences

- **Genome Instability** defined as damage that manifests itself in cell or organismal generations following the one in which exposure occurred.
  - Increased levels of new mutations or aberrations that remain elevated.
  - Heritable – do mutations arise in un-irradiated offspring?
- Cancer induction
- Life-Shortening / Accelerated Aging