DE LA RECHERCHE À L'INDUSTRIE

RADIATION AND THE IMMUNE SYSTEM: NORM EFFECTS AND USE OF RADON TO TREAT CHRONIC DISEASES

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OUTLINE

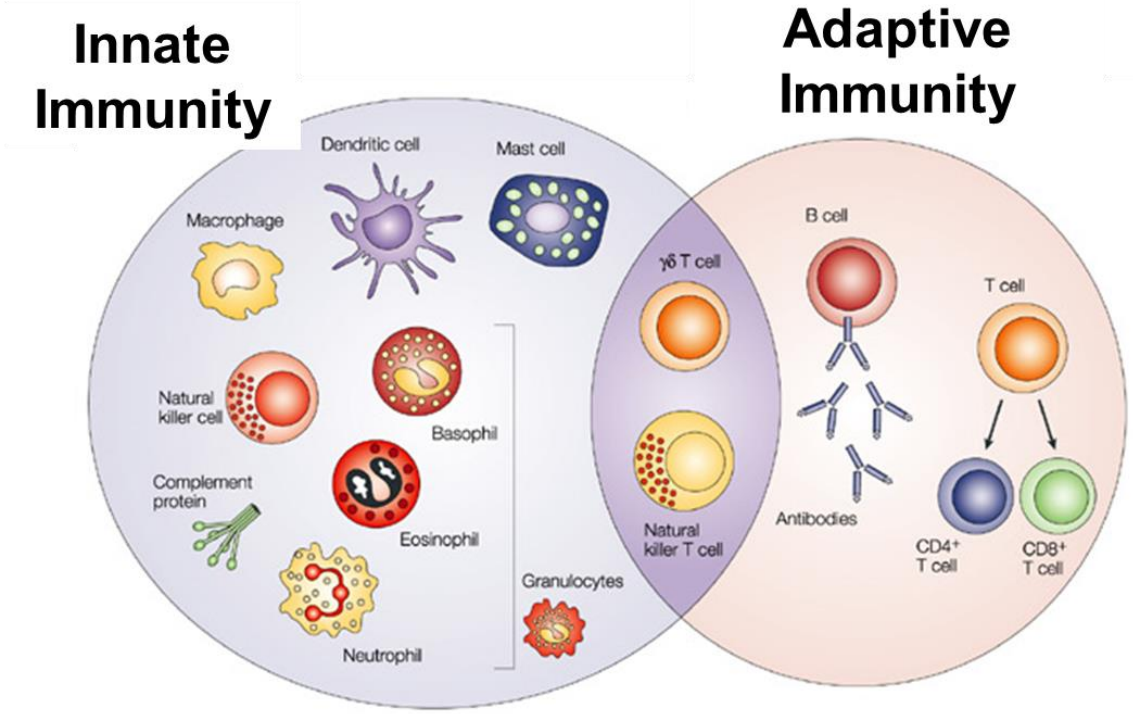
- Overview of the immune system

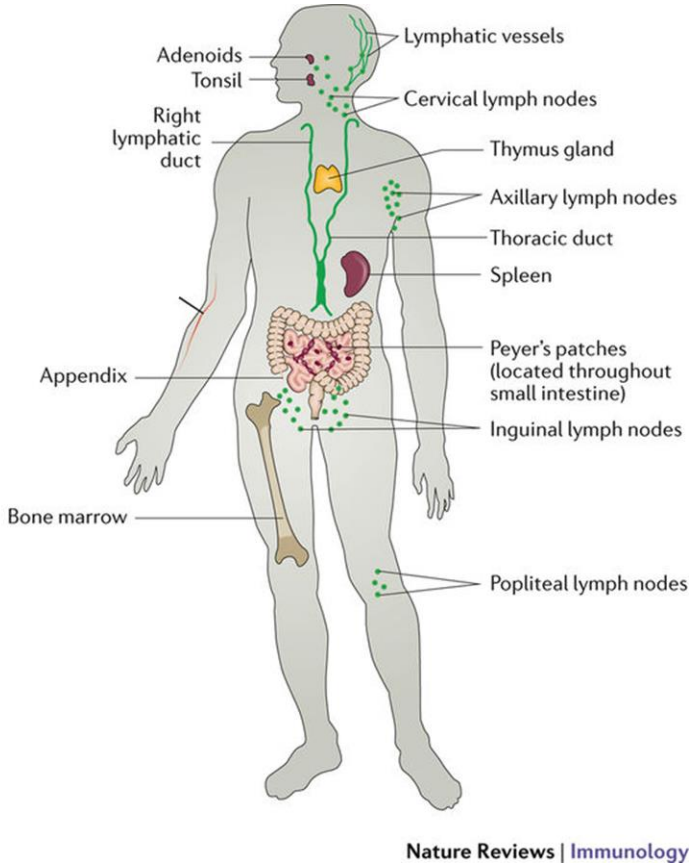
- The immune system in infectious diseases
- Immune system and Cancer

- The immune system in radiobiology

- Sterile inflammation - immunogenic cell death
- Radiotherapy - immunotherapy
- Effects of low-dose radiation on inflammation
- Immunomodulatory effects of radon therapy
- Tissue specific and inter-individual variations
- Effects of inflammation on the response to radiation

The immune system: a network of specialized cells in specialized structures



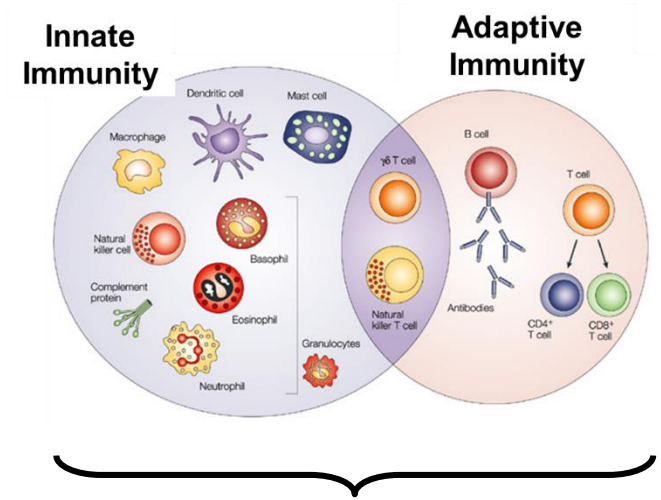


All these cells are generated from HSC
Most of them are found in blood

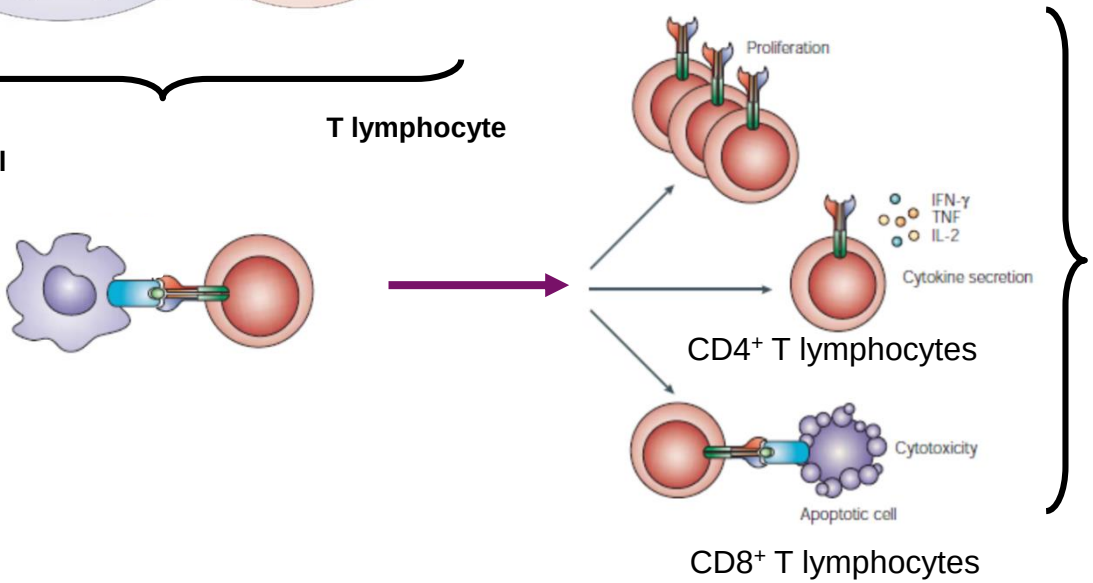
A systemic network, but with compatimentalization

Adapted from Dranoff, Nature Reviews Cancer, 2004

CELLULAR INTERACTIONS WITHIN THE IMMUNE SYSTEM

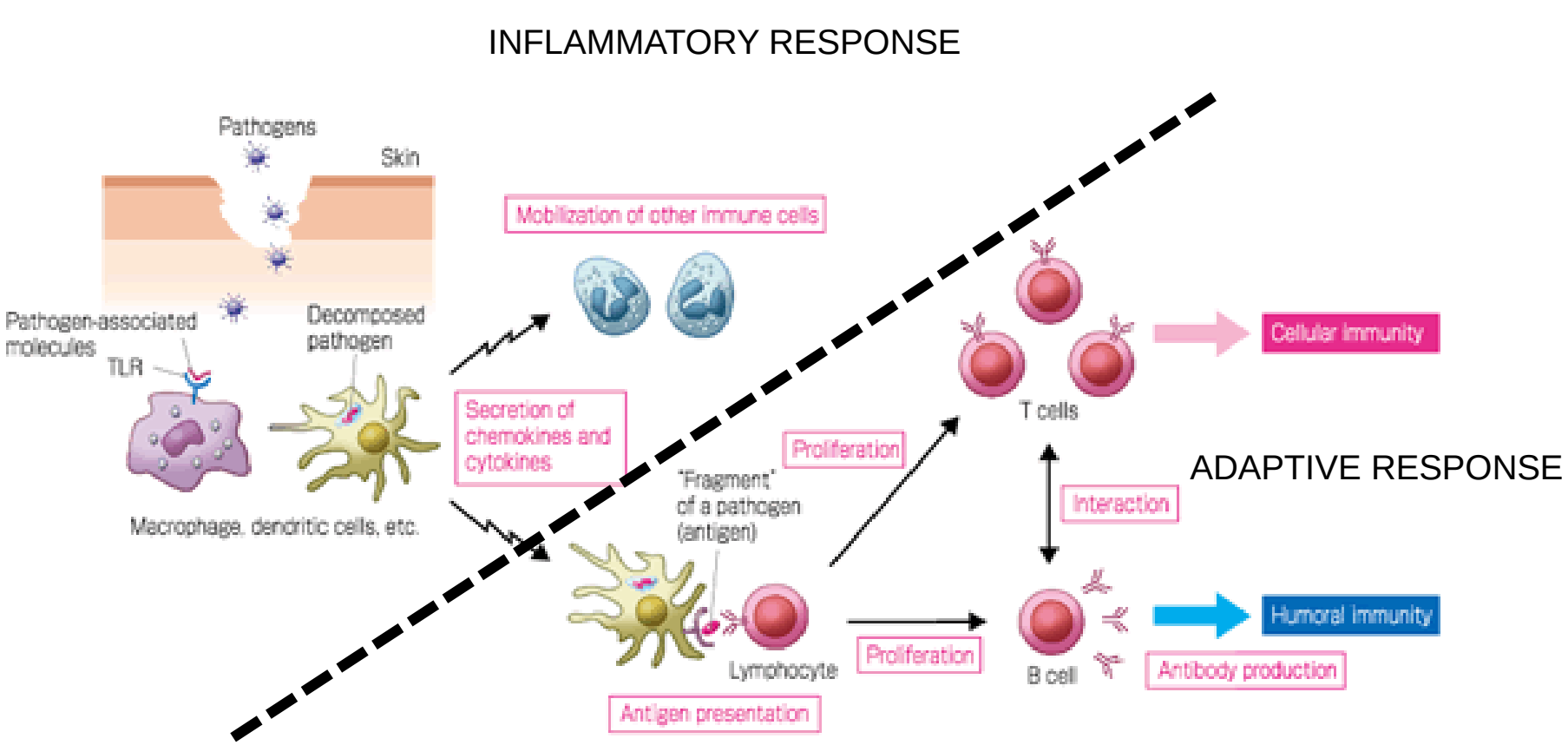


- A tight collaboration between myeloid cells and T lymphocytes is required to initiate an efficient immune response
- Functional maturation of immune cells during the immune response



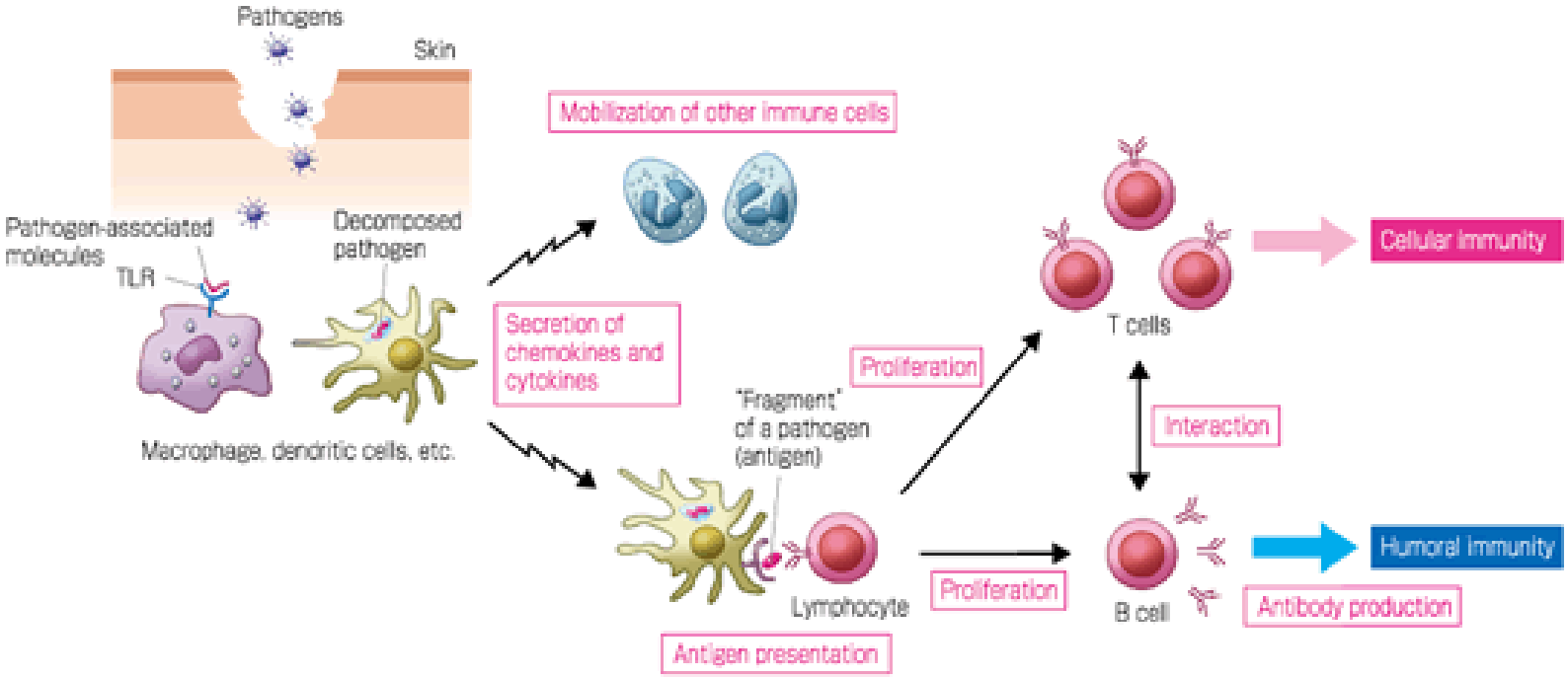
Dranoff, Nature Reviews Cancer, 2004

THE IMMUNE RESPONSE TO INFECTIOUS PATHOGEN: INFLAMMATION AND ADAPTIVE RESPONSE



Inflammation: broad specificity, immediately active, a lot of effector cells
Adaptive immunity: very narrow specificity, latence, few effector cells

THE IMMUNE RESPONSE TO INFECTIOUS PATHOGEN: INFLAMMATION AND ADAPTIVE RESPONSE

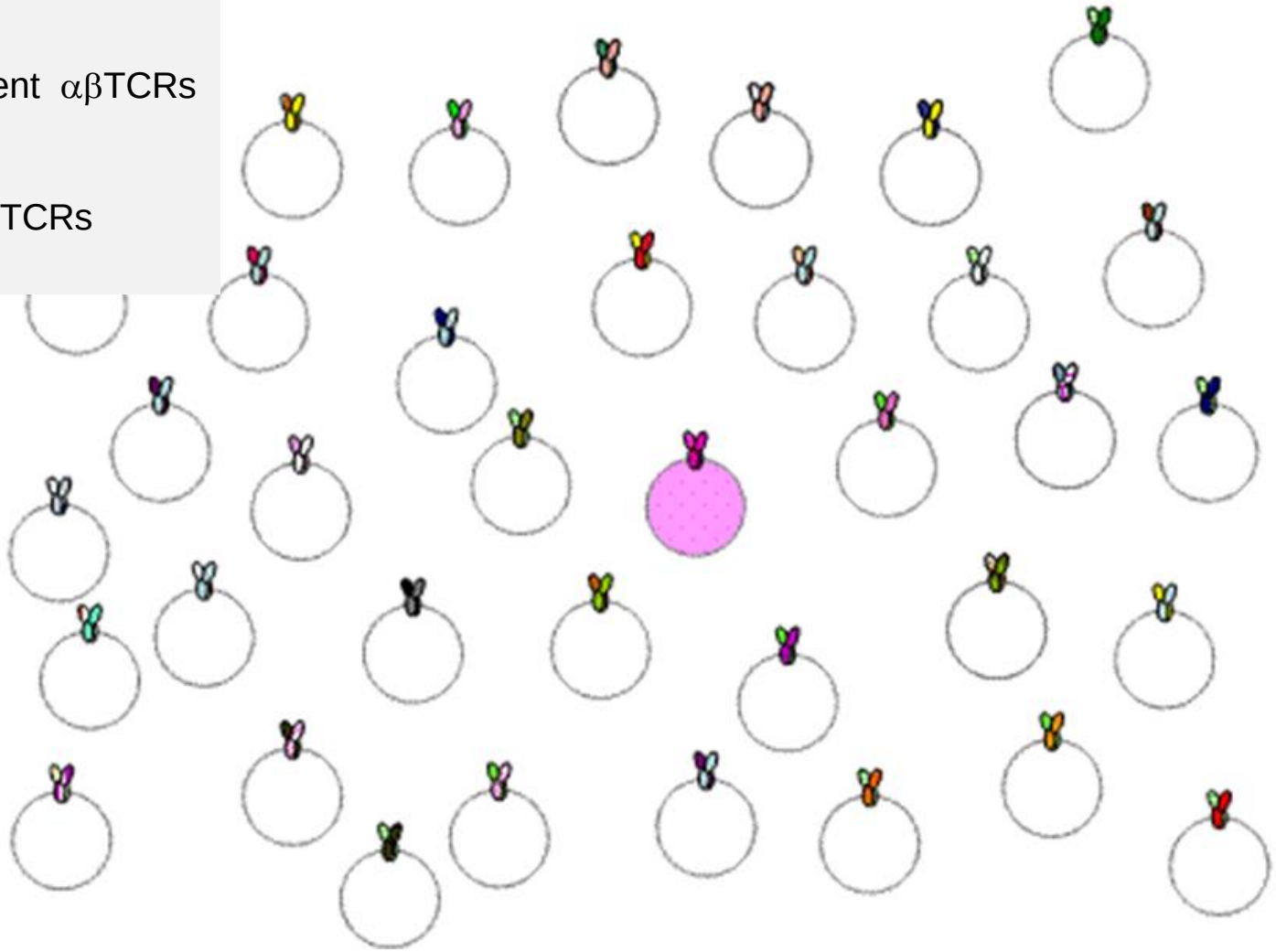


The immune response is initiated when TLRs (Toll Like Receptors) expressed by innate immune cells detect Pathogen Associated Molecular Patterns (PAMPs, LPS, flagelin, bacterial nucleic acids…).
It culminates with activation of antigen-specific T cells

