INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION

Challenges of Radiological Protection in Research and Society referring to Medical Field

Research updates on radiobiology and carcinogenic risk assessment: potential application of gene expression profiles to predict biological effects of *low dose* ionizing radiation exposure

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I declare no conflict of interest

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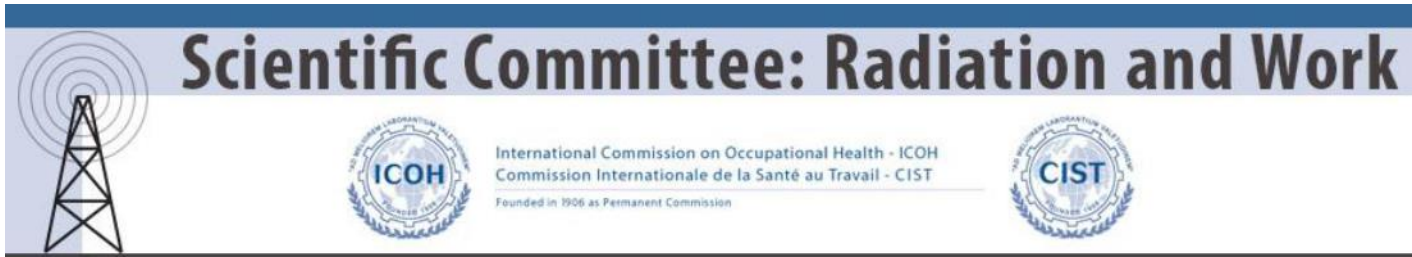
airm
Associazione Italiana di Radioprotezione Medica

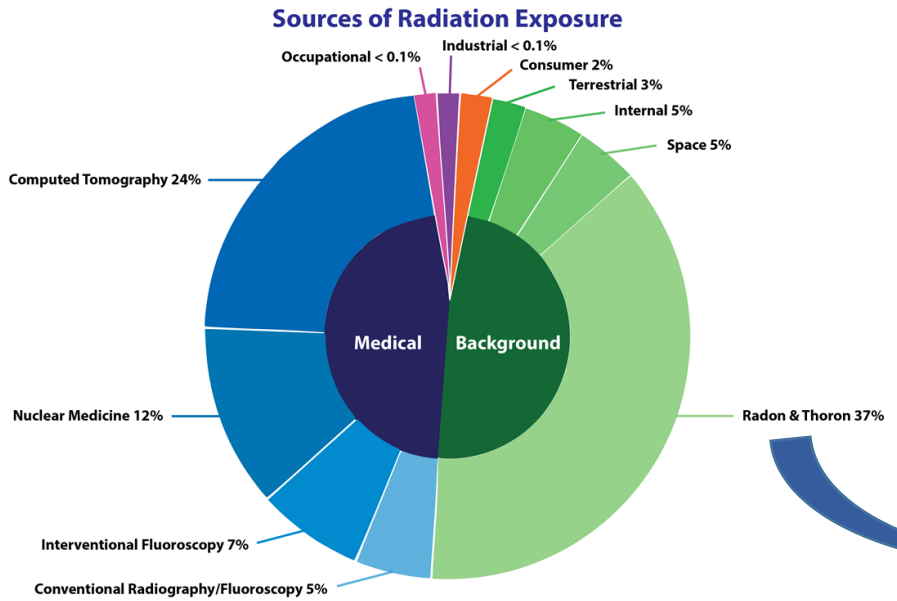


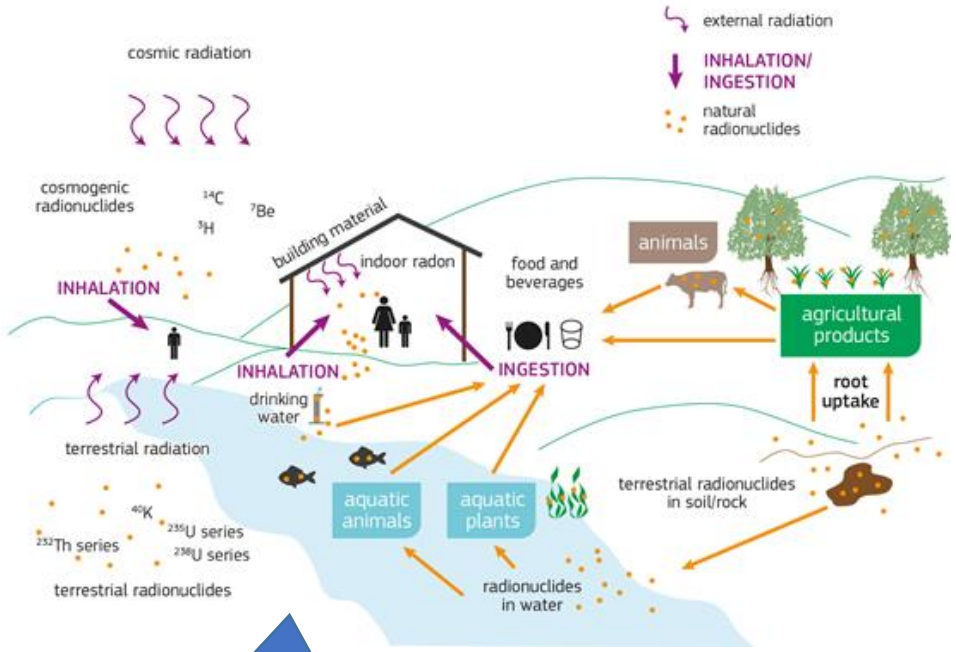
Ionizing Radiation (IR) is a ubiquitous environmental agent

