DE LA RECHERCHE À L'INDUSTRIE

THE IMMUNE RESPONSE TO LOW DOSE RADIATION

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CELET – Stockholm – Novembre 2021

WHY?

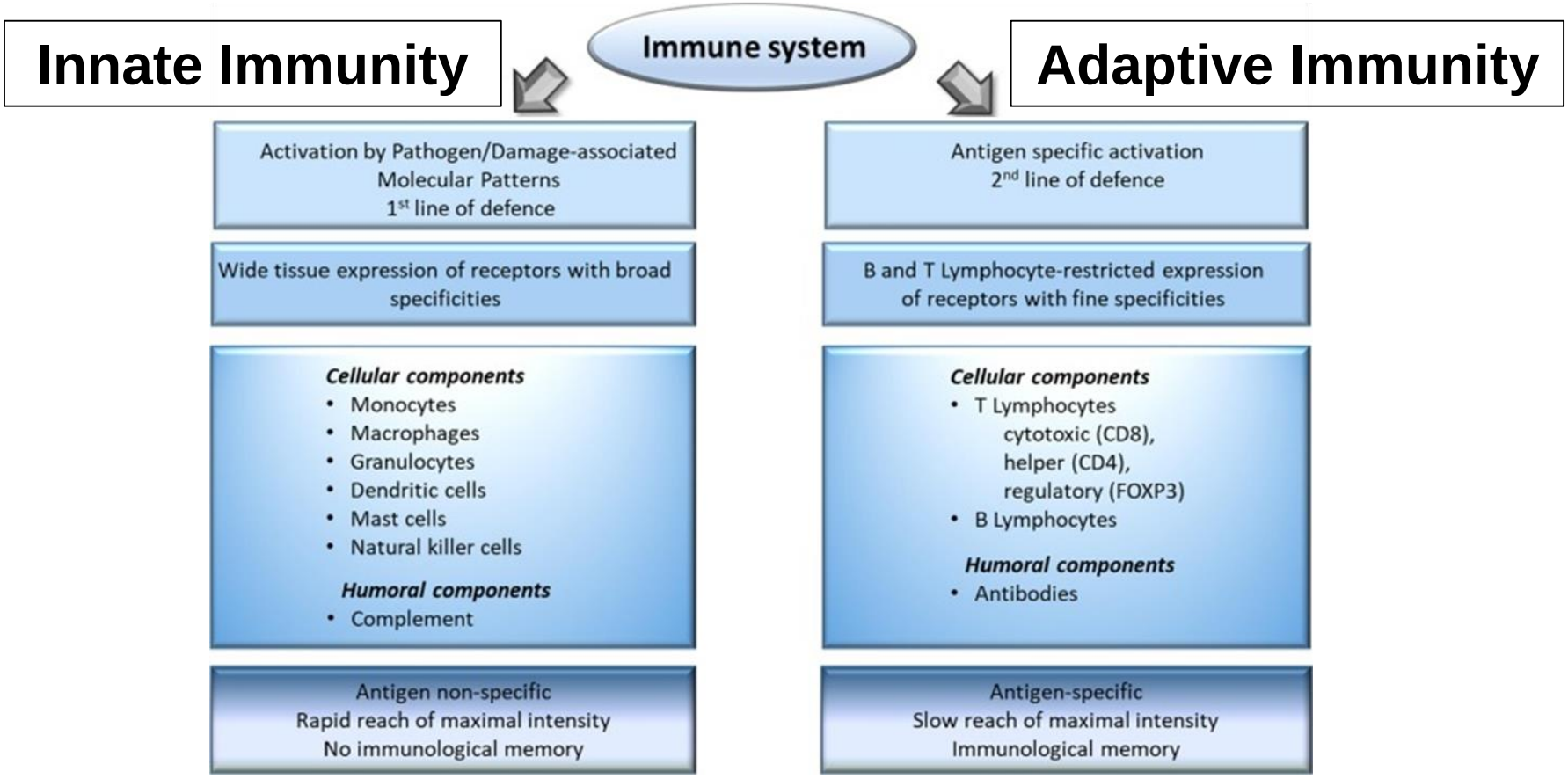
As an integrated systemic defense system, the immune system will attempt to counteract the deleterious effects of radiation and restore homeostasis and function of the exposed tissues