A large and diverse repertoire of T lymphocytes in peripheral blood

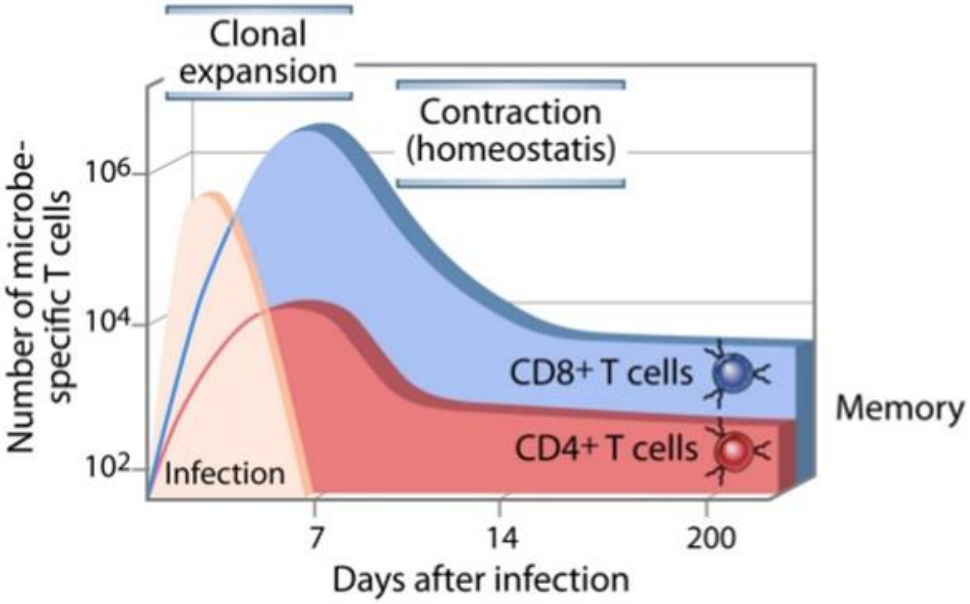
Human:
- 10^{11} T lymphocytes
- ~ 2.5 - 5 x 10^{7} different $\alpha\beta$TCRs

Mice:
- 10^{8} T lymphocytes
- ~ 2x 10^{6} different $\alpha\beta$TCRs



Same structure, different specificities, different sequences

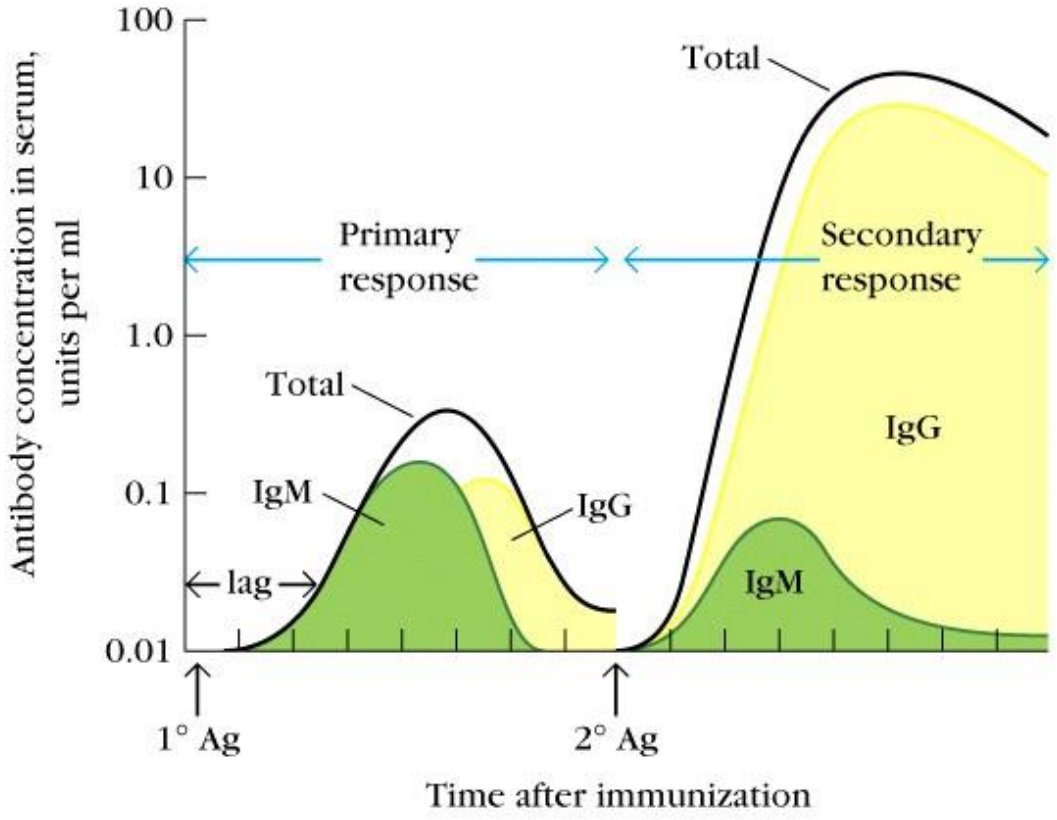
The peripheral T lymphocyte population is highly reactive and dynamic.



Recognition of their specific antigens induces expansion of T lymphocyte clones, followed by contraction (apoptosis) and differentiation of a fraction of the pool of amplified cells.

These changes are driven by their antigenic T cell receptor (TCR).

SECONDARY RESPONSES: VACCINATION



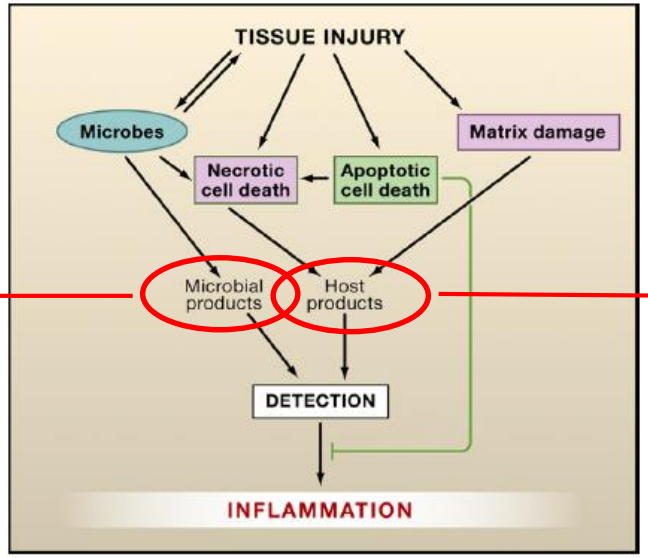
The secondary (recall) response to an antigen is qualitatively and quantitatively different

Inflammation: a response to tissue injury

Infectious inflammation

PAMPs
Pathogens Associated Molecular Patterns

LPS
Flagelin
Methylated DNA



Sterile inflammation

DAMPs
Damage Associated Molecular Patterns

Necrosis
Intracellular components
- Nuclear proteins
- Nucleosomes
- Un-maturedproteins

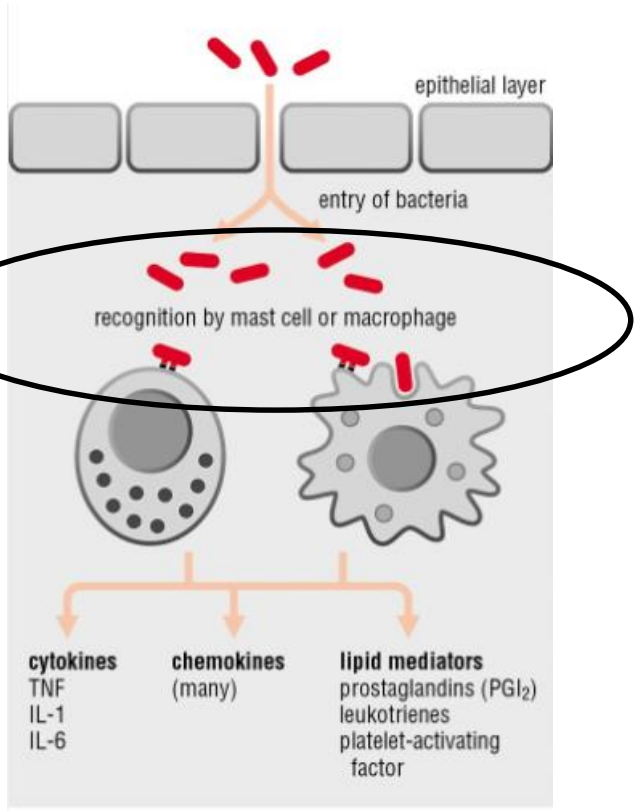
PAMPs and **DAMPs** are detected by **Pattern Recognition Receptors (PRRs),** including **Toll-like Receptors (TLRs)**

Elimination of micro-organisms
Elimination of damaged cells and cell debris

Tissue repair

Nathan and Ding, Cell, 2010

Infectious inflammation:
detection of pathogens - local production of soluble mediators

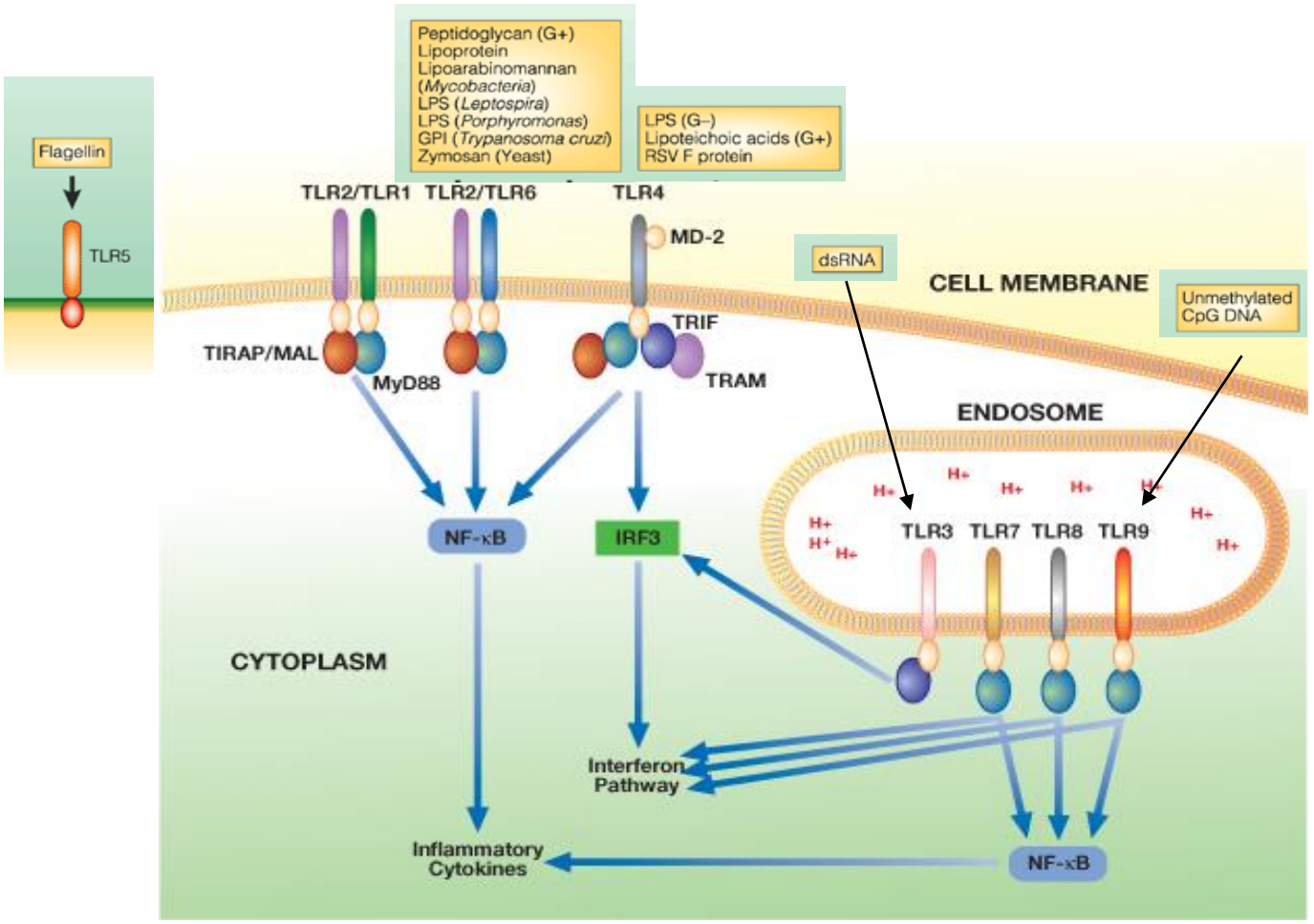


Sensing of pathogens or PAMPs by PRRs, including ***Toll-like receptors***

Production of various classes of soluble molecules:
chemokines, cytokines, lipid mediators.

From **Immunity: The Immune Response in Infectious and Inflammatory Disease**
by DeFranco, Locksley and Robertson

Toll-like receptors (TLRs) sense invading pathogens

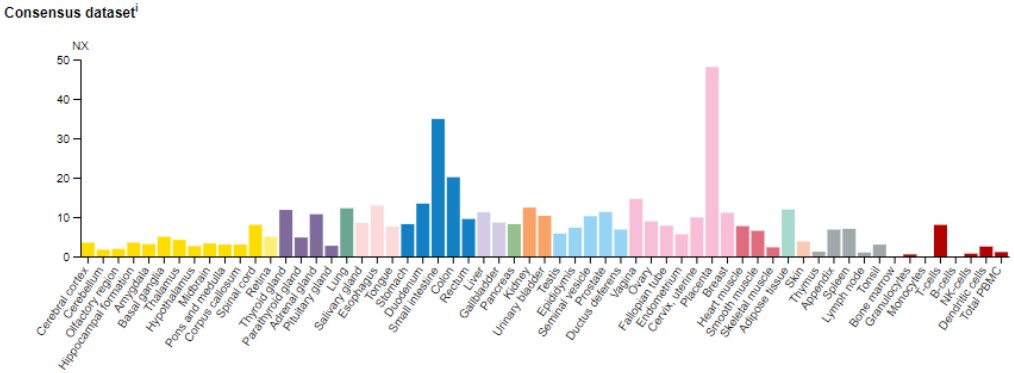


TLR signaling results in cell activation and the production of inflammatory mediators. TLRs belong to the Pattern Recognition Receptors (PRR) family

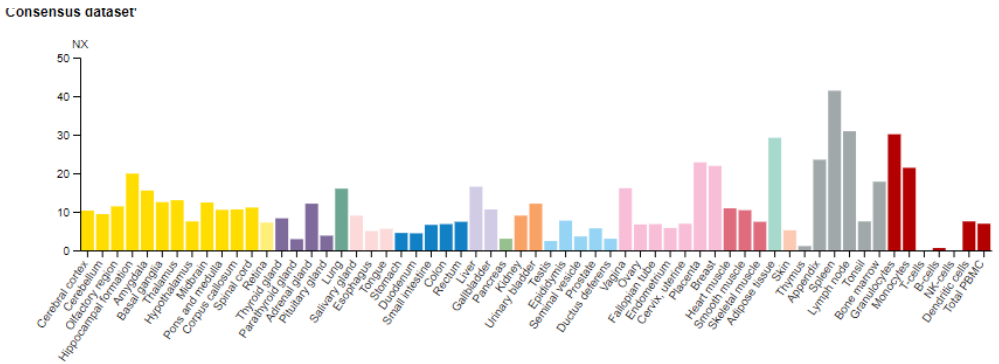
Adapted from http://www.iavireport.org/Back-Issues/Pages/IAVI-Report-9(4)-TollBridgetoImmunity.aspx