All living organisms are continually exposed to various **natural or man-made sources of IR**

IR sources and average annual radiation dose per person in the U.S.
(*NCRP report 93 e 160*)

https://www.epa.gov/radiation/radiation-sources-and-doses





Average Annual Radiation Dose											
Sources	Radon & Thoron	Computed Tomography	Nuclear Medicine	Interventional Fluoroscopy	Space	Conventional Radiography/ Fluoroscopy	Internal	Terrestrial	Consumer	Occupational	Industrial
Units											
mrem (United States)	228 mrem	147 mrem	77 mrem	43 mrem	33 mrem	33 mrem	29 mrem	21 mrem	13 mrem	0.5 mrem	0.3 mrem
mSv (International)	2.28 mSv	1.47 mSv	0.77 mSv	0.43 mSv	0.33 mSv	0.33mSv	0.29 mSv	0.21 mSv	0.13 mSv	0.005 mSv	0.003 mSv

(Source: National Council on Radiation Protection & Measurements, Report No. 160)

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BIOLOGICAL EFFECTS OF IONIZING RADIATION

SOMATIC
(Affects exposed individuals)

GENETIC
(Affects next generation)

Deterministic effects (*or Tissue reactions*)

- Severity proportional to absorbed dose
- With threshold value

- Acute radiation syndrome
- Erythema
- Sterility
- Epilation (loss of hair)

Cataract (?)

Stochastic Effects

- Probability of occurring proportional to absorbed dose
- Without a threshold value
- Severity independent of absorbed dose

- **Carcinogenesis (Solid Tumors)**
- **Leukemia**

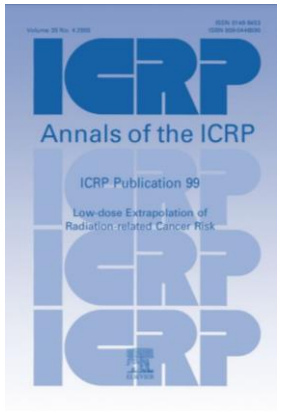
- Gene mutations
- Chromosomal Aberrations

