Immune system and low dose radiation: why and how?

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A workshop on low dose radiation effects on the immune system: current knowledge and future research needs
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Why?

The Immune System is disseminated throughout the body to protect it and preserve its integrity.

Radiations inflict damages to every cell and tissue, including the immune system components.
Two aspects should be considered

As an integral part of the body, the immune system will be exposed to the effects of radiation, and the homeostasis and/or functions of its different components can be altered

- **Effects of radiation on immune functions**
  As an integrated defense system, the immune system will attempt to counteract the deleterious effects of radiation, mend the insults and restore homeostasis and function of the exposed tissues

- **Role of the immune system in the response to radiation**
How?(1)

Influence on the outcome of the response to radiation

Radiation-induced damages may induce a sterile inflammatory reaction

Infectious inflammation

- TNF
- IL-1
- IL-6
- Chemokines (many)
- Lipid mediators

Sterile inflammation

- TLR
- DAMPs
- HMGB1
- RAGE

To what effects?

Adapted from Chen and Nunez, 2010
Tissue resident immune cells act as sentinel to sense tissue damage

- Tissue specific response

Murray and Wynn, 2011
Circulating immune cells patrol the body via the circulation and the lymphatic system.

From the NIAID website (http://www.niaid.nih.gov/topics/immunesystem/Pages/default.aspx)

➡️ Systemic response
Inflammation is a beneficial process
Persistent inflammation can lead/participate to disease

How does radiation-induced inflammation develops?
How is it controled?
The other way around

Influence of the immunological status on the outcome of the response to radiation?

« Non-specific » activation of the immune system protects from deleterious radiation effects

1 injection of recombinant IL-1 20 days before WB irradiation at 9.5 Gy (LD$_{100/17}$) protects mice from death

Journal of Immunology, 1986
Radioprotection by TLR5 agonists in mice and monkeys

Adapted from Burelya, Science, 2008

Mice

Monkeys

Intramuscular injection 6.5 Gy (LD$_{70/40}$)
How? (2)

Influence on functions?

Radiation exposure affects the development of the immune system

- Radiation-induced apoptosis
- Radiation-induced differentiation
- Exposure to inflammatory environment

No irradiation

\[
\begin{array}{c|c}
12.99 & 79.81 \\
3.35 & 3.85 \\
\end{array}
\]

8 Gy, 36 hrs

\[
\begin{array}{c|c}
204 \times 10^6 & 3.8 \times 10^6 \\
70.58 & 4.96 \\
8.18 & 16.28 \\
\end{array}
\]

How will the immune system regenerate?

Adapted from Candéias et al., Oncogene, 2004
All immune cells are generated from HSC

Immune system development/functions impairment due to radiation damage to HSC?

Dranoff, Nature Reviews Cancer, 2004
**Influence on functions?**
Long lasting alterations of the immune system in A-bomb survivors

**Diagram:**
- A-bomb radiation
  - Perturbation of T-cell homeostasis: Helper T cell counts, Immune functions
  - Inflammatory cytokines: IL-6 level, CRP level
    - Environmental factors
    - Infection
      - Persistent inflammation
        - Diseases (e.g., cardiovascular disease)

Kusunoki and Hayashi, IJR, 2008
Questions (1)

• Activation/inhibition of the immune system in response to radiation exposure
  – Which cells?
  – What effects?
  – How is it controled?

• Effects of radiation exposure on the immune system
  – Alteration of immunity to infectious agents?
  – Alteration of inflammation status?
  – Alterations in tumor immunosurveillance?

• Is there a **threshold** both for activation of and effects on the immune system?

• Does the immune system plays a role in distal/non-targeted/abscopal effects of radiation?
To be kept in mind

- Diversity, plasticity and homeostasis of the cellular components of the immune system
- Dynamic evolution of the immune response
- Infectious vs sterile inflammation
- Tumor immunosurveillance
- Inflammation-dependent carcinogenesis
- Interactions between inflammation and radiation response
- Long term effects
Questions (2)

• What do we know at high doses?
• What do we know at low doses?
• What can we propose to increase our knowledge on low dose health effects and radioprotection at low doses?
The immune system is a continuum

**The Nobel Prize** in Physiology or Medicine 2011

1. **Innate immunity**
   - rapid
   - halts infection
   - no memory

2. **Adaptive immunity**
   - slower
   - clears infection
   - memory

**The immune system**
Infection of the human body by pathogenic microorganisms such as bacteria, viruses, parasites or fungi triggers the immune response. It occurs in a two-step process: innate immunity halts the infection, and adaptive immunity subsequently clears it.

Prize attributed B. Beutler, J. Hoffman, R. Steinman
1. **Innate immunity**
Components of microorganisms bind to Toll-like receptors located on many cells in the body. This activates innate immunity, which leads to inflammation and to the destruction of invading microorganisms.

2. **Adaptive immunity**
Dendritic cells activate T lymphocytes, which initiates adaptive immunity. A cascade of immune reactions follows, with formation of antibodies and killer cells.
Thank you for your attention

Enjoy the workshop