TLRs expression in cells and tissues

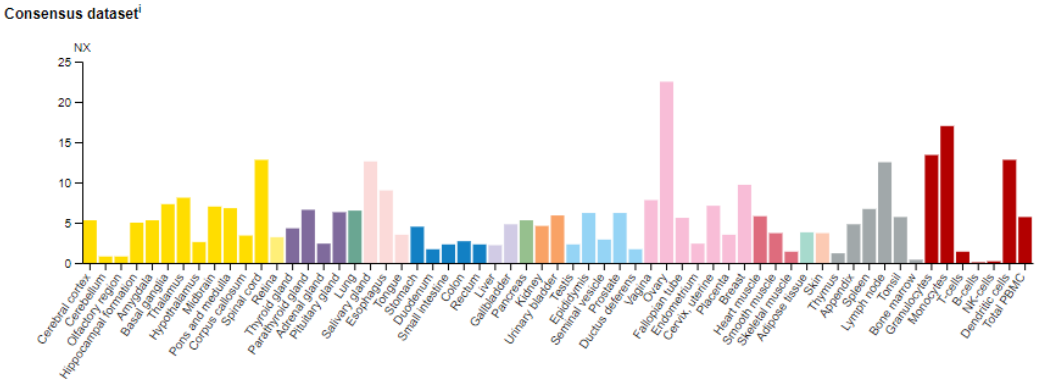
TLR3



TLR4

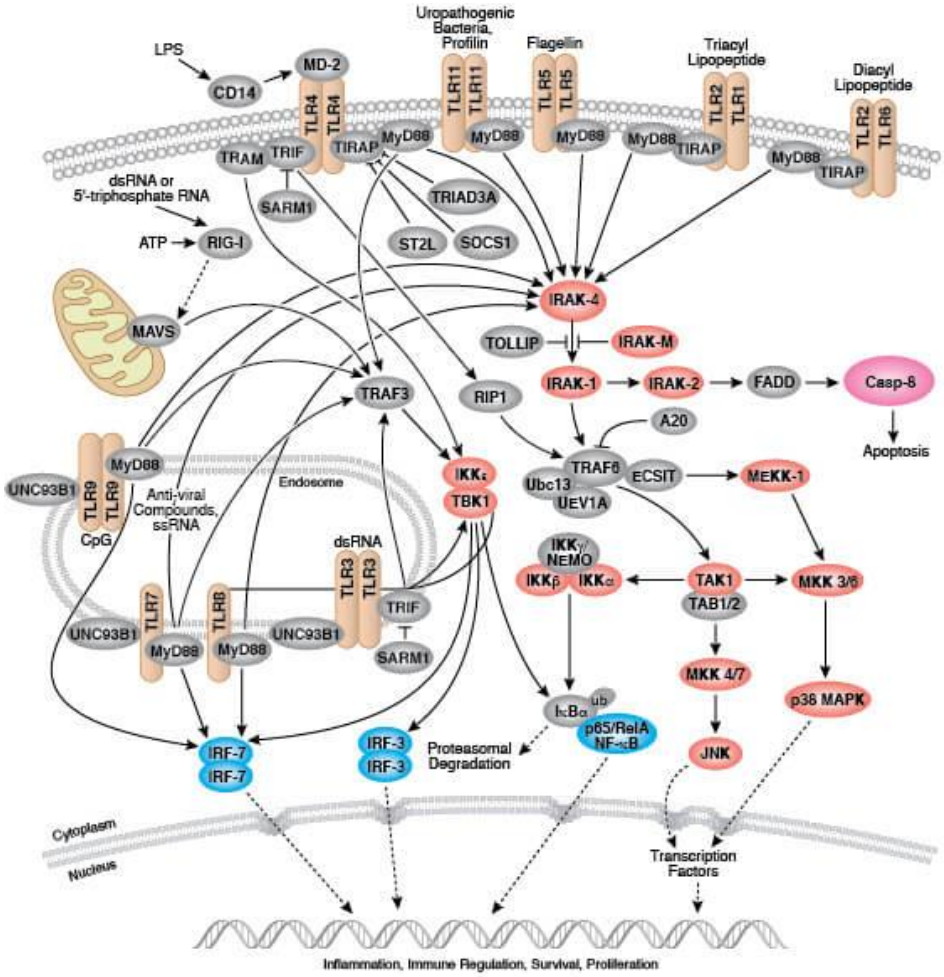


TLR5



The Human Protein Atlas

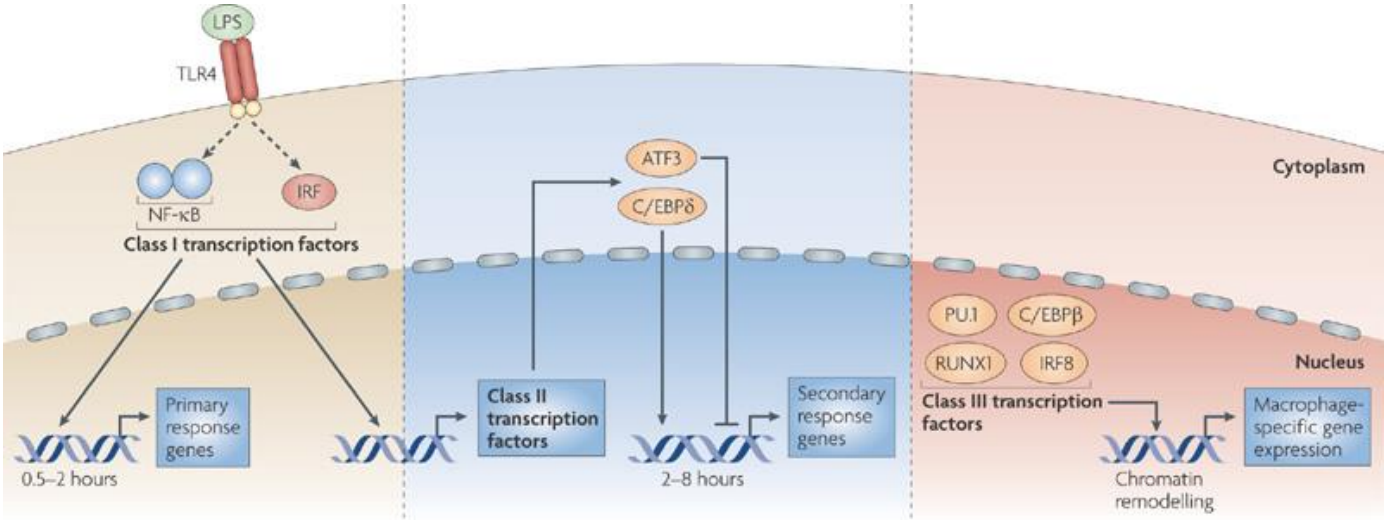
TLR signaling pathways



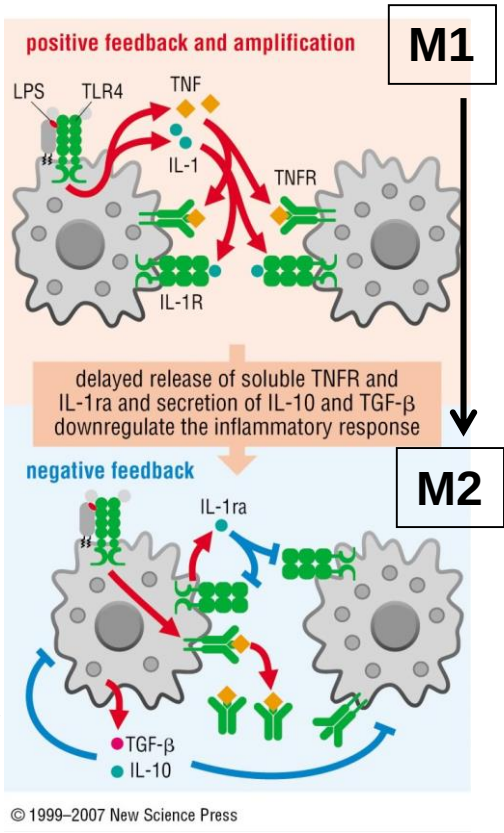
Different effects in different cell types according to their expression of the different TLRs and of their signaling pathways

https://www.cellsignal.com/

Transcriptional control of cytokine production during the inflammatory reaction



Medzhitov and Horng, Nature Rev. Immunol. 2009

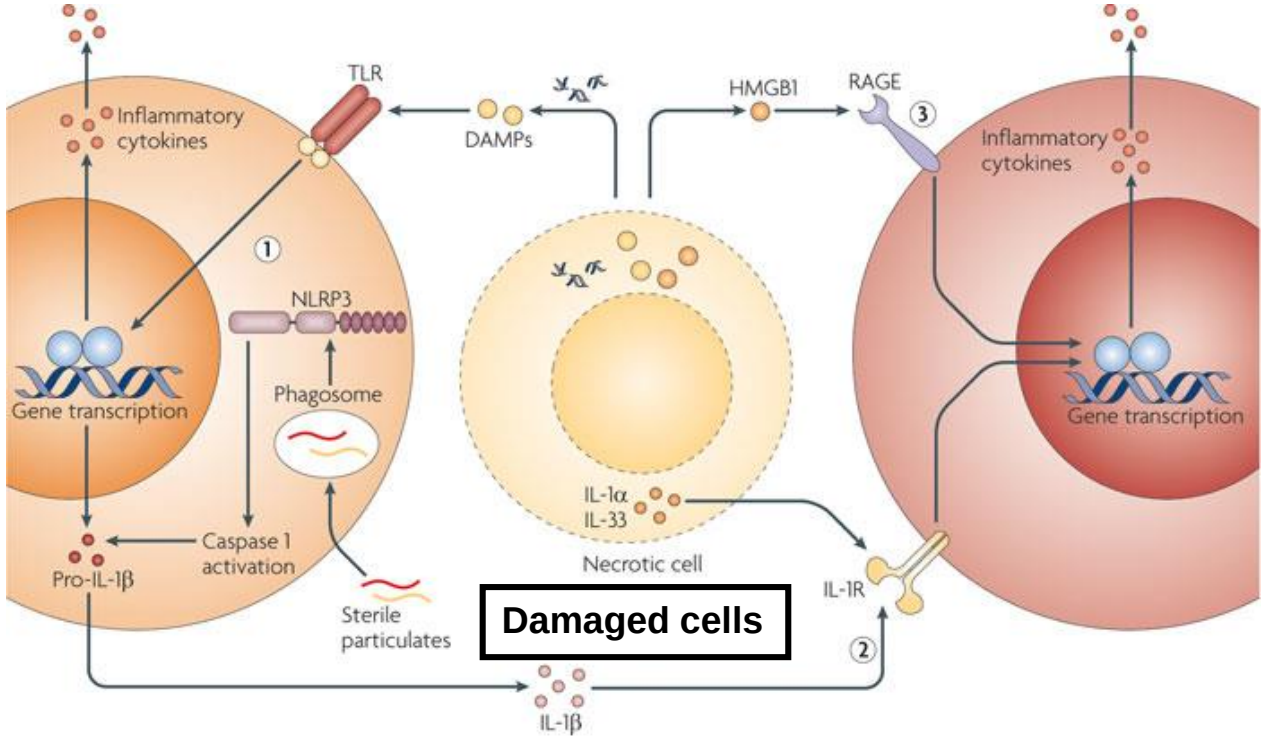


Sequential functional phenotypic changes, from pro-inflammatory to anti-inflammatory

Depends on the **cell type and the microenvironment**: localization, TLR ligands, cytokines, inflammatory mediators…….

From **Immunity: The Immune Response in Infectious and Inflammatory Disease** by DeFranco, Locksley and Robertson

Sterile inflammation

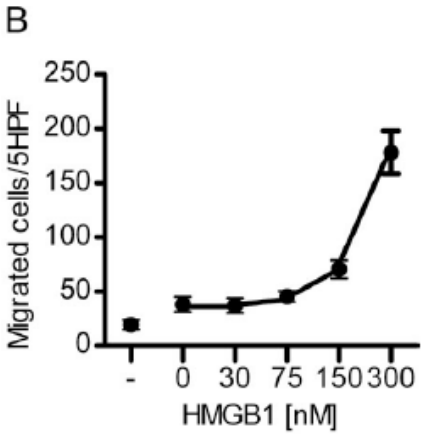


Necrotic and stressed/damaged cells, exposed to **non-infectious** physical trauma (UV radiation, **ionizing radiation**, heat, particles), release intracellular molecules that act as “danger signals” to signal the presence of tissue injury.

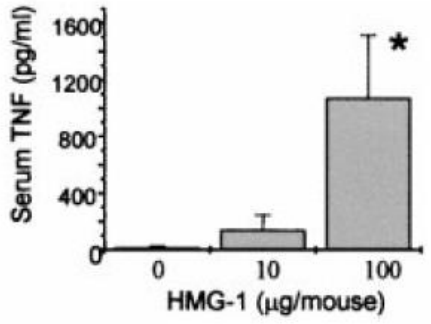
These **Damage-Associated Molecular Patterns** (**DAMPs**) induce an **inflammatory response** aimed at eliminating the effects of injury and restoring tissue homeostasis.

Chen and Nunez, Nature Rev. Immunol., 2010

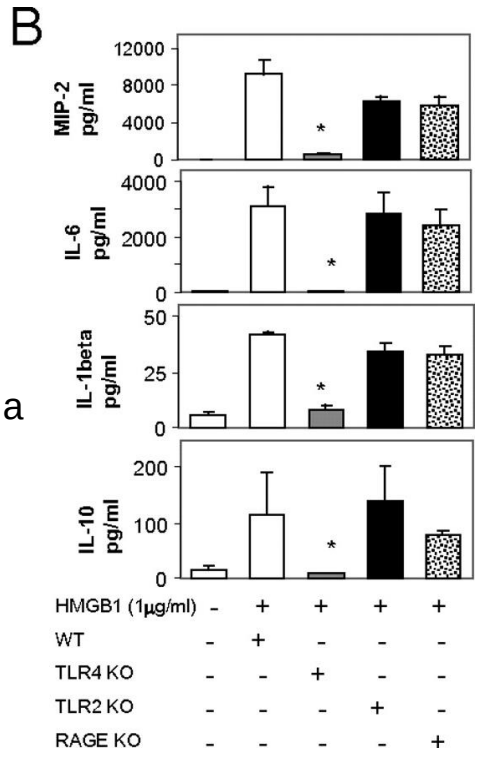
HMGB1 : a DAMP with chemotactic activity induces inflammatory cytokine expression through TLR4



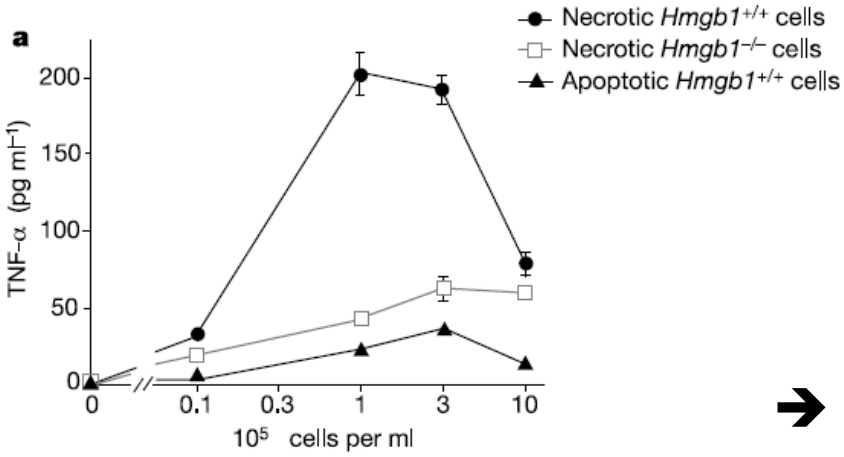
HMGB1 potentiates CXC12 chemotactic activity on human monocytes



Injection of purified HMGB1 induces a strong increase in circulating TNFα



TLR4 is required for HMGB1 signaling on murine macrophages.



HMGB1 released from ***necrotic*** cells activates human monocytes

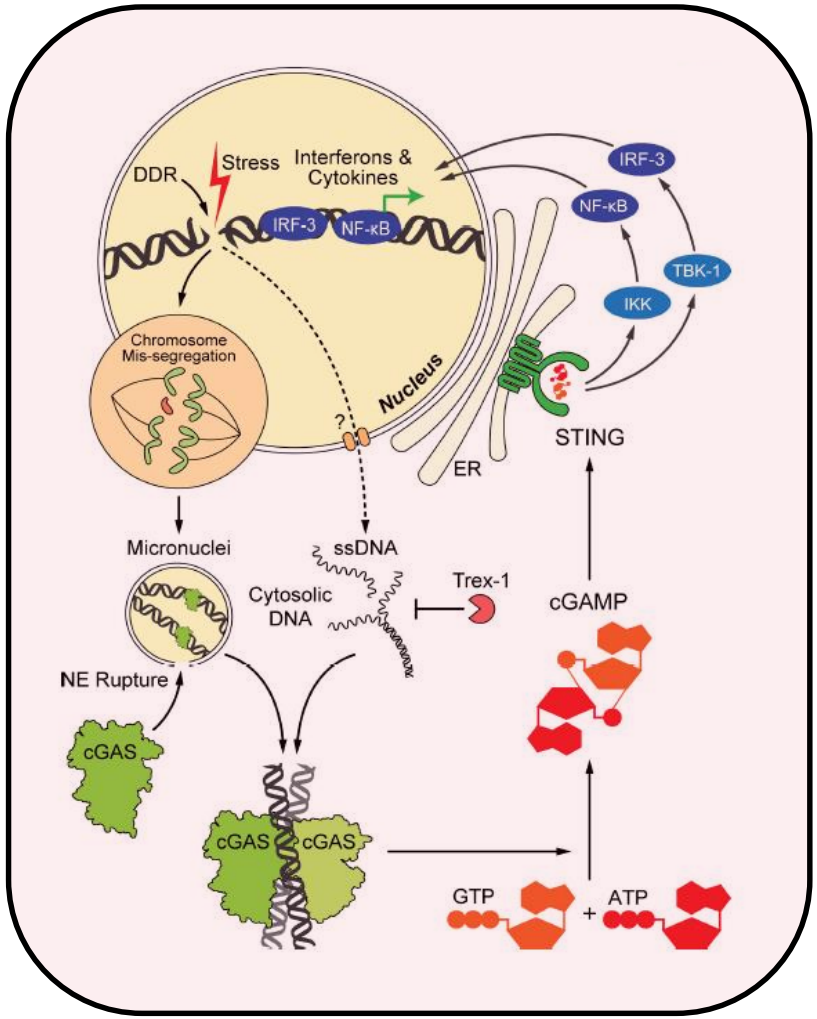
➔

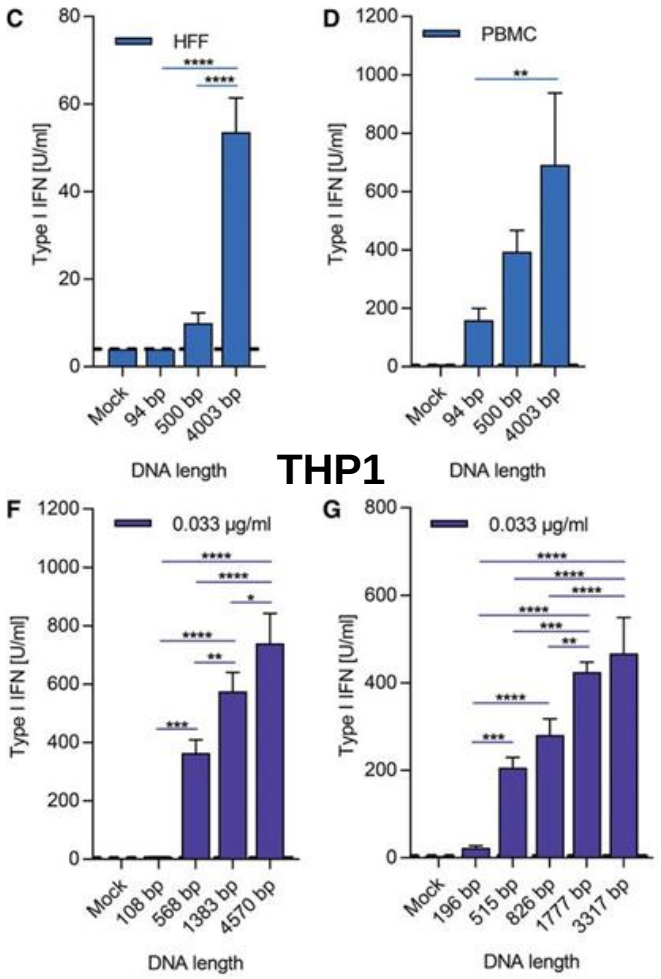
HMGB1 can mobilize and activate myeloid cells at the site of injury

Andersson U et al. J Exp Med 2000
Yang H et al. PNAS 2010
Schiraldi M et al. J Exp Med 2012
Scaffidi P et al. Nature 2002

Nucleic acids as DAMPs: DNA / Chromatin

The cGAS-STING pathway senses cytoplasmic DNA





Cytoplasmic DNA is seen as a danger signal by several sensors and induces the secretion of type I interferons