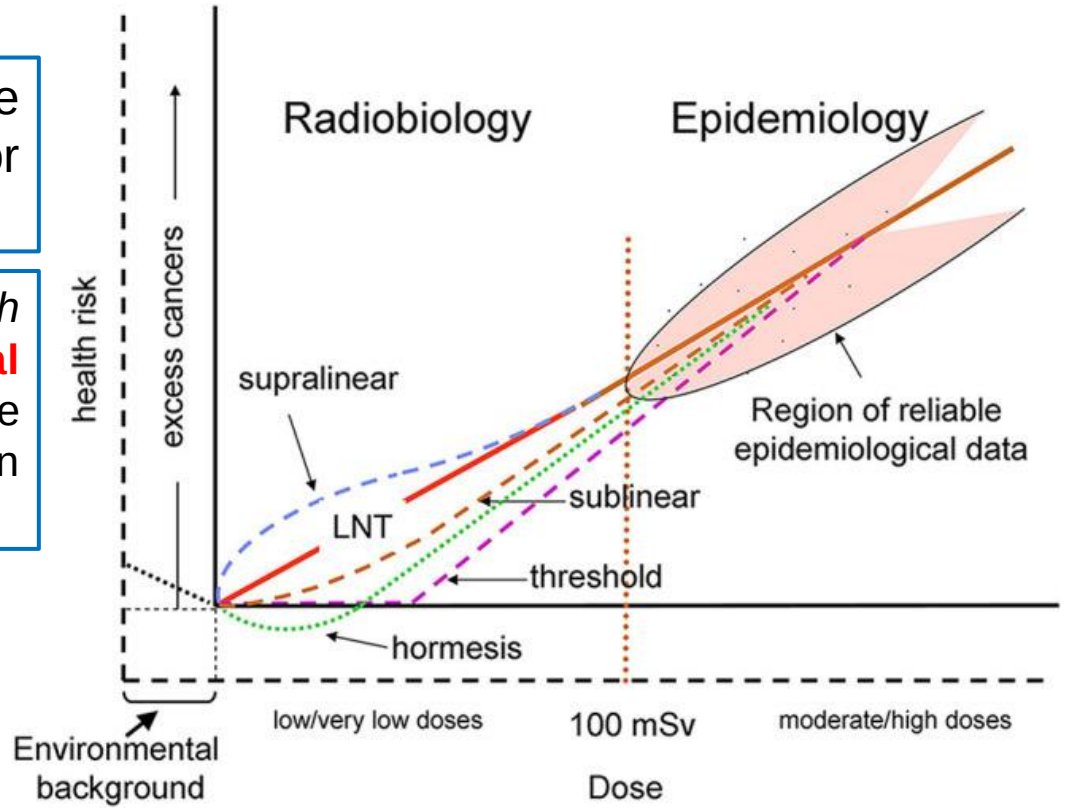
- It has become important to **characterize a dose-response curve** capable to explain the **health effects and risks of repeated exposure to low doses**.
- The probabilities of detrimental effects from exposure to LDIR (<100 mSv) are estimated by **"linear no-threshold" model (LNT)** only for radiological protection purposes.

The LNT model implies that there is no level of exposure to ionizing radiation below which there is zero risk of causing cancer. The scientific debate on the validity of this "hypothesis" is still open and numerous authors believe that this approach is not sufficient to describe the real risk of long-term health effects (i.e. cancer) related to LDIR exposure.

Several lines of experimental and epidemiological evidence demonstrate that the dose-response association with cancer or other diseases is not easy to estimate at low dose exposures

As suggested by the European Project DoReMi (*Low Dose Research towards Multidisciplinary Integration*) the adequate use of **potential radiation biomarkers** validated in large epidemiological studies could be of great support to improve the evaluation of the relationship between LDIR and increased oncogenic risk.



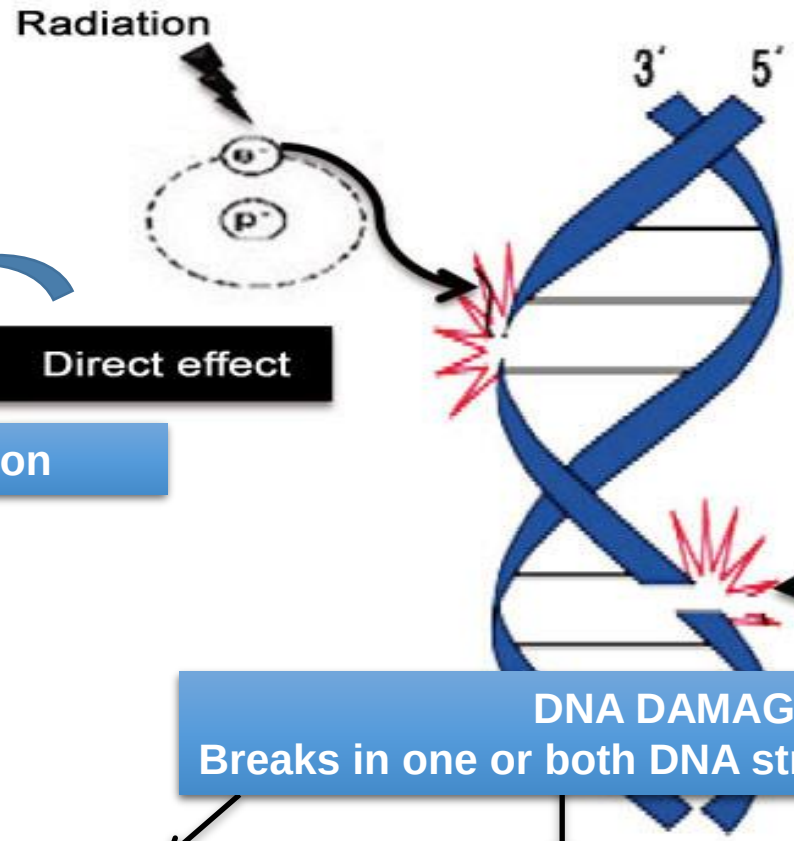


Belli M, Indovina L. The Response of Living Organisms to Low Radiation Environment and Its Implications in Radiation Protection. Front Public Health. 2020 Dec 15;8:601711. doi: 10.3389/fpubh.2020.601711. PMID: 33384980; PMCID: PMC7770185.