➔**Role of the immune system in the response to radiation**

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**

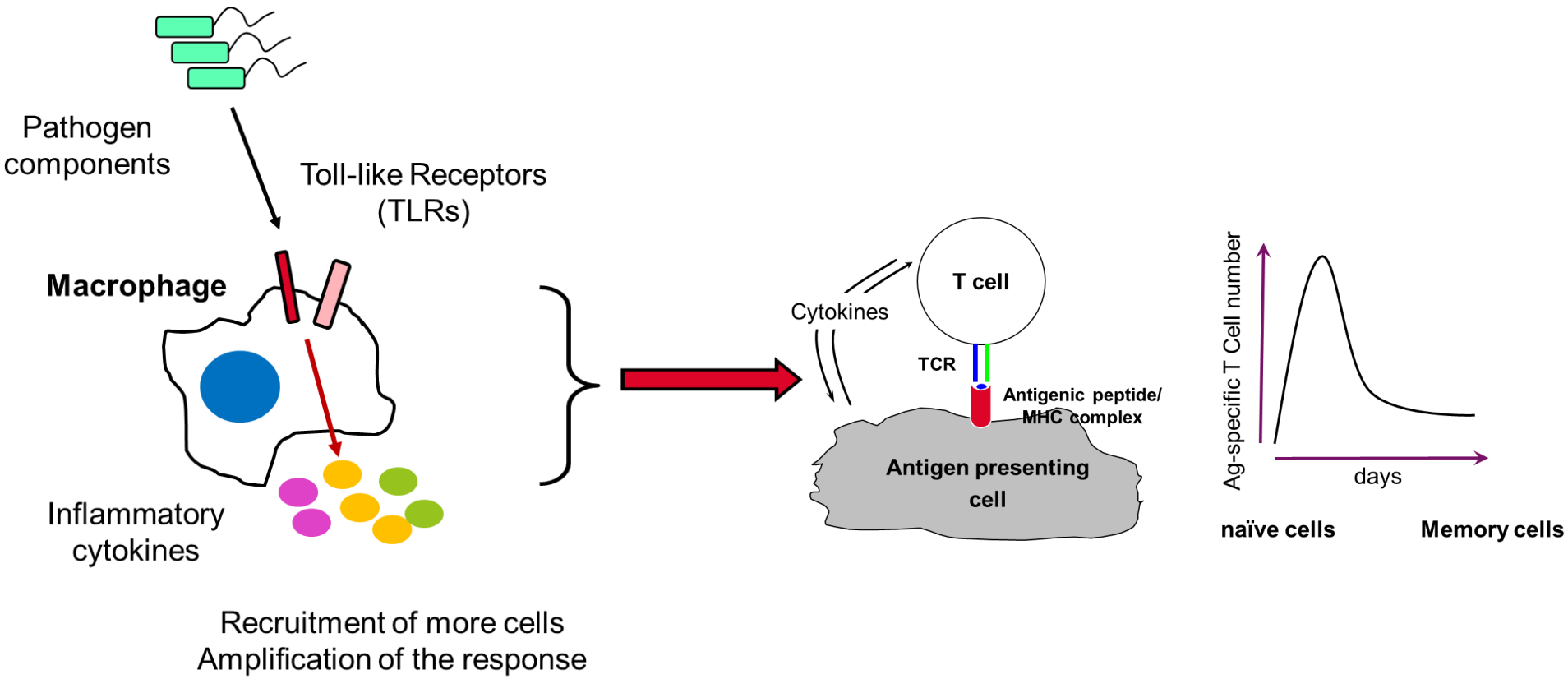
THE IMMUNE SYSTEM: OVERVIEW



All immune cells are generated from HSC
They circulate in blood and lymph
They home to tissues
The immune system is a systemic network, with compartimentalization