From Luecke S. et al., EMBO reports 2017

Cytokine secretion following nucleic acids sensing

Different DNA sensors collaborate for IL-1β production

RAD50

↓

NF-kB activation

↓

pro-IL-1β expression

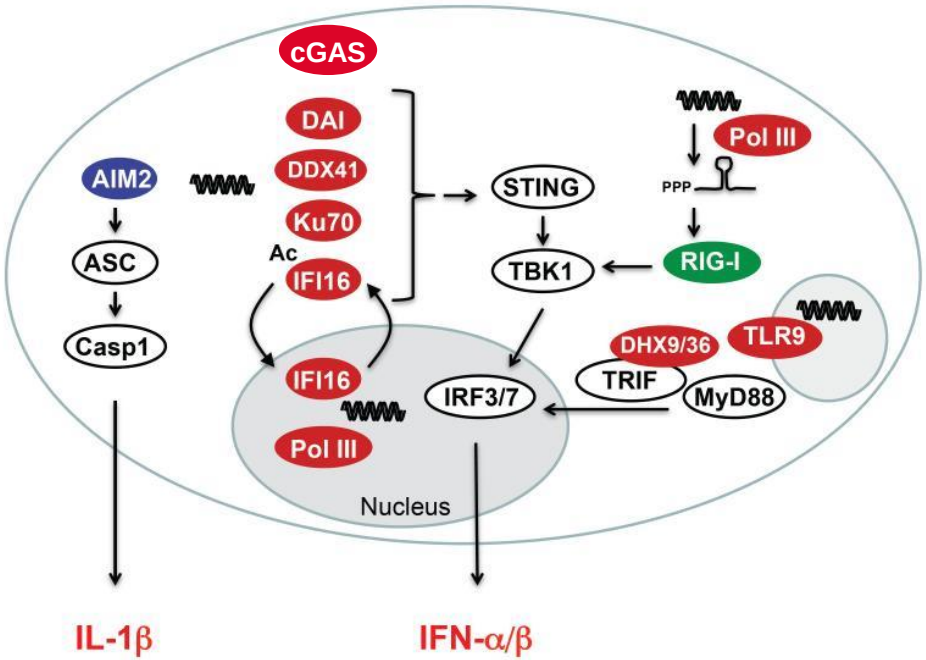
AIM2

↓

inflammasome activation

IL-1β maturation and secretion

DNA and RNA induce the secretion of interferons



Chatzinikolaou G et al. Trends in Immunology, 2014
Roth S et al. Nature Immunol. 2014

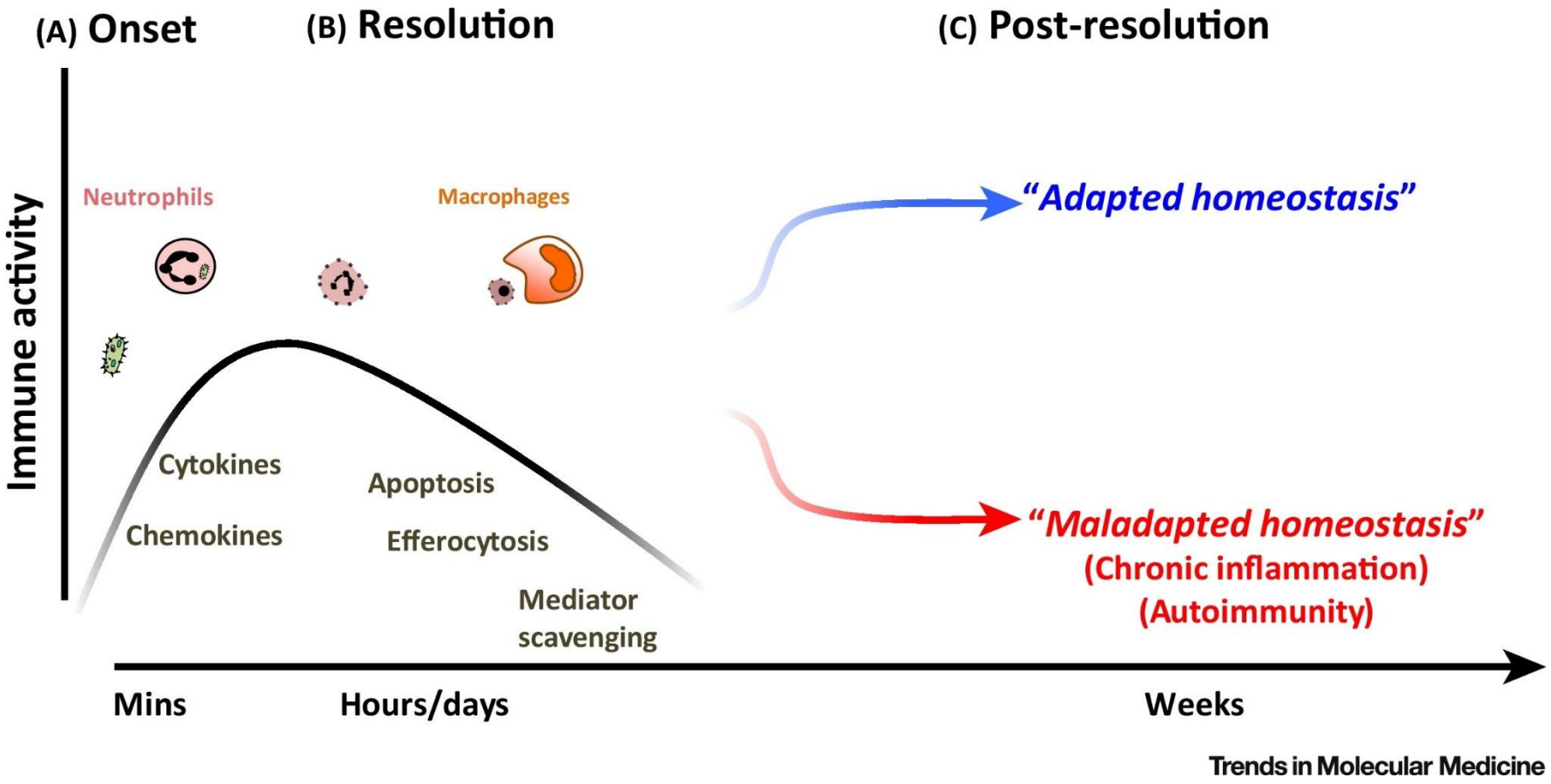
Table 1. Endogenous ligands of TLRs[a]

Endogenous stimulus		TLRs involved	Cellular responses triggered	Refs
Category or identity	**Other functions**			
HSPs: HSP60, HSP70, GP96	Numerous, including protein folding, assembly of protein complexes, stress responses	TLR4 (HSP60) TLR2/4 (HSP70, GP96)	NF-κB activation, DC maturation, cytokine synthesis	[14,15,17,18]
Hyaluronan	Extracellular matrix component	TLR4	NF-κB activation, DC maturation, cytokine synthesis	[16]
Lung surfactant protein-A	Pulmonary surfactant	TLR4	NF-κB activation, cytokine synthesis	[19]
Necrotic cells	Not applicable	TLR2[b]	NF-κB activation, induction of inflammatory and tissue repair genes, DC maturation	[13,22–24]
HMGB1	Chromatin binding	Not determined[c]	Inflammation	[31]
Chromatin–IgG complexes	Multiple	TLR9	B-cell activation	[42]
Others: fibronectin, fibrinogen, heparan	Multiple	TLR4	Inflammatory-gene induction, DC maturation	[43–45]

[a]Abbreviations: DC, dendritic cell; HMGB1, high mobility group 1; HSP, heat-shock protein; TLR, Toll-like receptor.
[b][13]
[c]It is not known whether HMGB1 functions through TLRs or a different pathway.

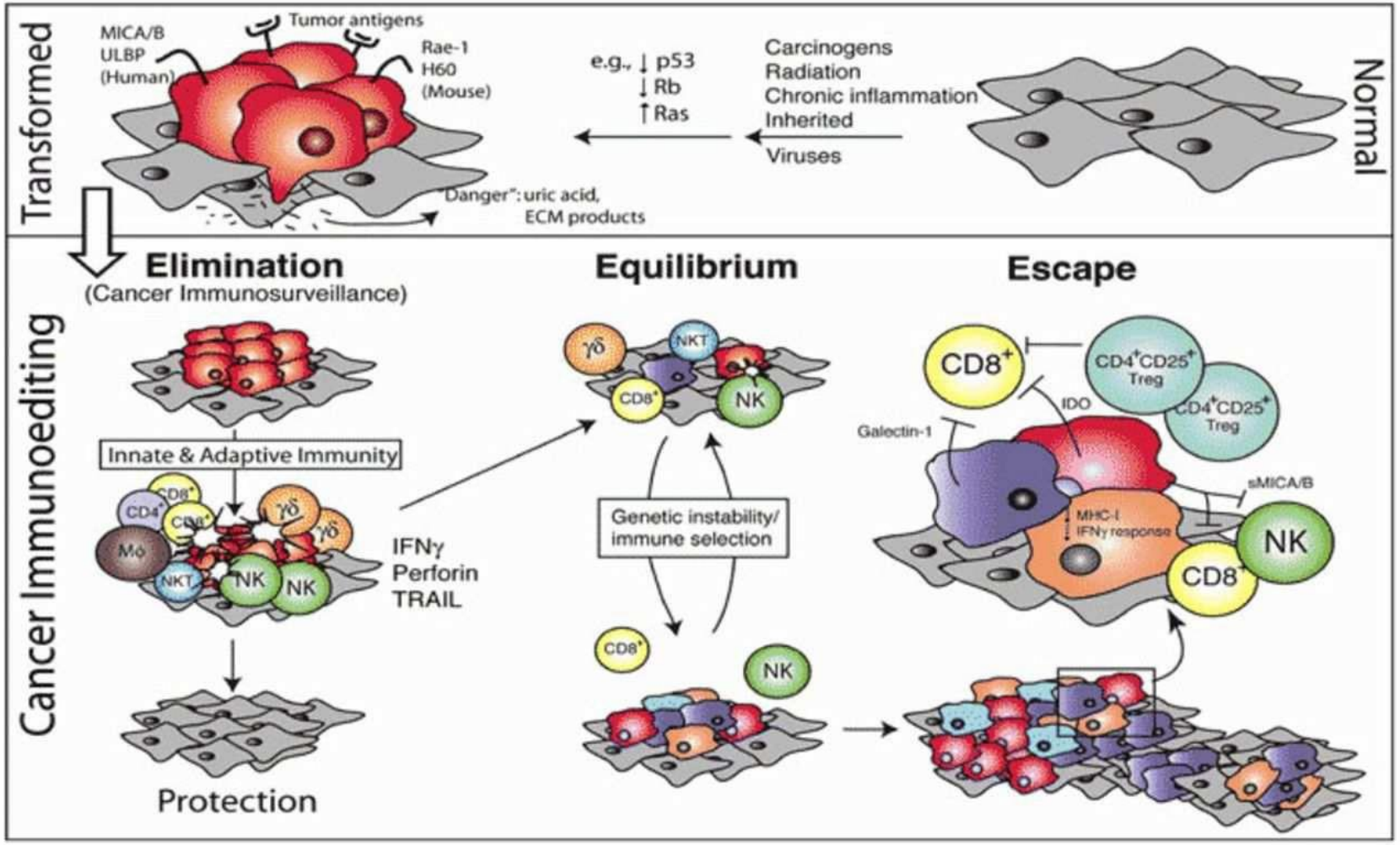
Beg, Trends in Immunology, 2002

Inflammation resolution is an *active* process



Feehan and Gilroy, 2019

The three Es of cancer immunoediting: Role of the immune system in cancer prevention and development.

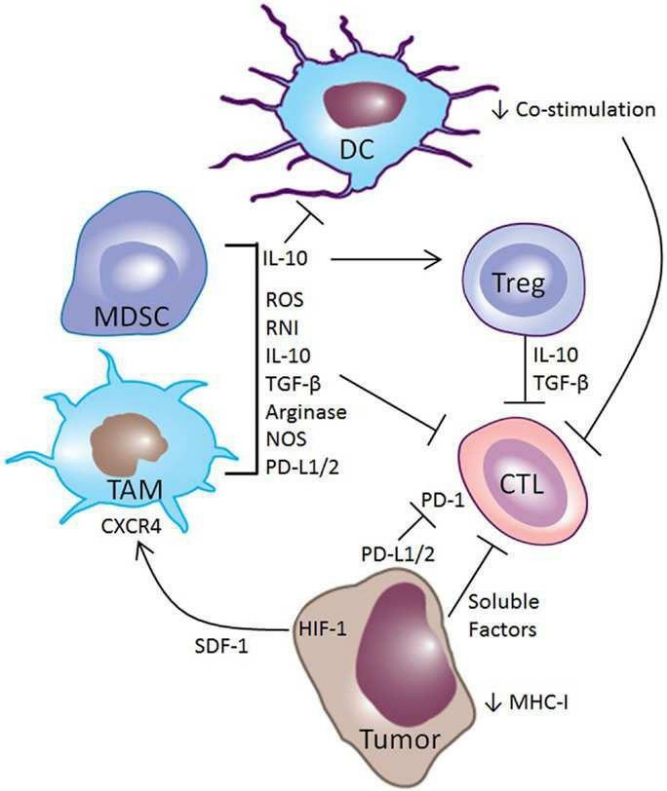


Cancer immunosurveillance: host protective vs tumour sculpting actions of immunity

Schreiber, Cancer Immun 2005

Tumours escape immunosurveillance by promoting an *immuno-suppressive* environment

Tumours use multiple mechanisms for avoiding immune detection



MDSC: myeloid-derived suppressor cells; TAM: tumour-associated macrophages, CTL: CD8+ cytotoxic T lymphocytes; DC: dendritic cells; Treg: regulatory T cells

•***Hiding from CTL killing:*** down-regulation expression of MHC-I makes them poor targets for CTL mediated killing.

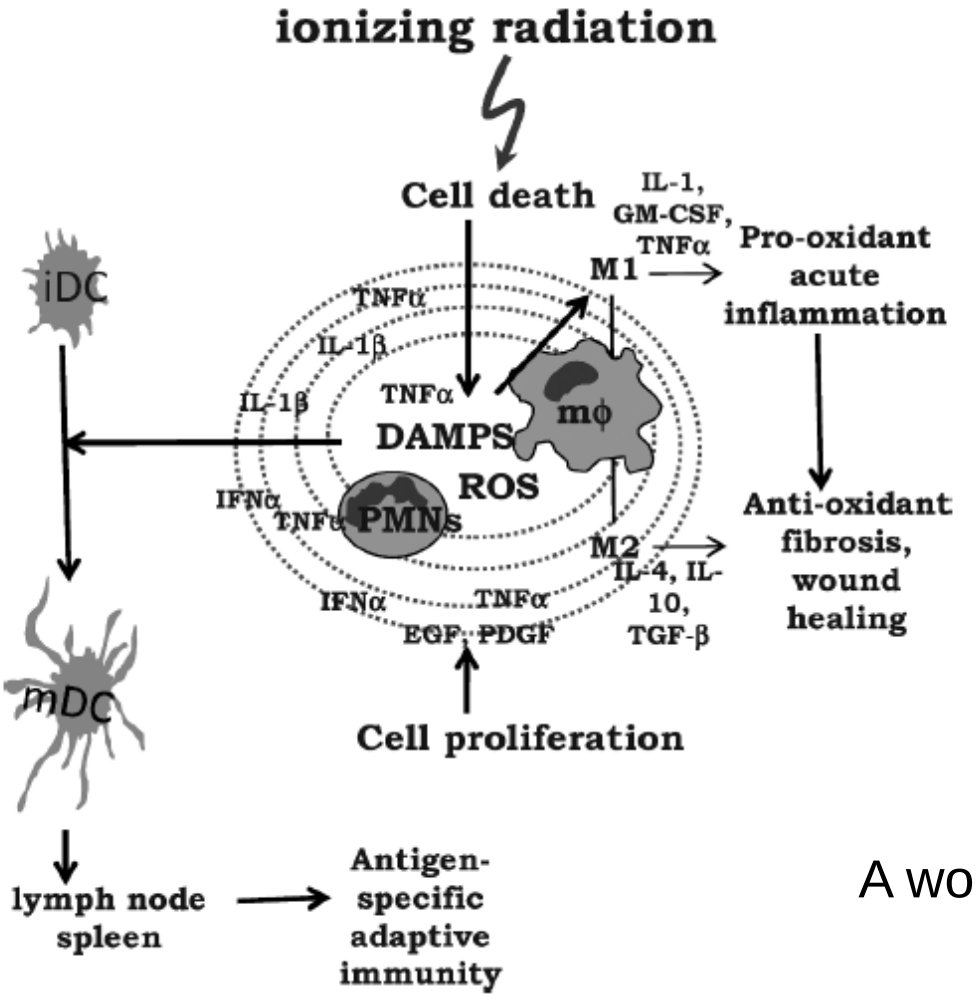
•***Protection from CTL killing***: expression of PD-L1 and PD-L2, which inhibit CTL function through the PD-1 receptor.

•***Recruitment of « protector » cells***:

- SDF-1 acts as a chemokine to attract MDSCs and TAMs to the tumour microenvironment through the receptor CXCR4.
- MDSCs and TAMs secrete cytokines such as IL-10 that promote a regulatory phenotype among intratumoural DCs, induce Tregs, and directly inhibit CTLs.
- MDSCs and TAMs also inhibit CTL activity by production of TGF-β, reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI), and arginase and nitric oxide synthase (NOS).