DoReMi
Integrating Low Dose Research

IONIZING RADIATION AT THE CELLULAR LEVEL

Nuclear DNA: primary TARGET of ionizing radiation



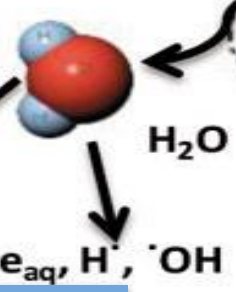
Direct effect

DNA ionization

Indirect effect

Radiation

Water radiolysis
Free Radical formation



DNA DAMAGE
Breaks in one or both DNA strands

Repair

Cell survival

Unrepaired

Cell death

Misrepair

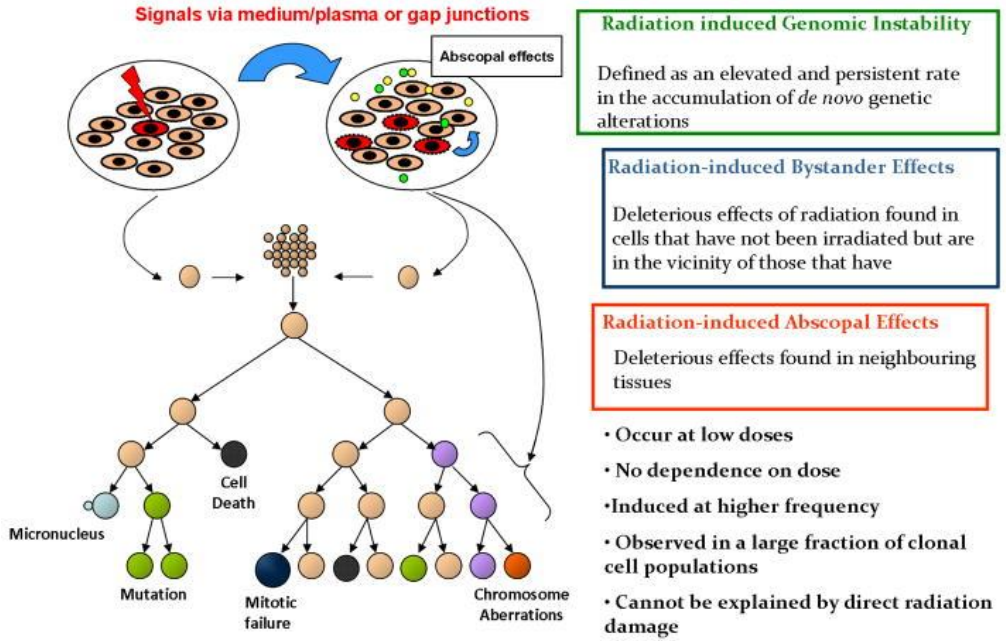
MUTATION

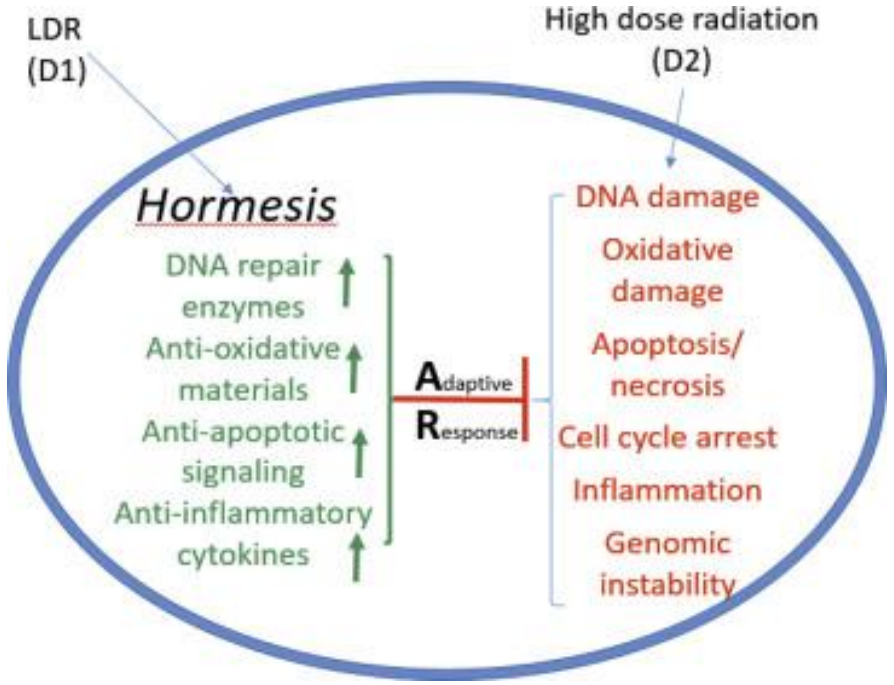
CANCER ?