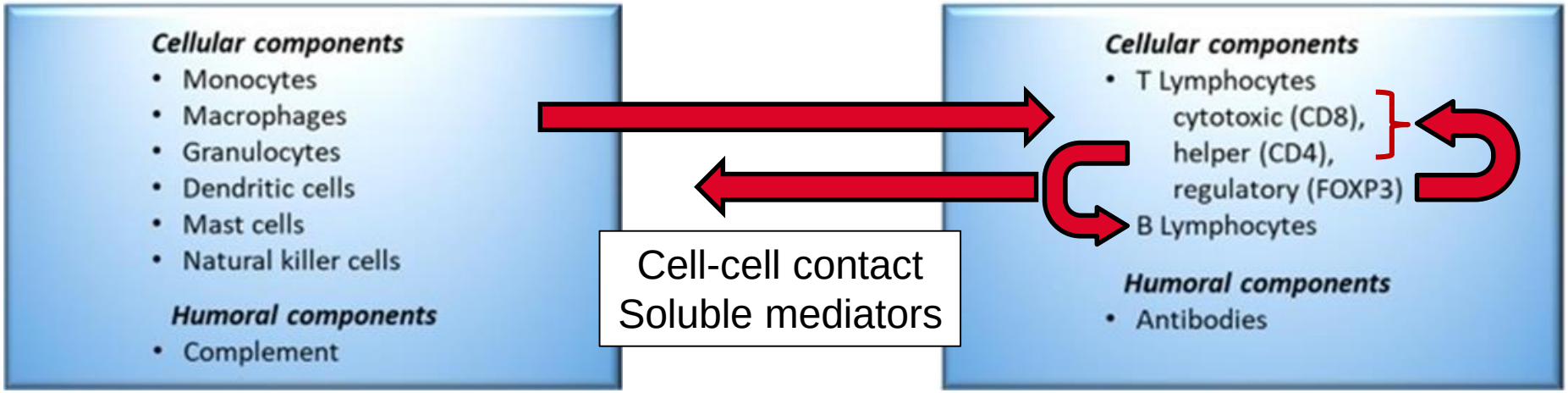
Adapted from Lumniczky et al., Environ Int. 149: 106212 (2021)

Innate and adaptive immunity



THE IMMUNE SYSTEM: OVERVIEW

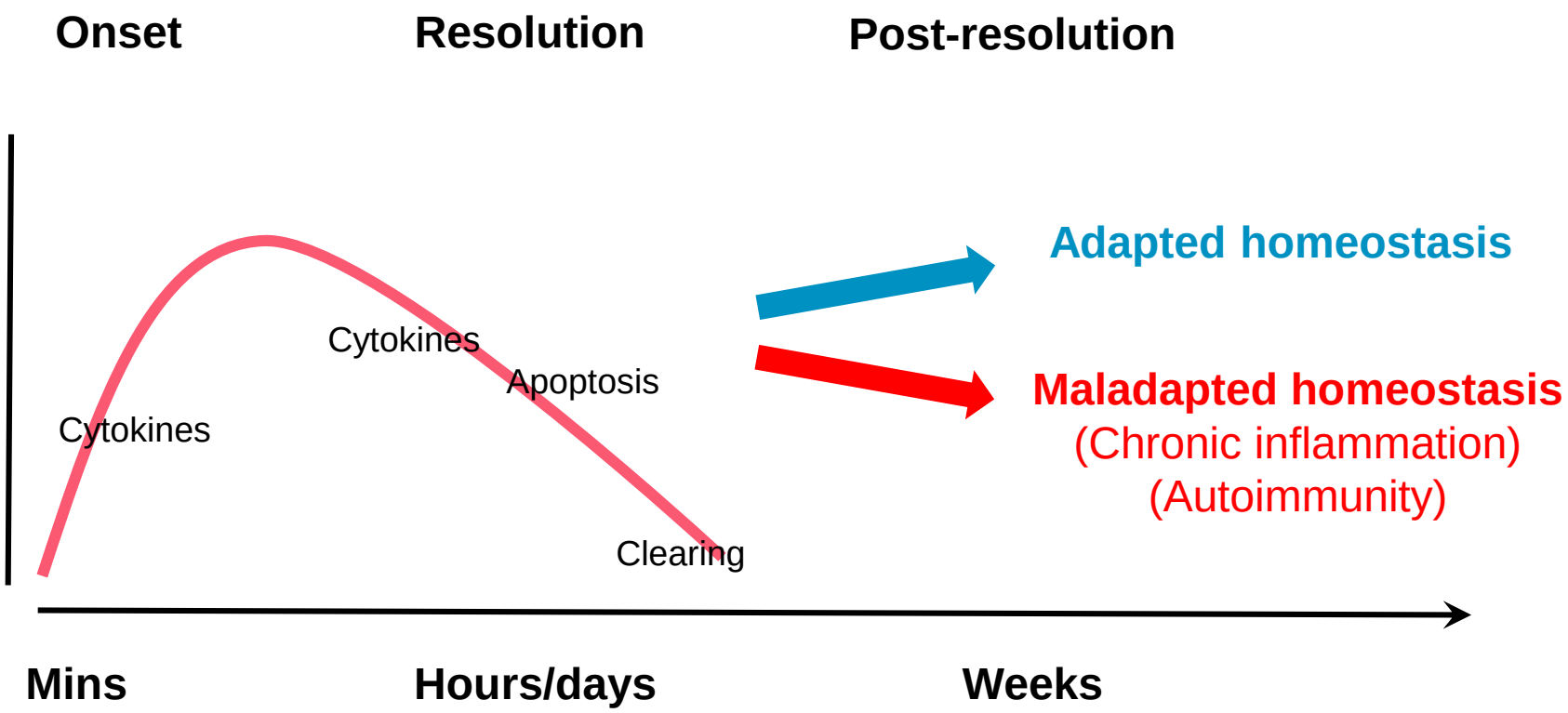
The immune system is a continuum
Innate and adaptive immunity cooperate to protect the organism