Vatner et al., Frontiers in Oncology, 2014

Radiation can activate adaptive immune responses

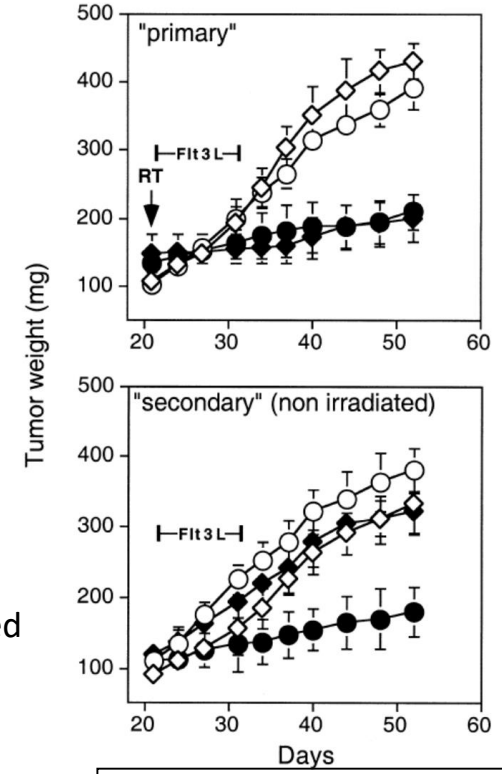


A working model for radiotherapy

Schaue and McBride, Rad. Research, 2010

Cooperation of the innate and adaptive immune system in RT-induced anti-tumor responses

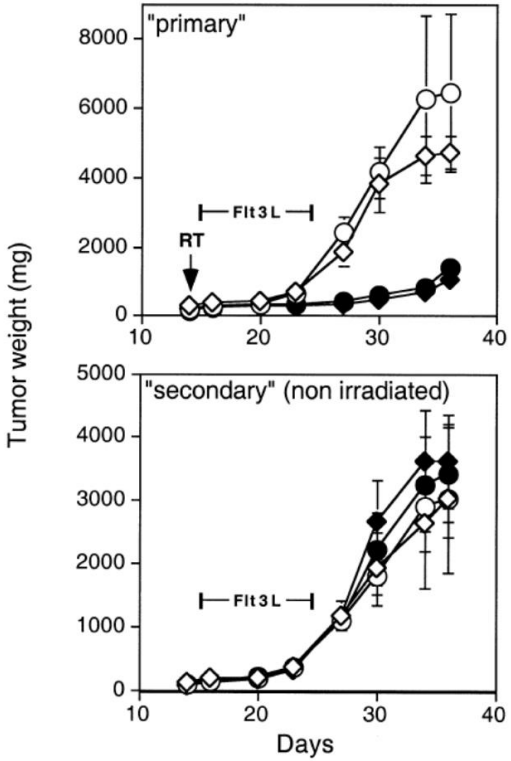
Immunocompetent mice



Abscopal effect

Athymic Nude mice

No T lymphocytes



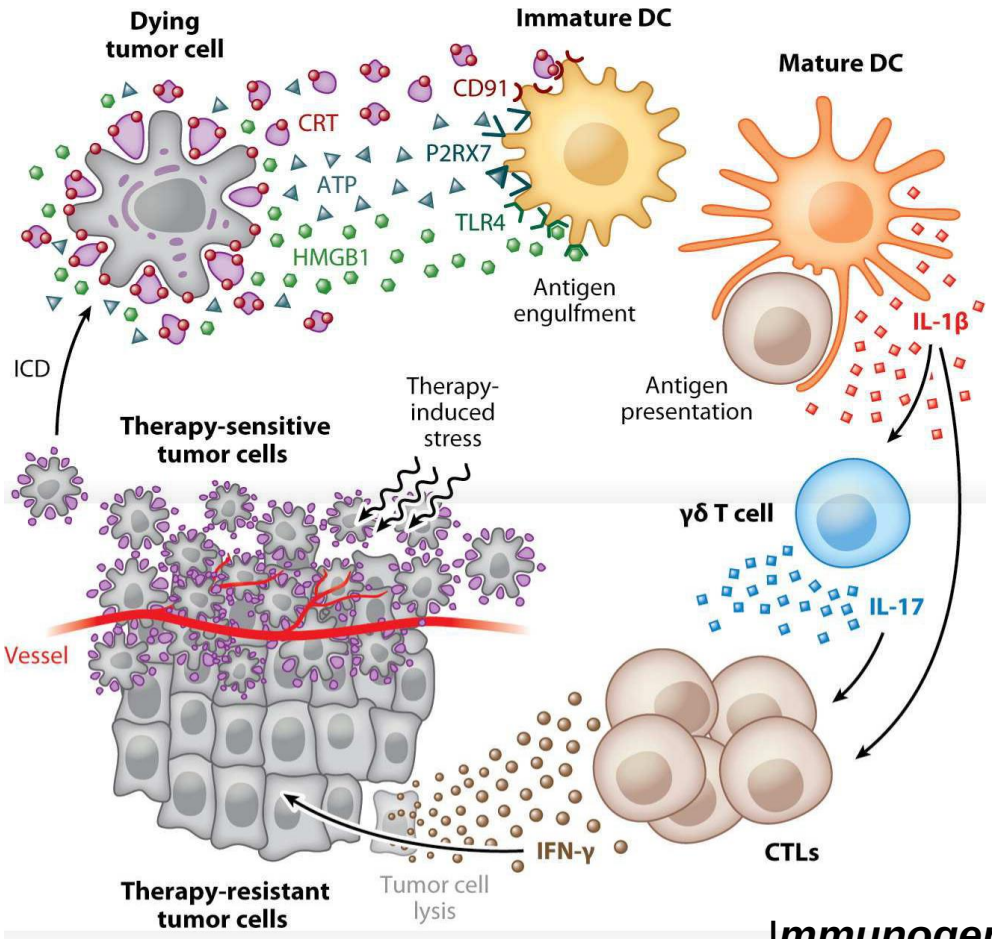
No abscopal effect

Empty diamond: untreated
Filled diamond: 2 Gy
Empty circle: Flt3 alone
Filled circle: Flt3 + 2 gy

Tumor cells engraftment on both flanks
RT treatment on only one flank, with or without injection of a growth factor for dendritic cells
Effect on secondary tumor (non-irradiated flank) only if dendritic cells are stimulated and T lymphocytes are present

Demaria, IJROBP, 2004

Induction of immunogenic cell death (ICD) promotes cancer elimination



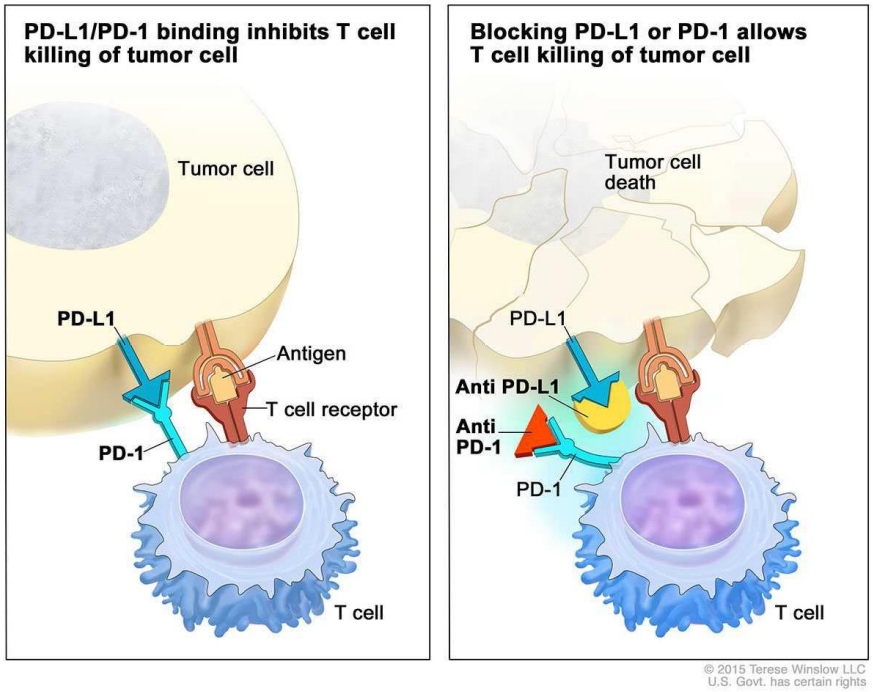
- Dying cancer cells expose calreticulin (CRT) on their plasma membrane at a preapoptotic stage, and secrete ATP during apoptosis.
- Cells undergoing ICD release the nuclear protein ***HMGB1*** as their membranes become permeabilized during necrosis.
- CRT, ATP, and HMGB1 bind to **CD91**, **P2RX7**, and ***TLR4***, and ***cooperatively*** promotes the recruitment of DCs into the tumour bed (stimulated by ATP), the engulfment of tumour antigens by DCs (stimulated by CRT), and optimal antigen presentation to T cells (stimulated by HMGB1).
- These processes result in a potent IL-1β- and IL-17-dependent, IFN-γ-mediated immune response involving both γδT cells and CTLs, which eventually can lead to the eradication of chemotherapy-resistant tumour cells.

I***mmunogenic cell death*** induces dendritic cells maturation to favor the activation of tumor-specific cytotoxic T lymphocytes.

ATP, adenosine triphosphate; CRT, calreticulin; CTL, cytotoxic CD8+ T lymphocyte; DC, dendritic cell; HMGB1, high-mobility group box 1; IFN, interferon; IL, interleukin; TLR, Toll-like receptor.

Kroemer et al, Ann. Rev. Immunol. 2013

IMMUNOTHERAPY: RELIEVING IMMUNE CHECKPOINTS TO INCREASE TUMOUR IMMUNOGENICITY



- The PD-1/PD-L1 checkpoint prevents killing of tumor cells by restraining the activation of tumor specific CTLs
- Drugs like Pembrolizumab targets PD-1 to inactivate this checkpoint.
- A combination of anti PD-1 and radiotherapy is more efficient than radiotherapy alone
- The development of an immune response against tumor antigens may promote systemic, long term « vaccination » that prevents the onset of metastasis in distant sites

Irradiation and anti–PD-L1 treatment synergistically promote antitumor immunity in mice

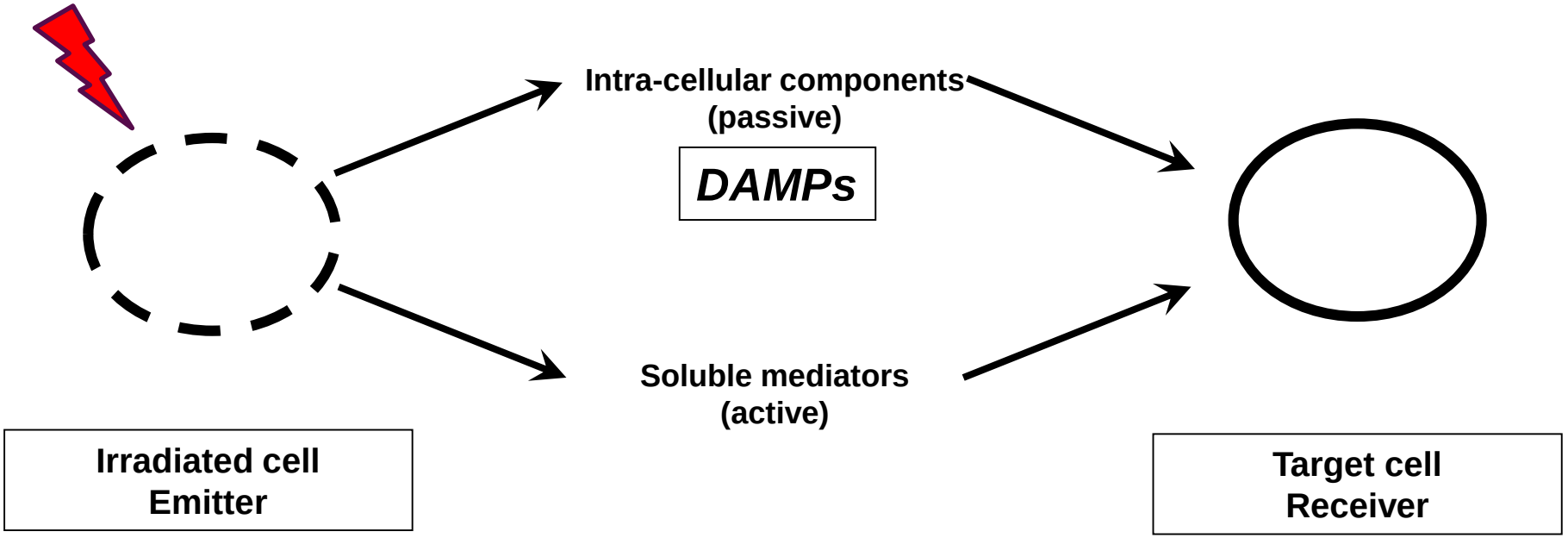
Liufu Deng,[1] Hua Liang,[1] Byron Burnette,[1] Michael Beckett,[1] Thomas Darga,[1] Ralph R. Weichselbaum,[1] and Yang-Xin Fu[2]

Combined Radiotherapy and Anti–PD-L1 Antibody Synergistically Enhances Antitumor Effect in Non–Small Cell Lung Cancer - *Xiaomei Gong, et al*.

The prevention of PD1/PD-L1 interactions increases RT efficiency

NCI, https://www.cancer.gov
J. Clin. Invest., 2014
J. Thor. Oncol., 2017

Irradiated cells communicate with other cells
bystander signaling



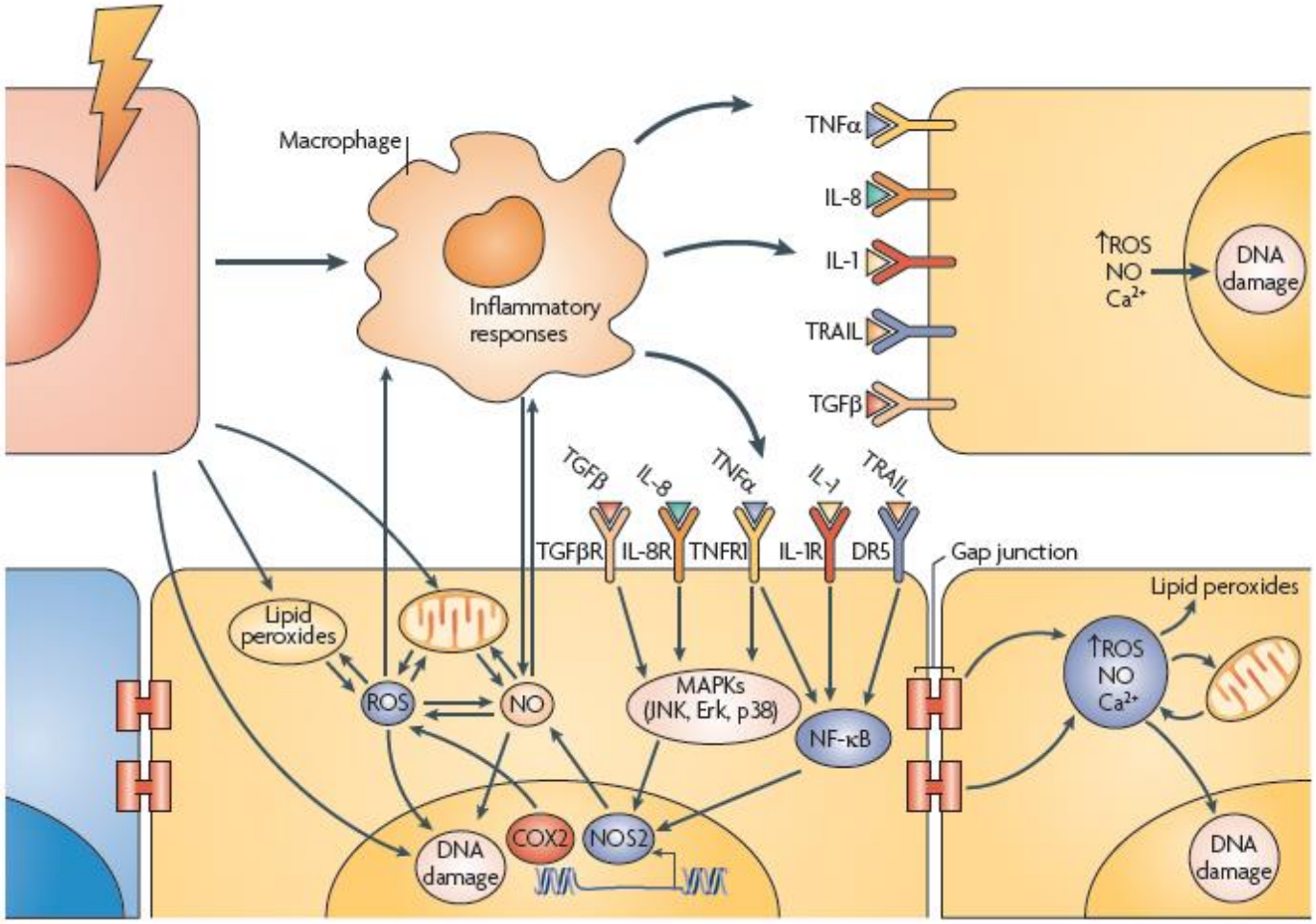
Tumour cell
Normal cell
Immune cell

Immune cell

Immune cells integrate radiation-induced signals to coordinate the response

Key pathways affecting bystander signal

Oxidative stress and cytokines are important mediators of bystander signaling
These signals are integrated and relayed by macrophages



A graphical summary of data obtained in many different systems

Prise and O'Sullivan, 2009

Immune modulatory properties of ionizing radiation: clinical point of view

RADIOTHERAPY

“Low” dose

Single dose:

< 1.0 Gy

Total dose:

< 12.0 Gy

Therapy of inflammatory and degenerative diseases

Anti-inflammatory effects

“High” dose

Single dose:

> 1.0 Gy (1.8 - 2 Gy)

Total dose:

> 30.0 Gy

Therapy of malignant diseases

Inflammatory effects

Clinical application of “low-dose” radiation therapy

Low dose Radiotherapy has been used for the treatment of benign chronic inflammatory diseases for several decades.

More than 50.000 patients are treated each year in Germany

First author	Disease	Number of patients	Main findings	Reference
Micke *et al.*	Painful heel spur syndrome (plantar fasciitis)	7947	Pain reduction for at least 3 months in 70%, persistent pain reduction in 65% of the patients. No radiogenic acute or chronic side effects.	[112]
Mücke *et al.*	Painful/refractory Gonarthrosis	502	Significant prognostic factors for pain relief are a single treatment series, age >58 years and high voltage photons.	[120]
Heyd *et al.*	Painful heel spur syndrome	130	RT is an effective treatment option, irrespective of treatment with a total dose of 3 Gy (single 0.5) or 6 Gy (single 1 Gy).	[121]
Niewald *et al.*	Periarthritis of the shoulder	141	Pain relief and improvement of motility was 69% and 89%, respectively, after 4.5 months (median) and 73% after 3.9 years with virtually no side effects.	[113]
Betz *et al.*	Early-stage Dupuytren's contracture	135	RT is effective in prevention of disease progression (59-87%) in a follow up of 13 years. RT improves patient's symptoms in early-stages with minor late toxicity.	[115]
Mücke *et al.*	Painful/refractory Gonarthrosis	4544/year	Median pain reduction for at least 3 months in 60%, at least 12 months in 40% of the patients.	[117]
Heyd *et al.*	Plantar fibromatosis (Morbus Ledderhose)	24	Complete remission of cords or nodules in 33%, reduced number in 54% and unchanged in 12.1% of the patients. Pain relief was achieved in 68.4% of the patients.	[122]
Adamietz *et al.*	Calcifying tendonitis of the shoulder joint	102	Pain relief was achieved in 82% at a follow-up of 18 months. Sonographic classification (Farin Type III) is predictive for response.	[114]

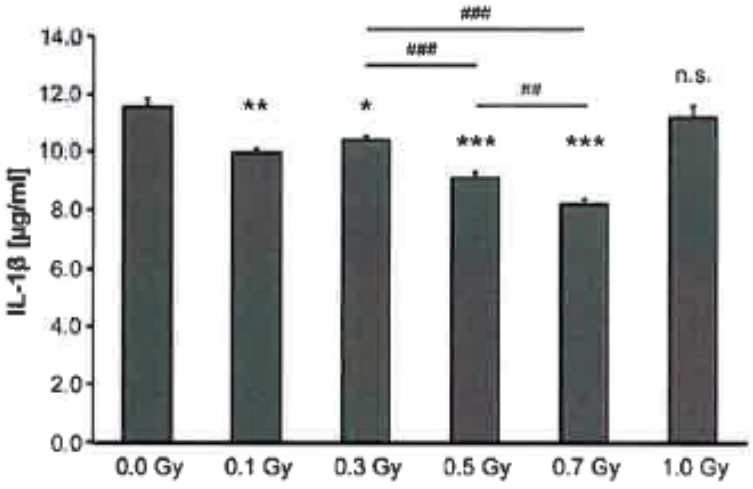
Abbreviations are: RT= radio- therapy.