Non-targeted effects

The detrimental effects of ionizing radiation are not restricted only in the irradiated cells, but also to non-irradiated bystander or even distant cells manifesting various biological effects.

Non-DNA targeted effects of ionizing radiation, which include genomic instability, and a variety of bystander effects including abscopal effects and bystander mediated adaptive response, have raised concerns about the magnitude of low-dose radiation risk.

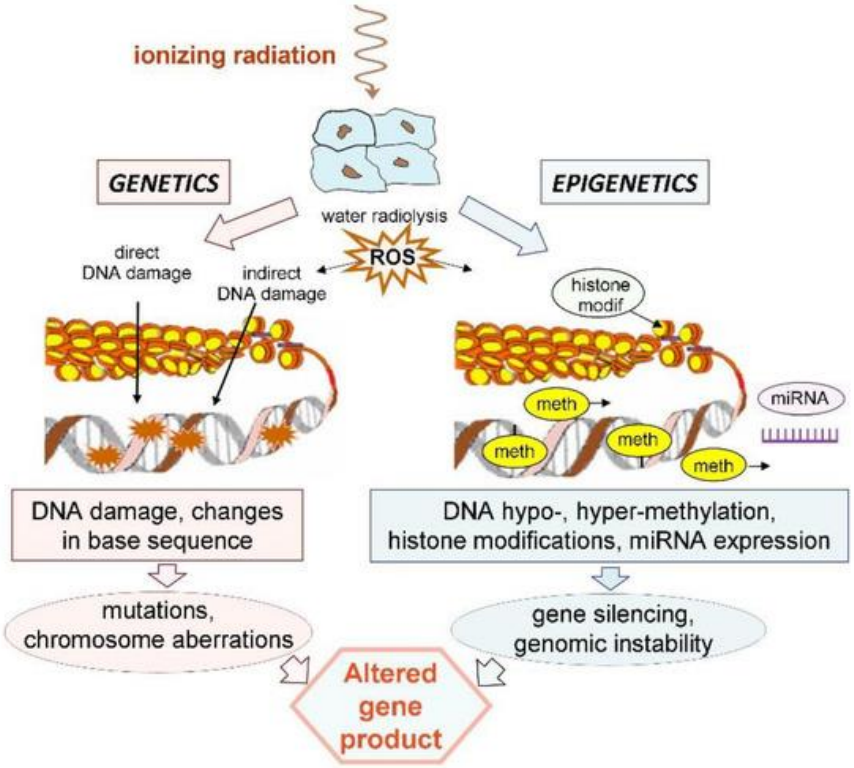


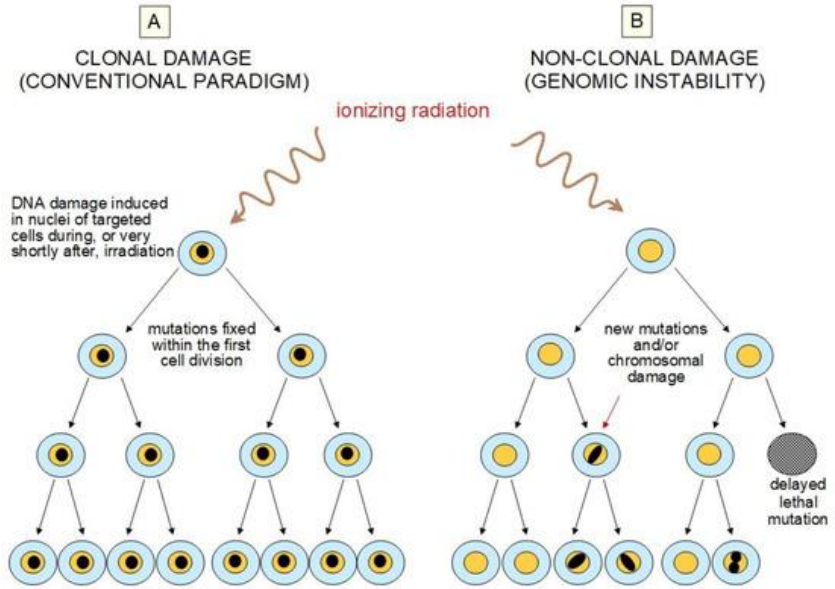


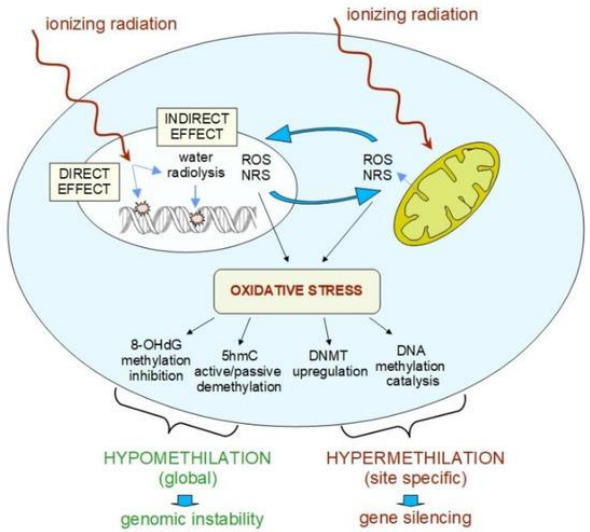
Kadhim M, Salomaa S, Wright E, Hildebrandt G, Belyakov OV, Prise KM, Little MP. Non-targeted effects of ionising radiation--implications for low dose risk. Mutat Res. 2013 Apr-Jun;752(2):84-98. doi: 10.1016/j.mrrev.2012.12.001.

Non-targeted effects

Understanding of the mechanisms of non-targeted and delayed effects is fundamental because there is some evidence for differential responses in gene and protein expression for high- and low-dose radiation exposures.







Ionizing Radiation-Induced Epigenetic Modifications and Their Relevance to Radiation Protection.