- Production of soluble inflammatory factors to recruit immune cells
- Antigen presentation to T cells
- Production of cytokines to coordinate the cellular and humoral responses
- Anti-inflammatory cytokines and regulatory T cells to prevent or limit over-reactive immune response

Adapted from Lumniczky et al., Environ Int. 149: 106212 (2021)

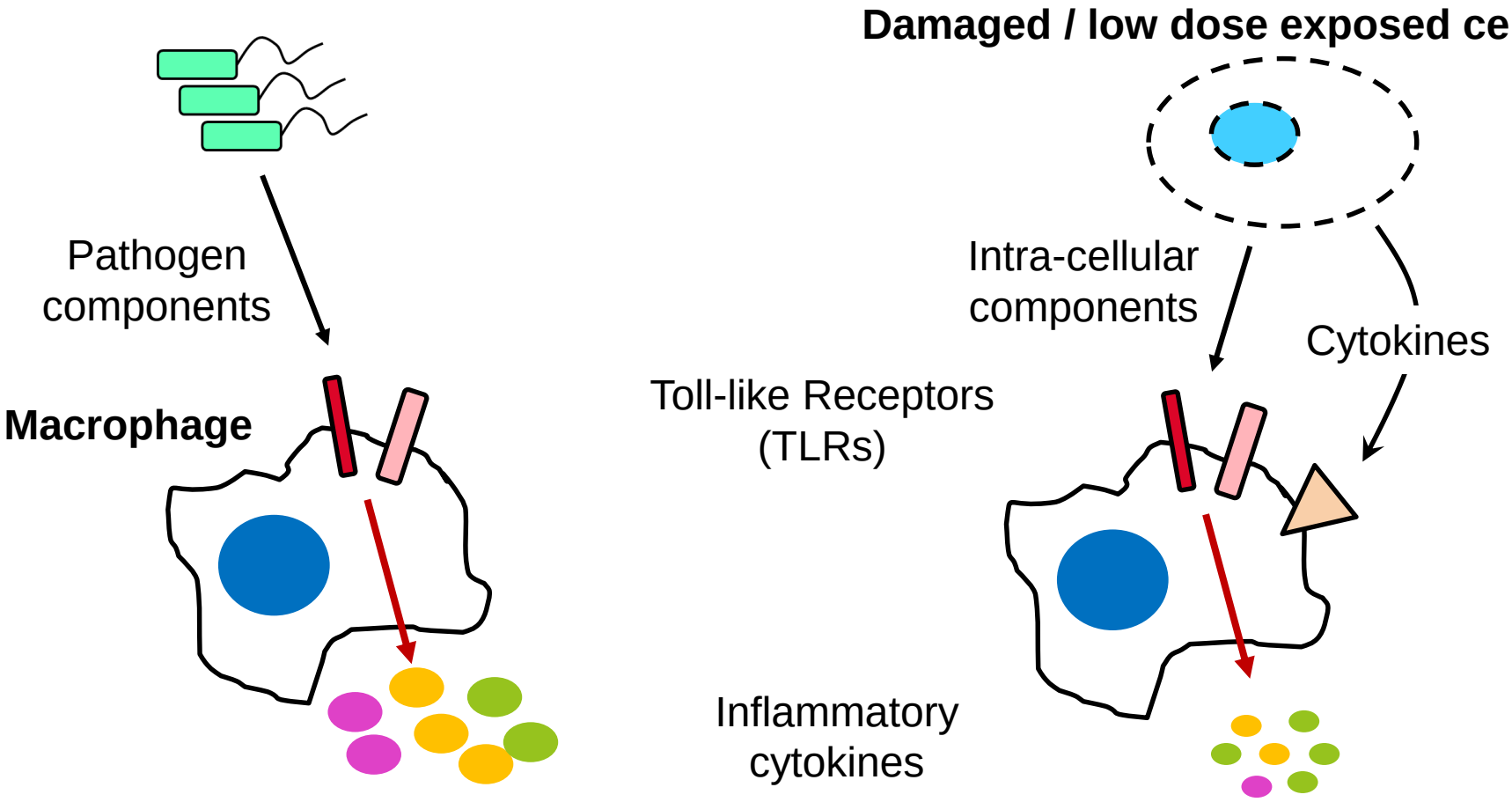
RESOLUTION OF THE INFLAMMATORY RESPONSE



- Inflammation is a dynamic process, largely controled at the transcriptional levels to produce pro- then anti-inflammatory cytokines and mediators.
- Inflammation resolution is an ***active*** process

Adapted from Feehan and Gilroy, 2019

INFECTIOUS vs STERILE INFLAMMATION



Recruitment/activation of immune cells?
Amplification/resolution of inflammation?
Effects of the adaptive immunity?

METHODS TO STUDY IMMUNE RESPONSES AT LOW DOSE

- **FACS analysis**: phenotype and activation of immune cells
- **ELISA**: cytokine secretion
- **Transcriptomics** (from RT-PCR to microarrays): modulation of gene expression
- **Proteomics**: modulation of protein expression
- **Western blots**: protein expression, activation
- **Epigenetics:** miRNA
- **Immunohistochemistry/histology**: inflammation markers in tissues
- **TCR profiling**: dynamics of the T cell population

IMMUNE CHANGES IN EXPOSED INDIVIDUALS

- **A-bomb survivors:**
  - lower levels of naïve CD4 T cells; restricted TCR diversity (V genes) in memory CD4 T cells; accelerated aging (Kusunoki, 1998, 2003, 2010)
- **Chernobyl accident/contaminated area:**
  - Clean up workers: changes in gene expression in blood cells of clean up workers (Ilienko, 2018)
  - Lower level of CD4 T cells in children with respiratory diseases living in contaminated areas (Chenyshov, 1997)
- **HBRA residents** : Kerala (India), Ramsar (Iran), Yangjiang (China)
  - Modulation of gene expression, including genes belonging to the TCR, TLR and cytokine signaling pathways (Jain, 2017)
- **Workers**:
  - Polarization towards a Th2 type immunity in NPP workers with exposures >100mSv (Gyuleva, 2015, 2018)
- **LD-RT / Radon spa therapy:**
  - Discrete changes in cell homeostasis and/or activation in blood, modulation of cytokines and adipokines after Radon spa therapy (Rühle, 2017; Cucu, 2017)