Acute: 0.3 to 1 Gy in 4 to 5 fractions/week, total doses 1-3 Gy
Chronic: 0.3 to 1 Gy in 1 to 3 fractions/week, total doses 12 Gy

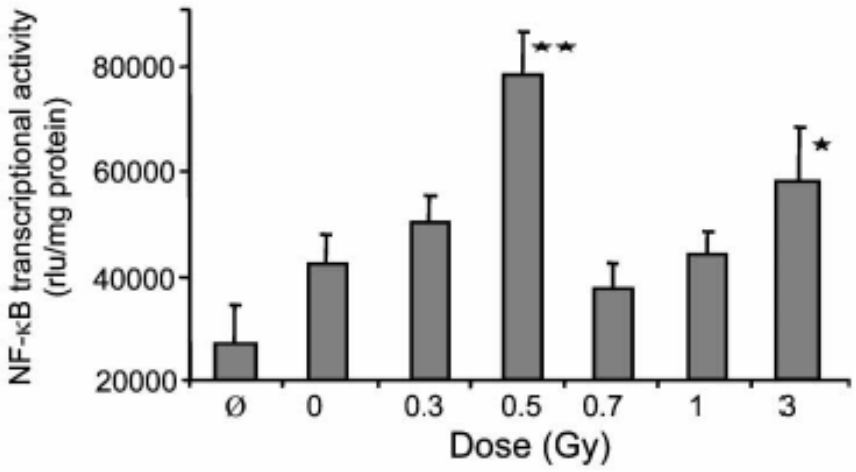
Rödel et al., Current Medicinal Chemistry, 2012

Biphasic effects following „anti-inflammatory“ X-irradiation

Secretion of IL-1β by X-ray irradiated activated THP1 cells



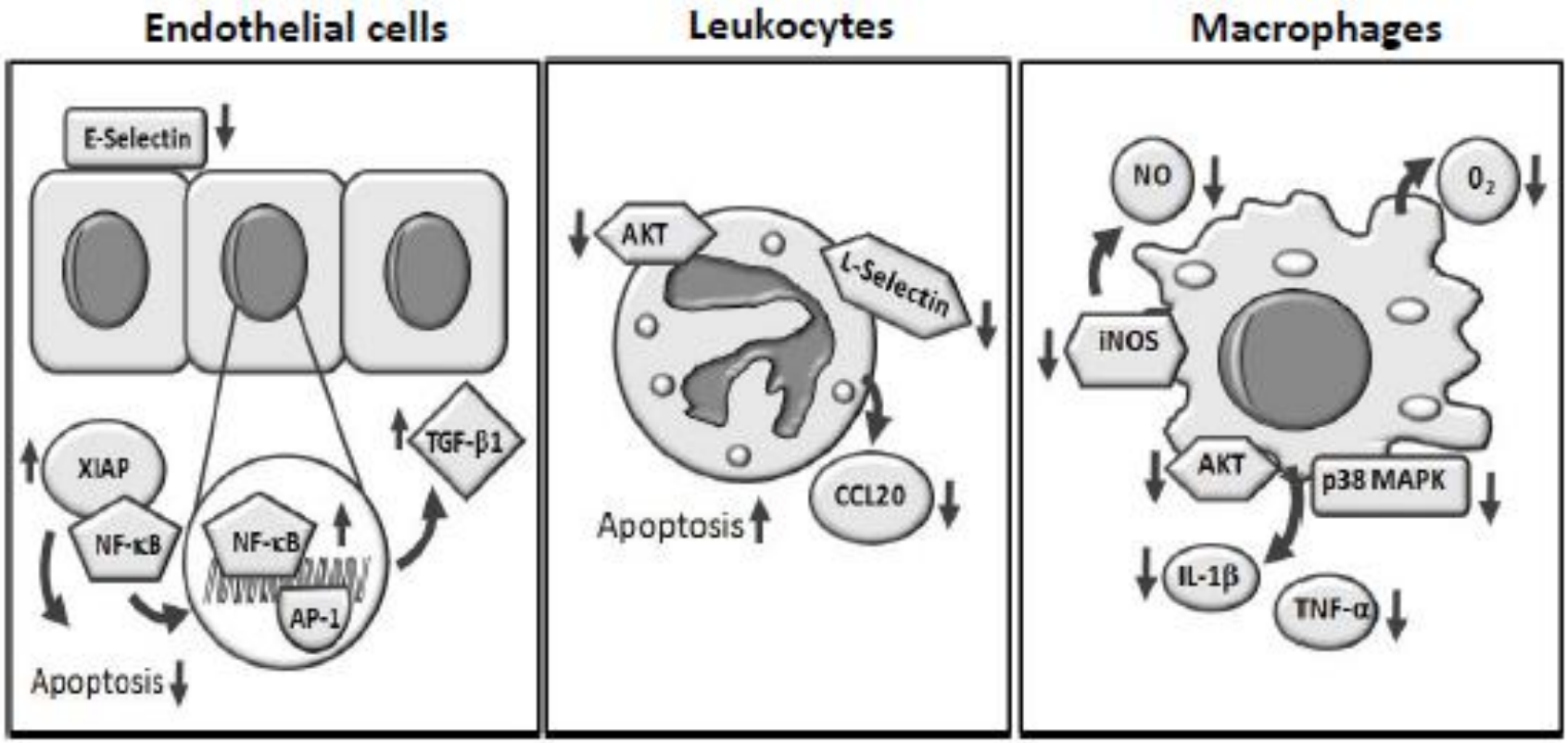
Activation of NF-kB in X-ray irradiated endothelial cells



Low dose radiation effects are often discontinuous

Lödermann et al., Int J Radiat Biol , 2012, Rödel et al. Int J Radiat Biol 2004

Mechanisms of LD-RT anti-inflammatory effects



Decreased recruitment of immune cells
Increased apoptosis of inflammatory cells
Reduced oxidative stress and inflammatory cytokines in tissues

Current Medicinal Chemistry, 2012, 19, 1741-1750

A special case of LD-RT: Radon « therapy »

List of recommended indications for radon treatment
as recommended by EURADON, the European Association Radon Spas.

Musculoskeletal disorders and chronic pain diseases	Ankylosing spondylitis and other spondylarthropathies (AS) Chronic polyarthritis (rheumatoid arthritis, RA) Chronic arthritis urica Psoriasis arthropathy Polymyalgia rheumatic Arthrosis and osteoarthritis (OA) Degenerative diseases of the spinal column Auxiliary treatment consecutive to intervertebral disc operations Osteoporosis Non-inflammatory soft tissue rheumatism (e.g., fibromyalgia) Chronic consequences of casualty or sporting injuries Auxiliary treatment consecutive to orthopedic operations Neuralgia, neuritis, polyneuropathy Multiple Sclerosis (MS)
Cutaneous disorders and diseases	Insufficiently healing wounds (e.g., ulcus cruris) Atopic dermatitis (neurodermatitis) Psoriasis Scleroderma Low grade circulatory problems of the skin
Pulmonary diseases	Asthma bronchiale Chronic-obstructive pulmonary diseases (COPD) Rhinitis allergica Chronic sinusitis
Gynaecological diseases	Praeclimacteric and climacteric disorders Pelvipethia spastica

Maier et al., IJMS, 2021

Country	Place (City)
Austria	Bad Gastein, Bad Hofgastein, Bad Zell, Gasteiner Heilstollen
Bulgaria	Hisarja
Czech Republic	Jáchymov
Chile	Jahuel Hot Springs
China	Nanshui, Taishan
France	Plombiers
Germany	Bad Brambach, Bad Kreuznach, Bad Münster am Stein, Bad Schlema, Bad Steben, Sibyllenbad, Menzenschwand St. Blasien, Weissenstadt
Greece	Ikaria, Polichnitos, Eftalou
Hungary	Abaliget Cave, Budapest, Beke Cave, Eger, István Cave, Tapolca Hospital Cave, Szemlöhegy Cave
Italy	Ischia, Meran
Japan	Misasa
Poland	Długopole-Zdrój, Ladek-Zdrój, Świeradów-Zdrój, Szczawno-Zdrój, Przerzeczyn-Zdrój
Romania	Felix Spa
Russia	Pyatigorsk (Caucasus). Belokuriha (Altai, Siberia) and Yangan Tau (Ural)
Ukraine	Khmelnik
USA	Boulder (Montana)

Radon therapy: clinical trials

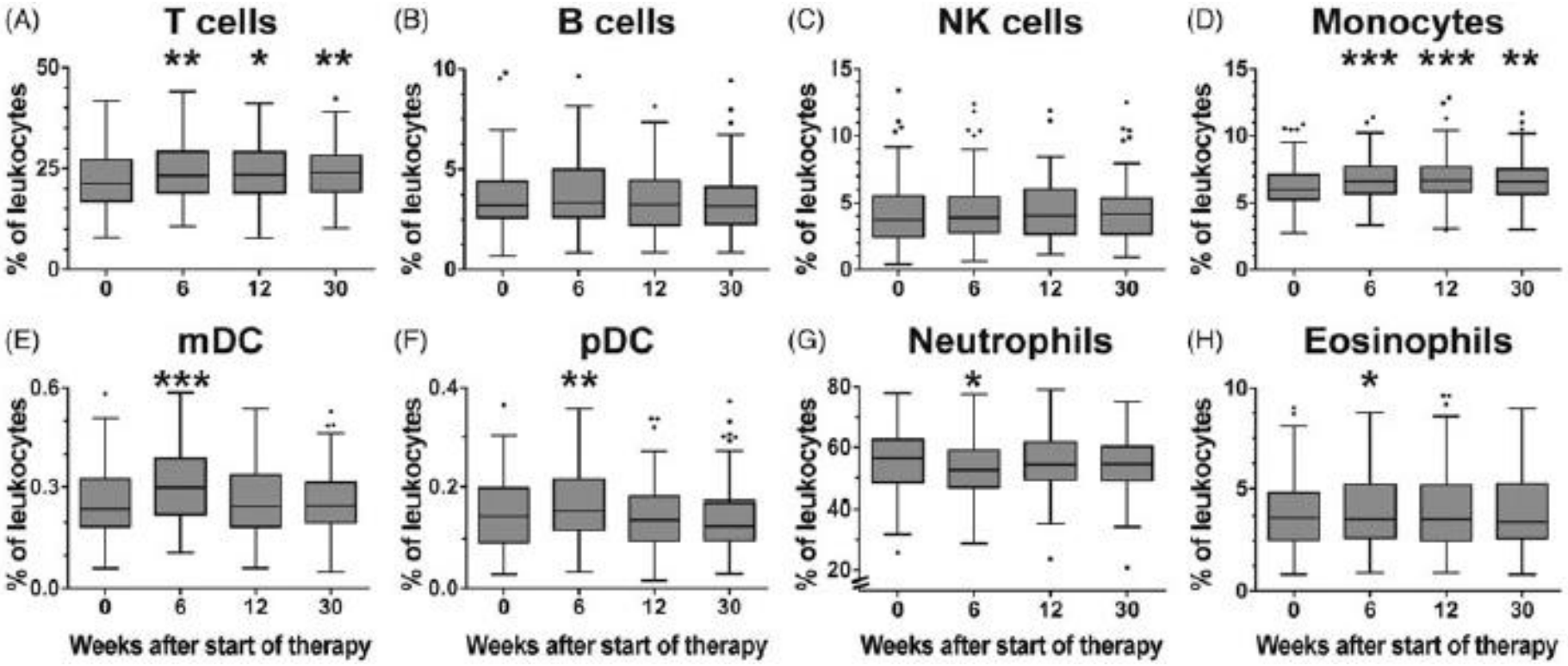
12 Clinical trials since 2000: most found a positive effect of radon therapy

These effects are:

- long lasting decreased pain intensity
- decreased drug intake from 9 m after therapy
- decreased disease associatedd scores
- increased activity of ROS detoxifying enzymes (SOD, catalase)
- increased levels of anti-inflammatory enzymes: TGFβ1, IL-10
- decreased levels of collagene type I fragments
- decreased levels of vifstatins
- decreased levels of RANKL
- increased levels of OPG

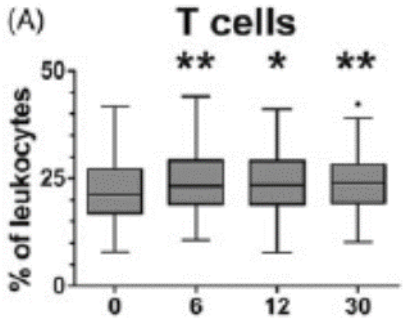
Maier et al., IJMS, 2021

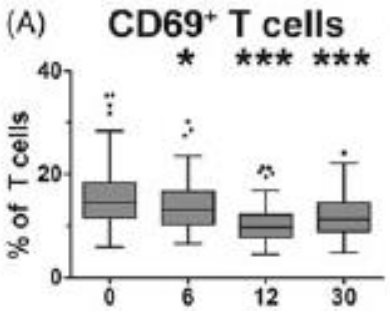
Immunomodulatory effects of Radon therapy

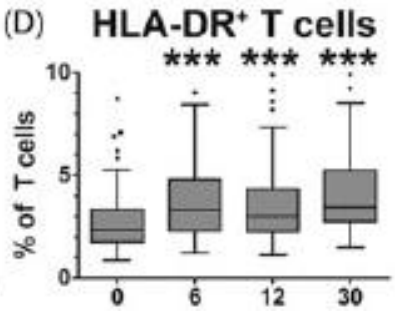


Some effects transiently appear 6 wks after the start of the therapy, some last for the 30 wks of the study period

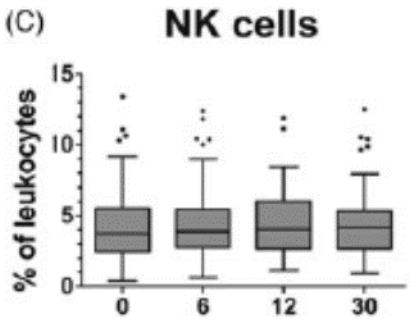
Immunomodulatory effects of Radon therapy

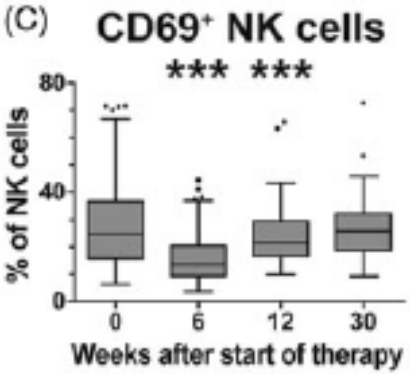




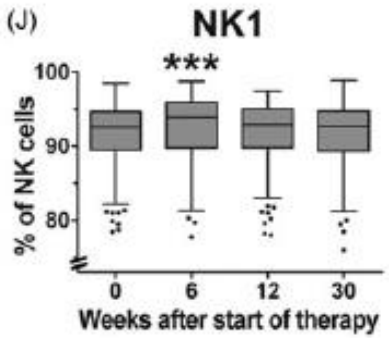


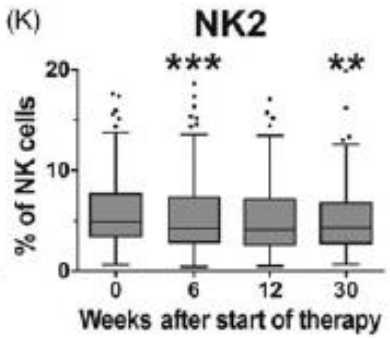
CD69, HLA-DR: activation markers

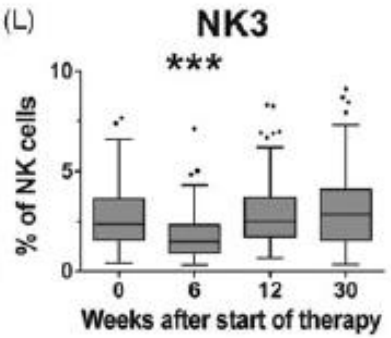




Discrete effects on various sub-populations



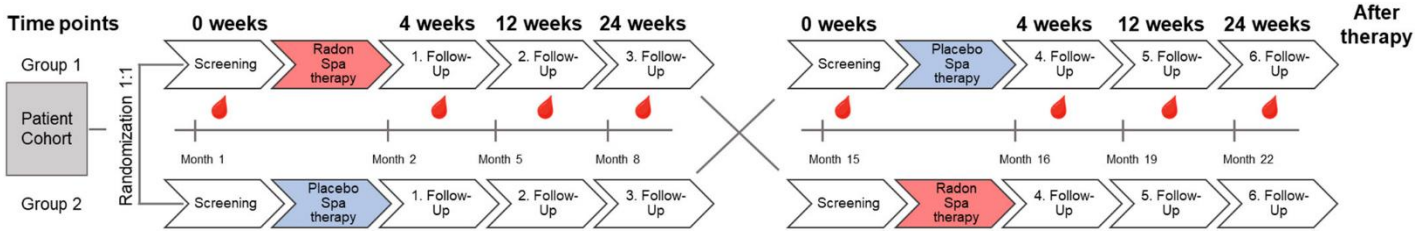


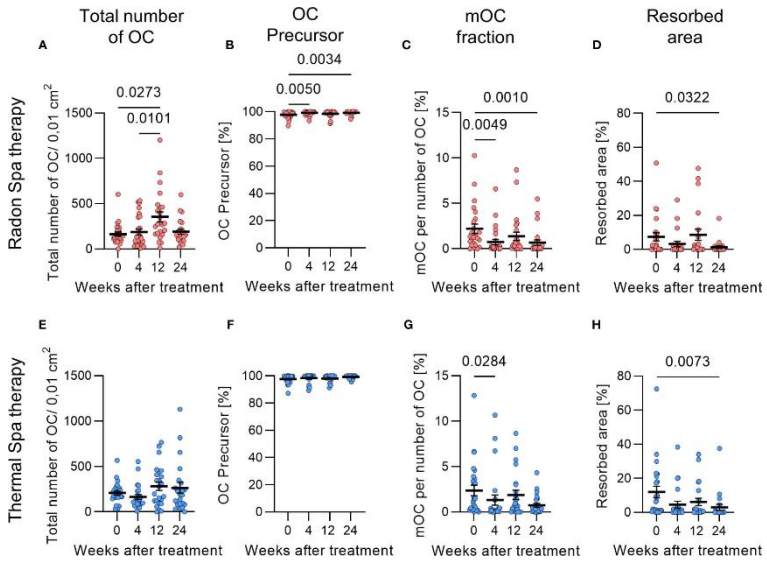


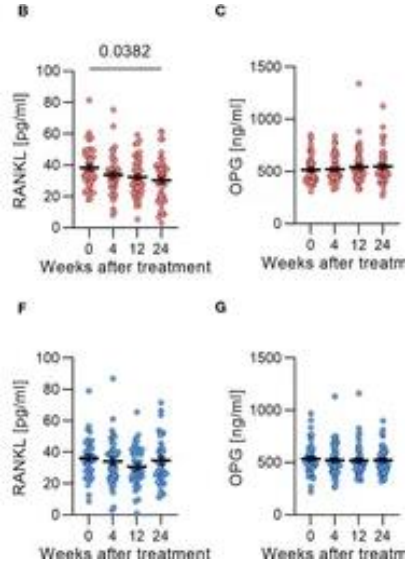
Rühle et al., Autoimmunity, 2017

Osteo-immunological impact of radon spa treatment: due to radon or spa alone? Results from the prospective, thermal bath placebo-controlled RAD-ON02 trial