Belli M, Tabocchini MA. Int J Mol Sci. 2020 Aug 20;21(17):5993. doi: 10.3390/ijms21175993.

Biodosimetry and LDIR exposure

Currently physical and biological dosimetry is unable to identify early biological responses and long-term pro-oncogenic effects induced by LDIR, so the discovery of intrinsic biomarkers is a priority especially for **increasing occupational exposure**

Principal issues

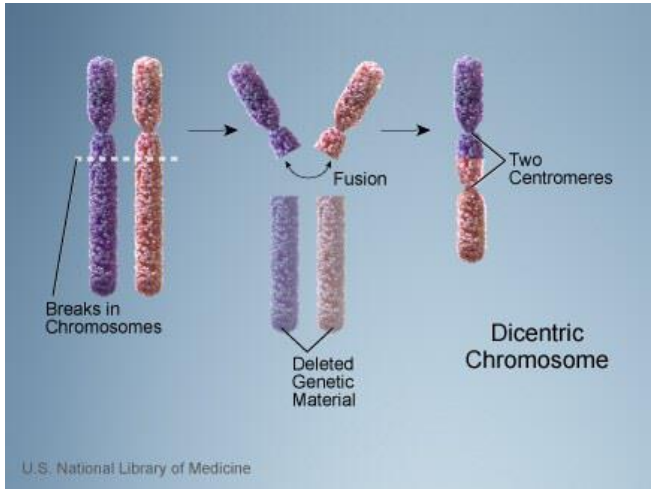
- Characterize a dose-response curve that can explain the health effects and risks of repeated LDIR exposure;
- **Responses to (very) low doses are difficult to predict**, and the relationship between absorbed dose, DNA damage, and health risk remains an open question to date;
- **Large-scale epidemiological studies are limited** because hundreds of thousands of samples are needed to provide statistically significant data related to risk assessment;
- Current evidence is based on **few studies conducted on ex-vivo** irradiated human blood samples, mouse or primate (NHP) animal models.

Paunesku T, Woloschak G. Reflections on Basic Science Studies Involving Low Doses of Ionizing Radiation. Health Phys. 2018 Nov;115(5):623-627. doi: 10.1097/HP.0000000000000937. PMID: 30260853; PMCID: PMC6226262.