ANIMAL STUDIES: HEALTHY MICE AND DISEASE MODELS

- **Low-dose rate exposure** of C57BL/6 mice to 0.2 Gy in 12 d does not impact splenic B and T lymphocytes but modulates circulating cytokine levels 7 d post exposure (Shin, 2010)
- **Acute exposure** of C57BL/6 mice to 0.01 to 2 Gy leads to modulation of apoptosis, cellular homeostasis of the different immune cell populations (B, T, NK, DC) and circulating cytokine levels from 4 h to 7 d post irradiation (Bogdandi, 2010).
- TCR gene profiling in mice exposed to **acute** 0.1 or 1 Gy X-rays showed that radiation exposure accelerates aging of the T cell population (Candéias, 2017)

- **Low dose and low dose rate** X-ray exposure can modulate the response to a subsequent exposure to 2 Gy high LET radiation (Rivzi, 2011).
- **Repeated low dose exposure** (25 mGy every other days for 2 to 16 wks) reduces inflammation symptoms associated with type I diabetes (Zhang, 2009, 2011)
- **Chronic low dose/low dose rate exposures** (0.3 Gy and 1 Gy in 24 days) significantly reduce lung and systemic inflammation in asthma (Kim, 2015)
- **Intra-peritoneal injection of ^{137}Cs** (accumulated dose of 2.5 – 2.7 Gy in the next 50 days) in 2 wks-old mice does not significantly impair their response to influenza A infection at 6 m (Misra, 2015)

IN VITRO EXPERIMENTS

- **Human primary cells**:
  - total blood, purified PBMCs, purified blood cells (lymphocytes, monocytes (El-Saghire, 2013), NK cells), dendritic cells, endothelial cells (Baselet, 2017), fibroblasts, keratinocytes, dental mesenchymal stromal cells

- **3D culture**
  - Skin explants, organoïds

- **Immortalized cells**:
  - Cancer cells, telomerase-transformed endothelial cells and fibronlasts

CHALLENGES TO IMPROVE UNDERSTANDING OF IMMUNE RESPONSES AT LOW DOSE RADIATION

- **Analysis of low dose/low dose rate response in *healthy* individuals**
  - A pre-existing inflammatory status may influence the effects of radiation on the immune system
- **Analysis of the *long term* effects of low dose radiation exposure**
  - Immunoscenesence may mask the eventual long term impact of low dose radiation on immune cell homeostasis and function
- **Qualitative and quantitative aspects of immune responses at low and high radiation dose**
  - Low dose/inflammation vs high dose/DDR activation?
- **Differences between chronic and acute low dose exposure effects**
  - Relationship with the DNA damage response/chekpoints?

- **Attract immunologists to low-dose/low dose rate radiation studies**

OPPORTUNITIES TO IMPROVE UNDERSTANDING OF IMMUNE RESPONSES AT LOW DOSE RADIATION

- **Use high throughput or higher dimensions approaches:**
  - single cell RNA-Seq, multi-color immunophenotyping, e.g. identification of 20 cell subsets in one tube, (Donaubauer, 2020), imaging flow cytometer, CyTOFF, gene expression profiling
- **« Molecular » epidemiology:**
  - Possible with existing cohorts? New cohorts?
  - longitudinal studies, to limit the problem of inter-individual sensitivity
- **AOP approaches:**
  - Pathways for immune relevant endpoints?

- **Advertise**:
  - Organize dedicated workshops to inform the (outside) community of the needs

RESEARCH PRIORITIES

- **Functionality of the immune system after low dose exposure**
  - Is there a loss of immune function?
  - Does the immune system protect from the (detrimental) effects of low dose radiation? (cancer/non-cancer)

- **Comparison of the relative importance of direct vs bystander effects**

- **Comparison of low vs high LET radiation effects**

TO BE KEPT IN MIND:

- Diversity, functional plasticity and homeostasis of the cellular components of the immune system
- Aging of the immune system – immunosenescence
- Interactions between inflammation and radiation response
- Individual immune variation vs individual radiation sensitivity

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Thank you for your attention