116 patients over 2 years





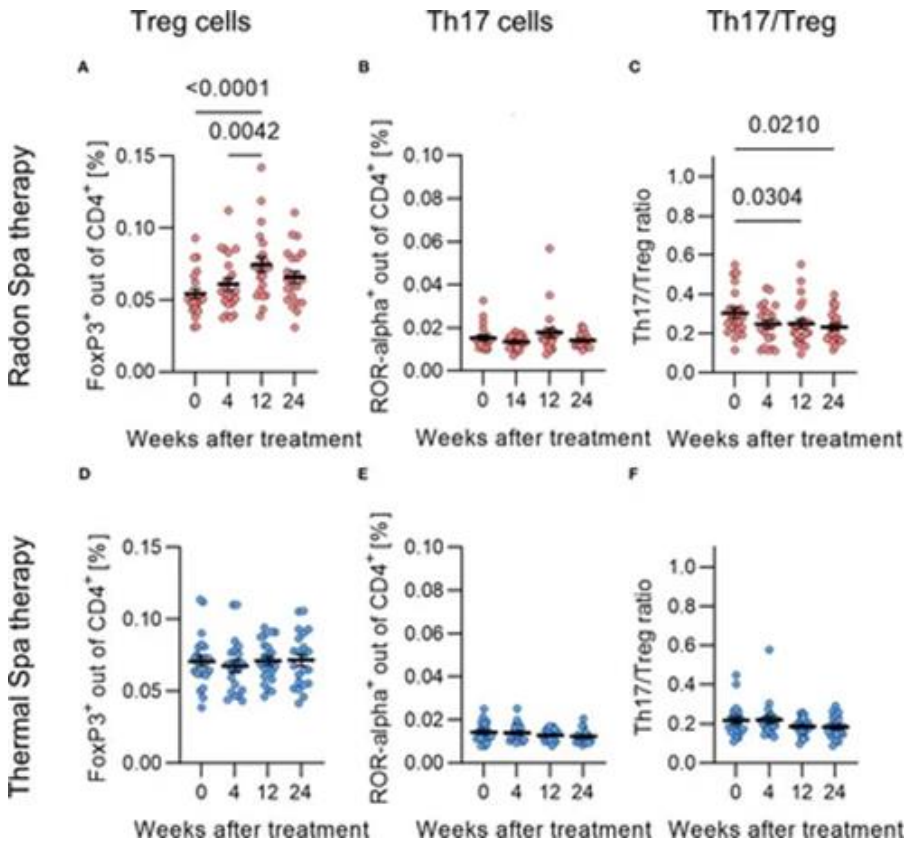


Increased number of osteoclasts and osteoclast precursors and increased level of circulating RANKL only on patients exposed to radon but not thermal spa therapy.
Thermal spa have effects on its own !

Eckert, Front. Immunol, 2024

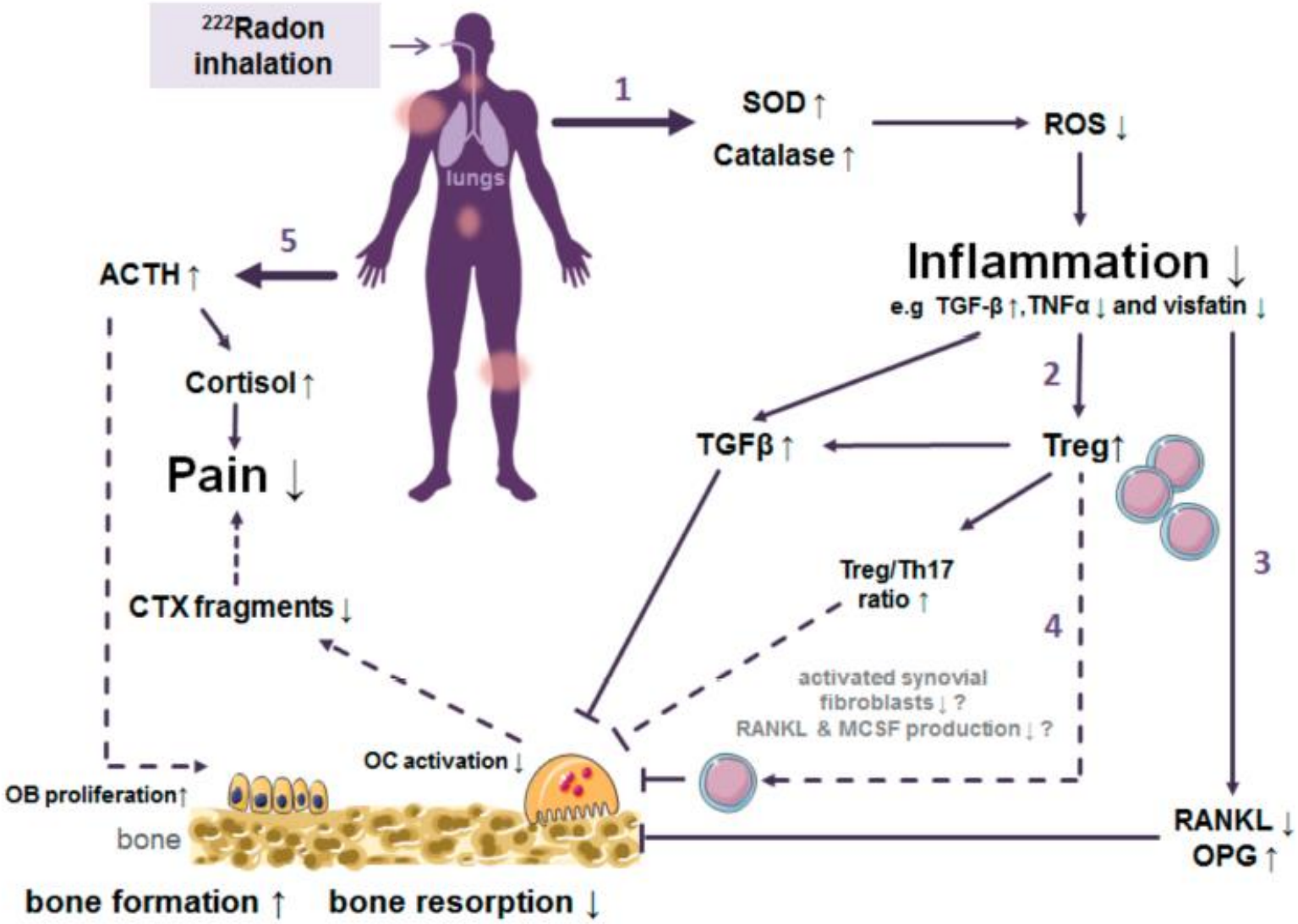
Osteo-immunological impact of radon spa treatment: due to radon or spa alone? Results from the prospective, thermal bath placebo-controlled RAD-ON02 trial

Only radon-spa therapy specifically induces an increases in Treg cells



The overall effects of radon spa therapy are probably an addition of ionizing radiation and thermal spa effects

Putative mechanisms of Radon immunomodulatory effects in chronic muckulosqueletal diseases



Maier et al., IJMS, 2021

What about increased cancer risk from radon-therapy?

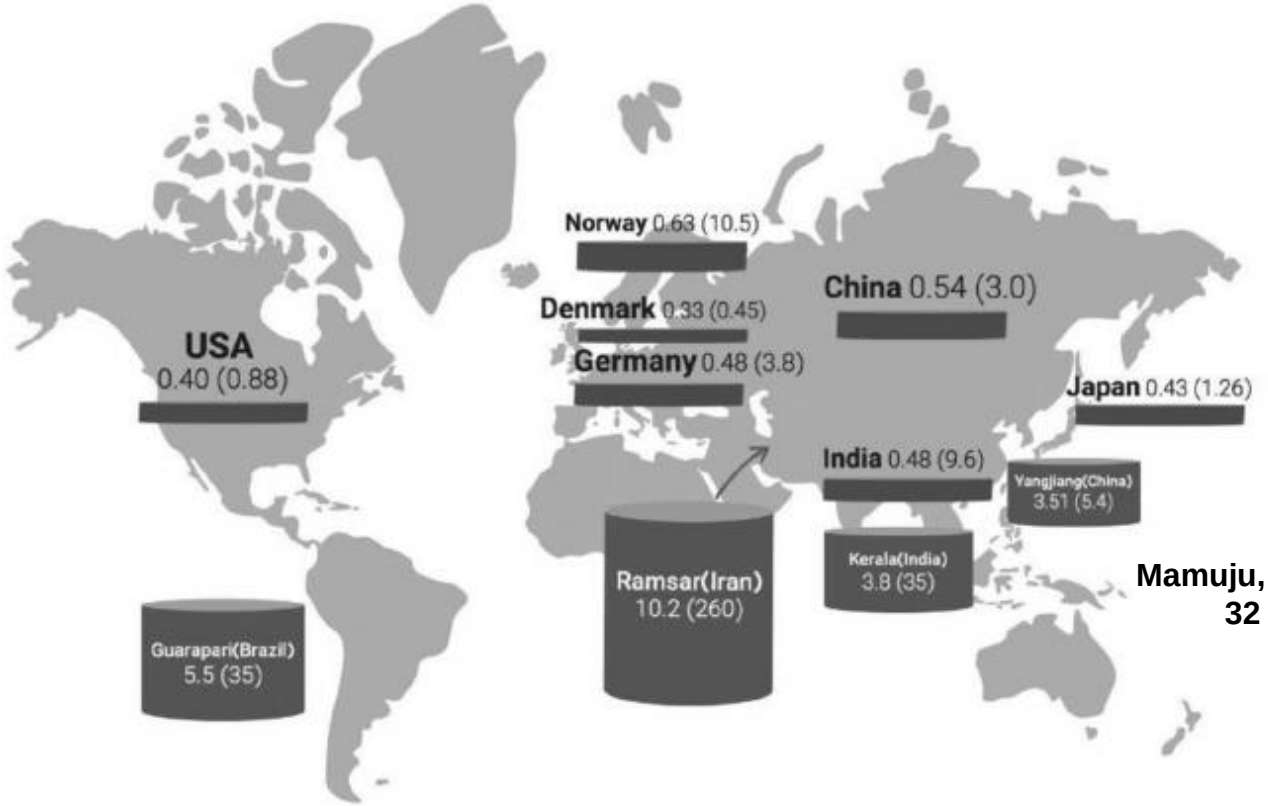
Lung cancer: the doses received by the patients in the course of one treatment series (typically consisting of ten sessions of one hour each) are in the same order of magnitude as for the natural annual background radiation due to radon. The major difference is the much shorter time period in which the patients obtain this dose and consequently, the higher dose rate.

Skin cancer: two studies of people leaving in areas with high natural levels of radon suggest an excess of basal cell carcinoma, but confounding factors, including sun exposure, cannot be excluded.

Animal studies are/have been developed to better understand the effects of radon exposure and the mechanisms underlying radon therapy

Maier et al., IJMS, 2021

High Natural Background Radiation Areas



Four representative HBRAs on Earth with median annual doses in mSv and highest doses in parentheses.

www.health-physics.com

- high natural concentration of radionucleides (Thorium-232, Radium-228, Uranium-238)
- exposure, inhalation, ingestion
- level of exposure depends on time of residency, time indoor, food consumption ...

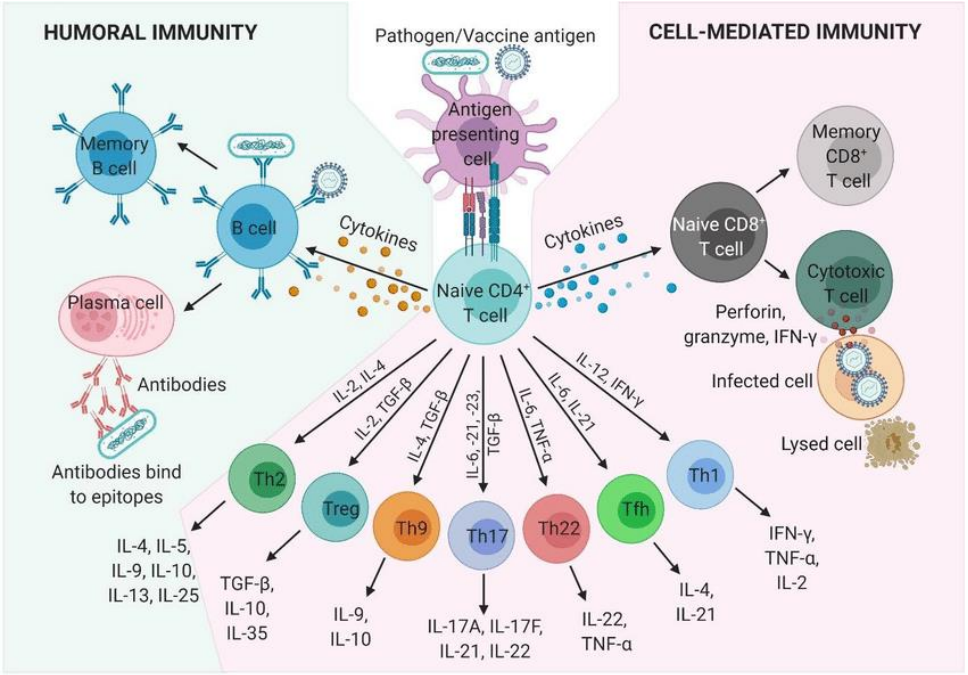
Welsh, Health Physics, 2022, Nugraha, Sci Rep, 2021

Effect of High Dose Natural Ionizing Radiation on the Immune System of the Exposed Residents of Ramsar Town, Iran

Cytokine secretion from PHA-activated T cells

Residents	IL-2 (pg/ml)	IL-4 (pg/ml)	IL-10 (OD)	INF-γ (OD)	Proliferation (SI)	P value*
High Dose Area	399±221	220±28	0.26±0.04	0.12±0.04	3.7±0.8	<0.05
Control	760±275	145±34	0.17±0.03	0.17±0.05	3.9±0.7	-

* Mean of the two groups of exposed and controls were used.



Increased secretion of Th2 cytokines:
→ shift towards a wound healing/anti-inflammatory

Attar, Iranian journal of allergy, asthma and immunology, 2007

Effect of High Dose Natural Ionizing Radiation on the Immune System of the Exposed Residents of Ramsar Town, Iran

9.77 mSv (4.51 – 57 mSv)

Table 1. Effect of natural ionizing radiation on peripheral lymphocytes.

Residents	IL-2 (pg/ml)	IL-4 (pg/ml)	IL-10 (OD)	INF-γ (OD)	Proliferation (SI)	P value*
High Dose Area	399±221	220±28	0.26±0.04	0.12±0.04	3.7±0.8	<0.05
Control	760±275	145±34	0.17±0.03	0.17±0.05	3.9±0.7	-

* Mean of the two groups of exposed and controls were used.

Table 2. Effect of natural ionizing radiation on peripheral neutrophils.

Residents	NBT (%)	Phagocytosis (pI)	Locomotion (μm)	P value*
High Dose Area	84±13	92±6	124±16	<0.05
Control	65±12	80±5.8	84±8.5	-

* Mean of the two groups of exposed and controls were used.

Table 3. Effect of natural ionizing radiation on serum antioxidant.

Residents	Total antioxidant (μmole)	P value*
High Dose Area	686±170	<0.05
Control	1187 ±199	-

* Mean of the two groups of exposed and controls were used.

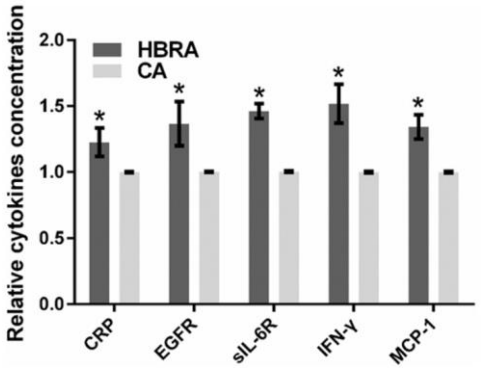
- Increased secretion of Th2 cytokines: shift towards an anti-inflammatory state
- Increased activity of neutrophils: ongoing inflammation
- Lower antioxidant defenses: ongoing inflammation

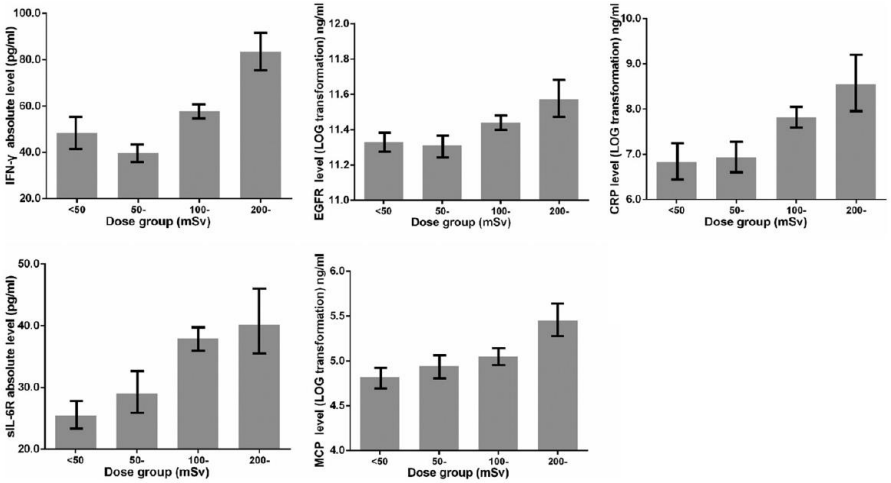
These results suggest that the immune system tries to counter a chronic inflammation in HBRA residents

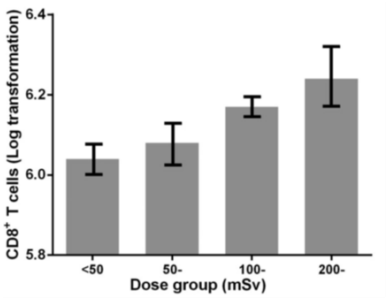
Attar, Iranian journal of allergy, asthma and immunology, 2007

Long-term immune effects of high-level natural radiation on Yangjiang inhabitants in China

163.83 mSv (58.5 – 249.1 mSv)







Cumulative dose estimated from time of residency
Dose-dependent increase in cytokine levels suggests persistent inflammation
Increased CD8+ but not CD4+ peripheral T lymphocytes suggest differential effects on peripheral T lymphocytes. Similar to ageing?