THE DISCOVERY OF SENSITIVE BIOMARKERS REPRESENTS A PRIORITY AREA OF INTEREST

Biomarkers can be used for multiple purposes:

- **estimation or validation of received dose, improving the validity of a correlation between exposure and biological responses**
- **investigation of individual susceptibility**
- **early detection of a radiation induced health effect**



BIOLOGICAL DOSIMETER

Easily measured

Easily obtainable

IR-sensitive

Acute / Chronic exposure

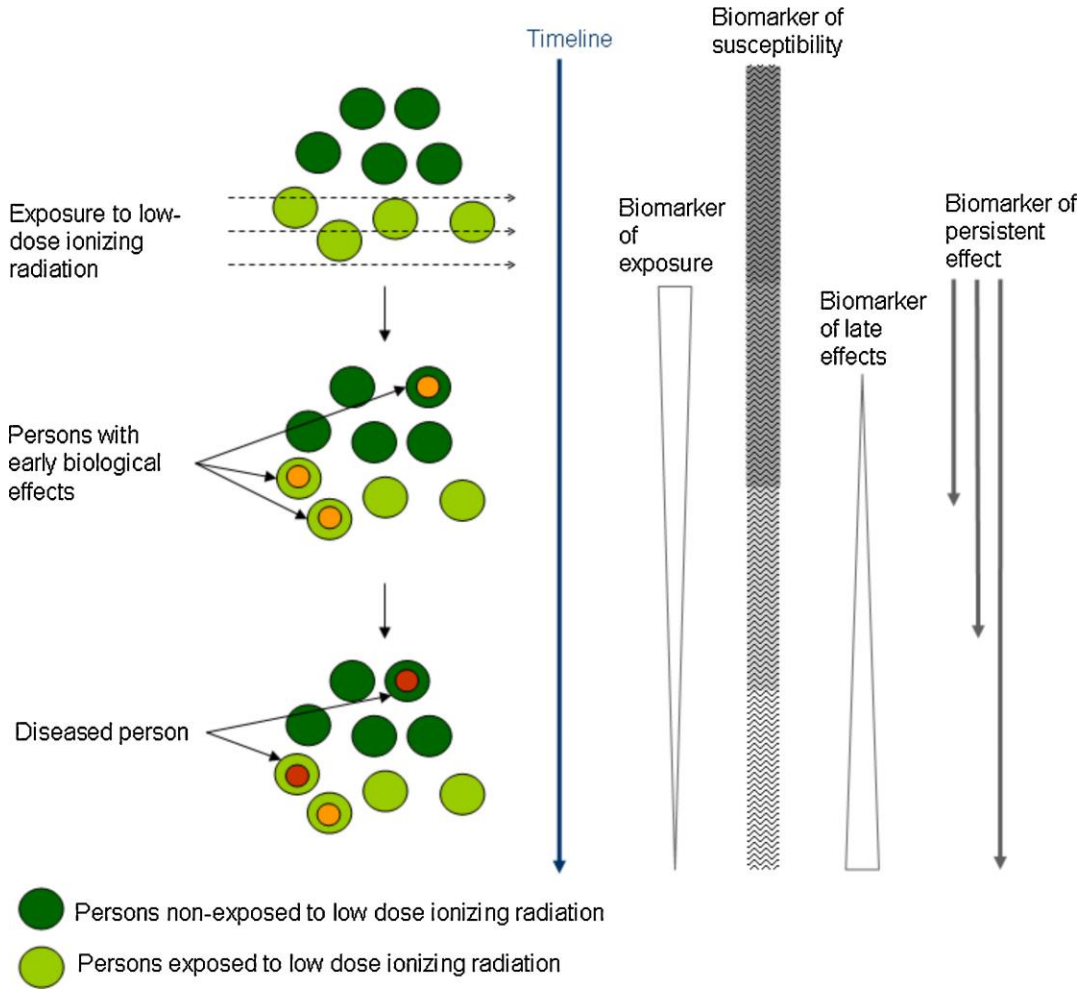
Biomarker = any measurement reflecting an interaction between a biological system and an environmental agent, which may be chemical, physical or biological

Biomarkers of exposure: available at some point after exposure and are suitable for estimating the dose received;

