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

Wendy Kuhne, Ph.D.
Senior Scientist
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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

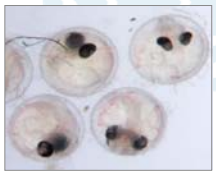
- **Sensitive markers to measure and observe the pathways for repair**
- **Markers and model systems that have characteristics relevant to humans and human health conditions**
- **Models that can yield good statistical power**

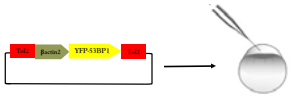
Japanese Medaka Fish

- **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

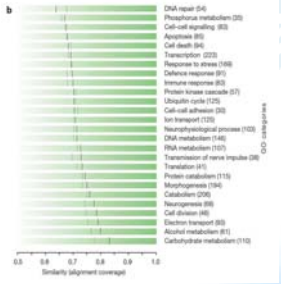
- **Hatching Time**
  - 7-14 days
  - Temperature dependent
- **Characteristics**
  - Clear chorion
  - 45 described stages of development
  - Can be genetically manipulated





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.



Kasahara M. et al. (2007) *Nature* 447:714-719

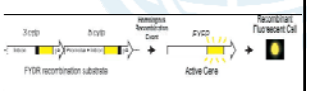
Medaka Strains

- CAB Wild-type
- STII "See-Through"
  (Drs. Wakmatsu 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.**



LoDIF Facility Mesocosoms

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**