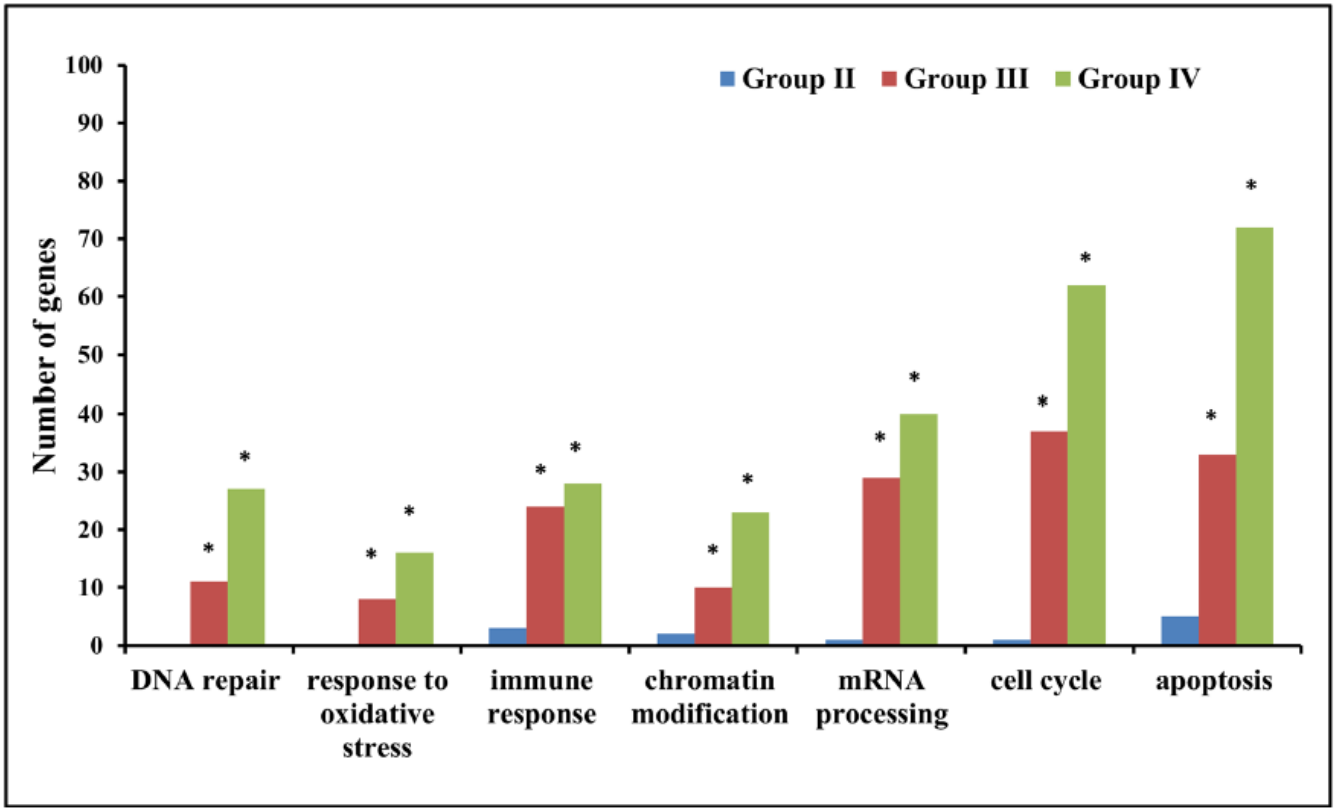
Li, 2019, IJRB

Global transcriptome profile reveals abundance of DNA damage response and repair genes in individuals from high level natural radiation areas of Kerala coast

Group I (NLNRA, control group <1.5 mGy/year, N = 9)
Group II (HLNRA, 1.51±5.0 mGy/year, N = 9)
Group III (HLNRA, 5.01±15.0 mGy/year, N = 11)
Group IV (HLNRA, > 15.0 mGy/year, N = 7).

1.51 to >15 mSv

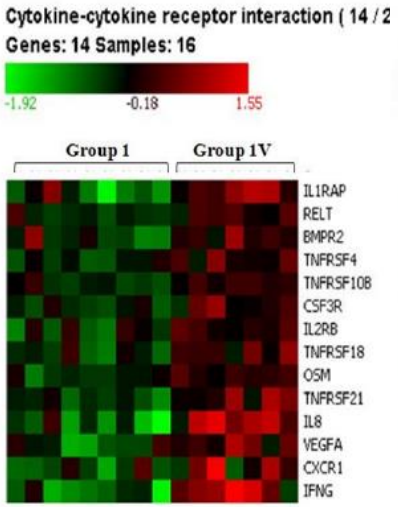
Transcriptomics analysis on PBMCs

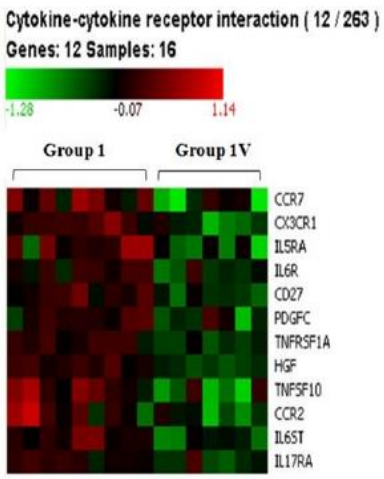


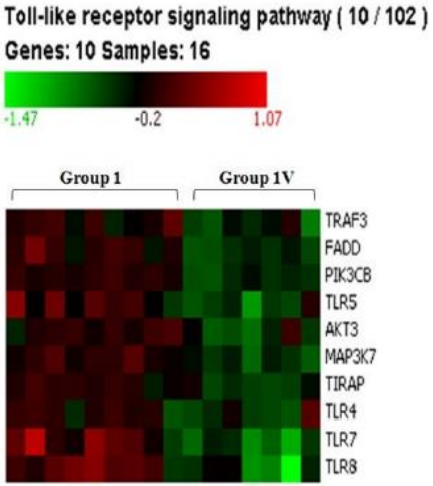
DDR related biological processes over-represented in GO pathways analysis

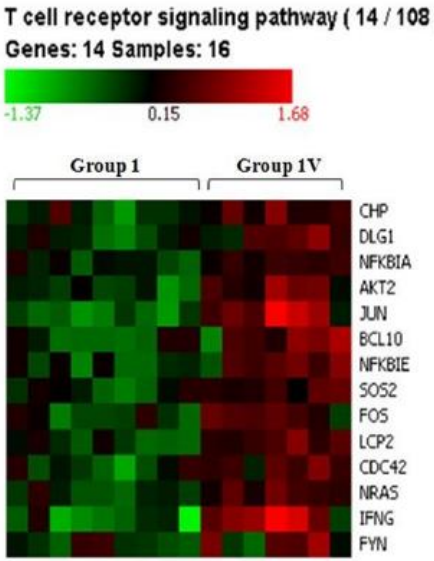
Jain, PLOS One, 2017

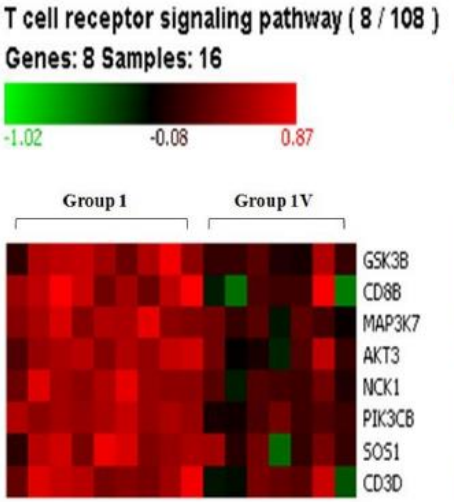
Different genes from a same signaling pathway are up- or down-regulated in Kerala coast residents











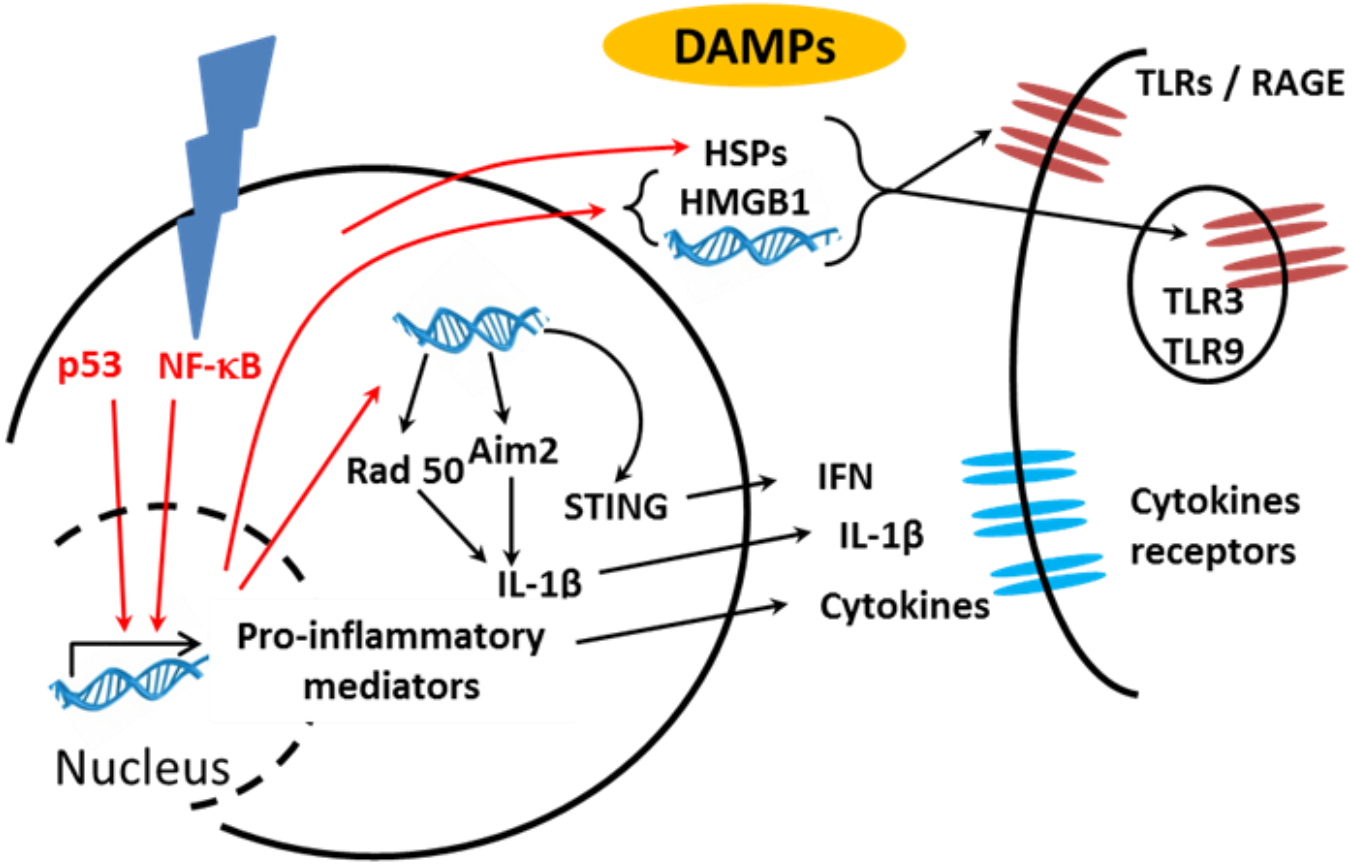
Induction and repression of :

- **pro- and anti-inflammatory genes,**
- **genes participating in T cell activation**

Overall result?

Direct or indirect effects?

Immune signaling following radiation exposure

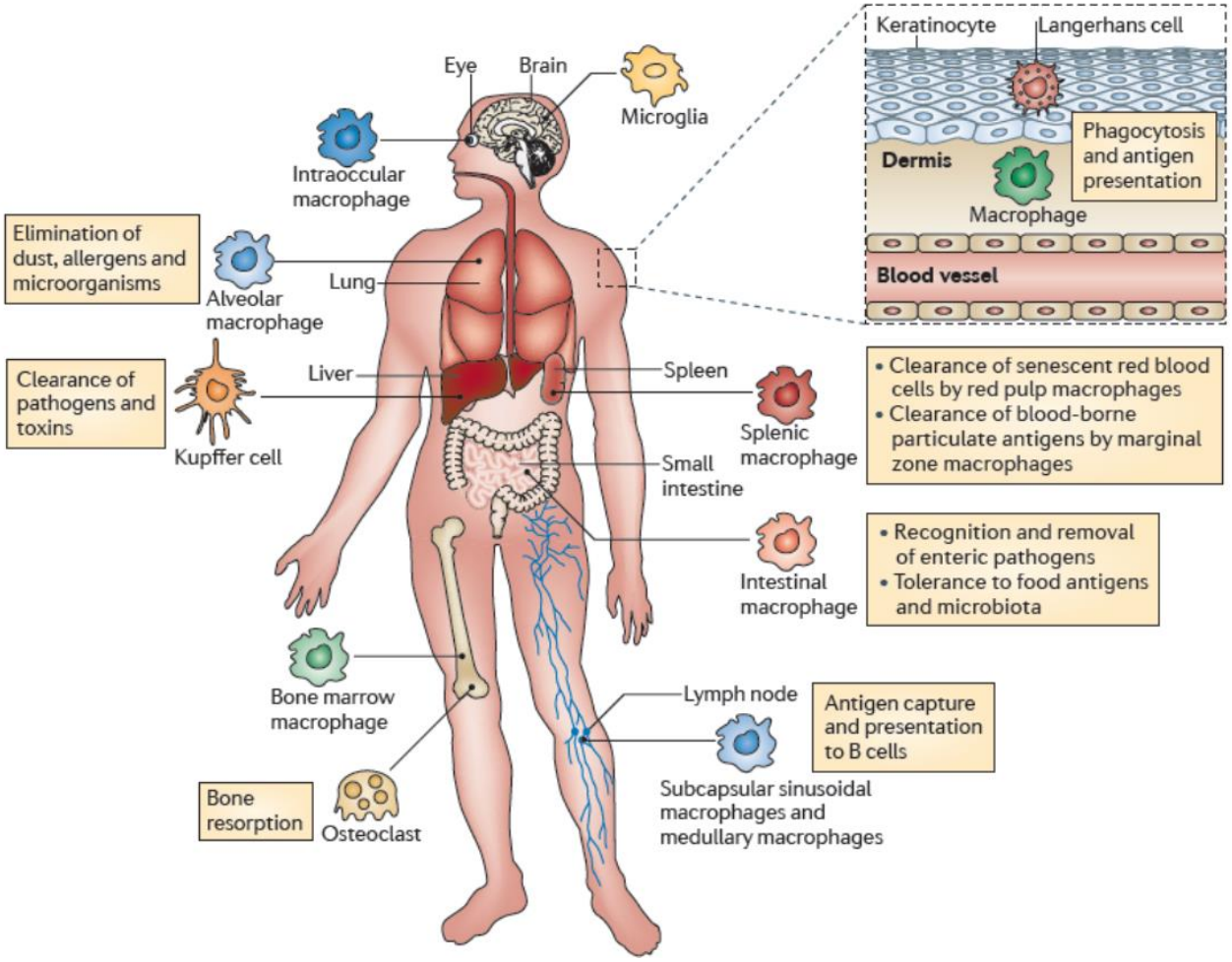


Stromal cell ➔ **Immune system**

Stromal cell	➔	Stromal cell
Immune system	➔	Stromal cell
Immune cells	➔	Immune cells

Candéias and Testard, Cancer Letters, 2015

Tissue resident macrophages act as sentinel to sense tissue damage

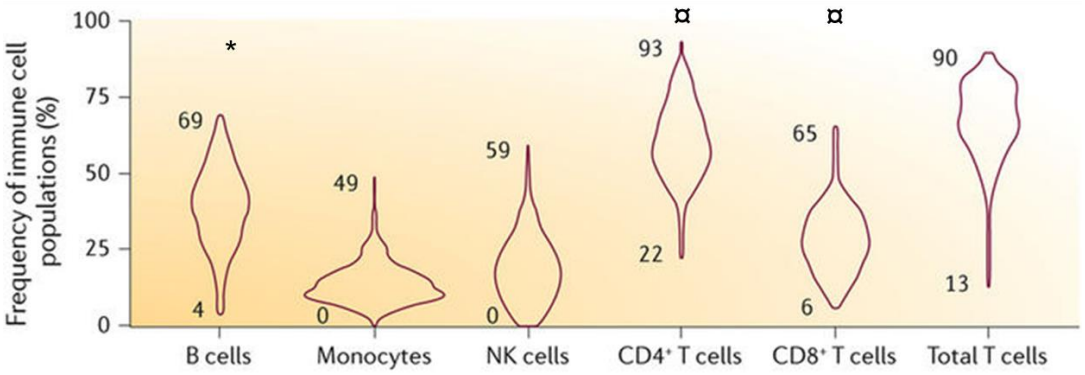


Different types of macrophages in different tissues

➔Tissue specific responses after DAMP sensing

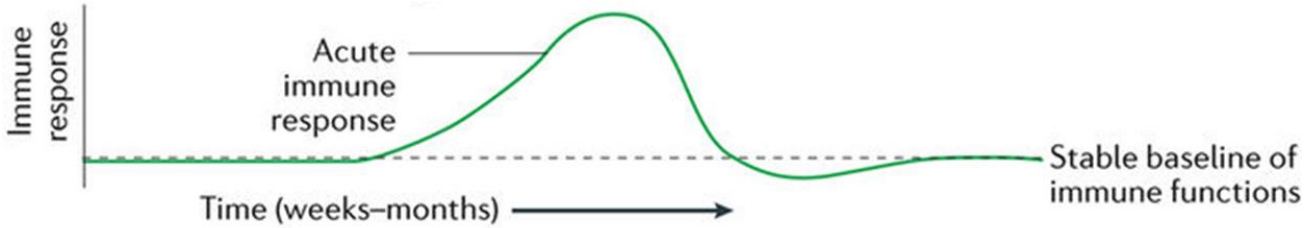
Murray and Wynn, 2011

LARGE INTER-INDIVIDUAL VARIABILITY BUT INDIVIDUAL STABILITY IN TIME



« Stanford » cohort
398 healthy adults

*: % of lymphocytes
¤: % of total T lymphocytes



- Large inter-individual variability in the composition of immune cells, but preservation of « important » functions
- Major influence of environmental factors
- Stablity and elacticity ➔ status at the time of exposure
- Variations with age ➔ age at exposure

Brodin and Davies, Nature Rev Immunol. 2016

CONCLUSIONS

A strong connection between innate immunity and normal tissue radiobiology

Radiation exposure can induce and modulate inflammatory reactions

Activation of the immune system increases the efficiency of cancer radiotherapy

Inflammatory signals modulate radiation-induced effects

The cellular and tissue context shape the outcome of the response (*cell specific immune/radiation responses*)

Individual responses will be the resultant of individual radiosensitivity and inter-individual immune variability

CEA - Grenoble

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MIRACLe

Thank you for your attention

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