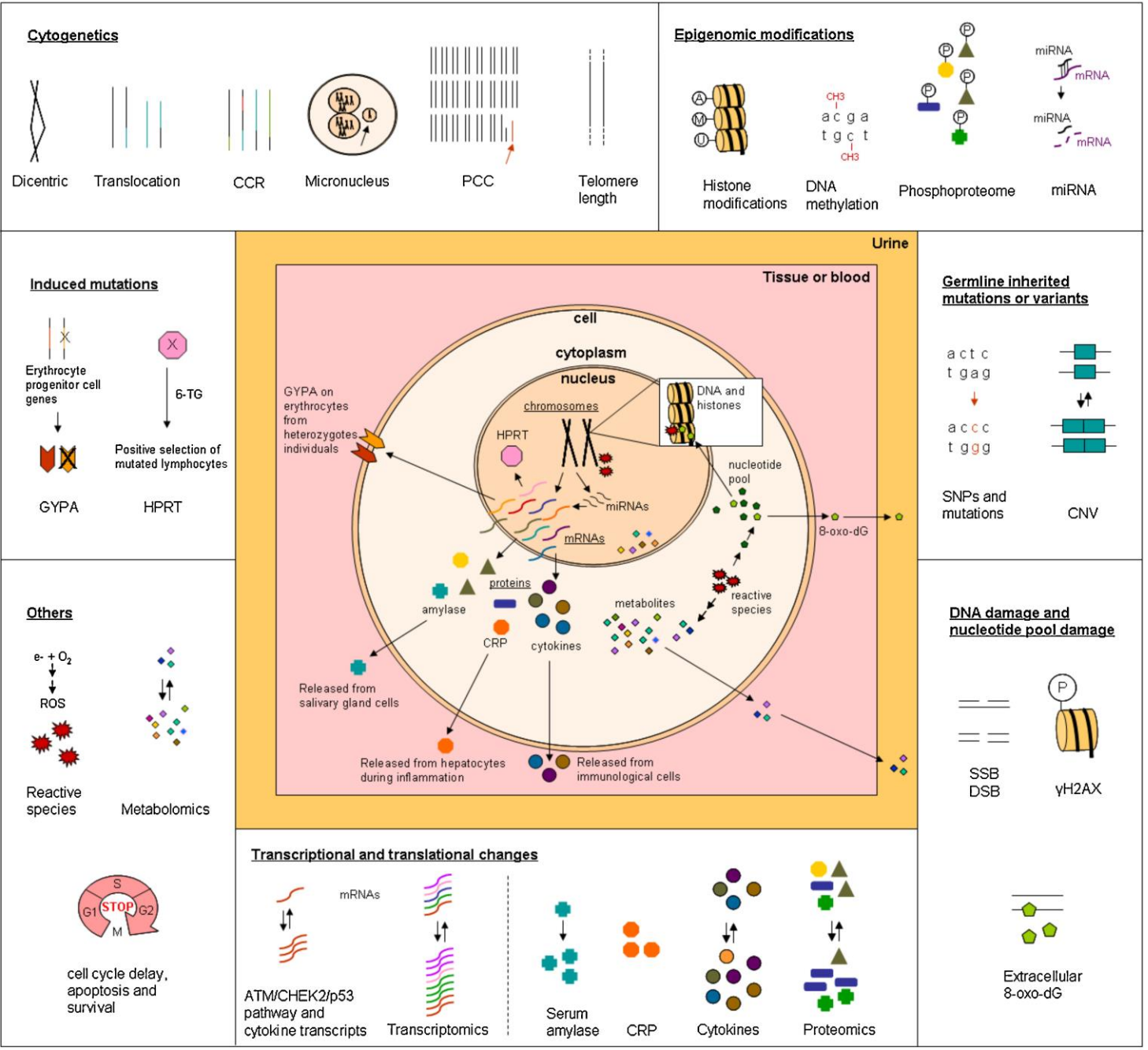
Biomarkers of susceptibility: available before, during or after exposure and can predict an increased risk of radiation effects;

Biomarkers of late effects: used to assess health effects that are present a long time after exposure, before clinical detection of the radiation induced disease or death;

Biomarkers of persistent effects: allow the assessment of radiation effects present a long period of time after exposure.



Pernot E, et al. **Ionizing radiation biomarkers for potential use in epidemiological studies.** *Mutat Res.* 2012 Oct-Dec;751(2):258-286. doi: 10.1016/j.mrrev.2012.05.003. Epub 2012 Jun 4. PMID: 22677531.



Overview of potential IR biomarkers

1. Cytogenetic biomarkers;
2. Biomarkers related to nucleotide pool damage and DNA damage;
3. Biomarkers related to germline inherited mutations and variants;
4. Biomarkers related to induced mutations;
5. Biomarkers related to transcriptional and translational changes;
6. Biomarkers related to epigenomic modifications;
7. Other biomarkers (including biophysical markers of exposure)

Pernot E, et al. **Ionizing radiation biomarkers for potential use in epidemiological studies.** *Mutat Res.* 2012 Oct-Dec;751(2):258-286. doi: 10.1016/j.mrrev.2012.05.003. Epub 2012 Jun 4. PMID: 22677531.

Potential biomarkers of IR exposure/effects

Type of biomarkers	Assay	IR dose range	Time for detection of response (hours, days, years)
Blood cell count	– Count of peripheral blood lymphocytes	• from 2/3 to 8 Gy	• 12-24 hours
Cytogenetic			
• **Dicentric chromosomes**	– Dicentric chromosome	• from 0.1 to 5 Gy	• Years
• **Choromosome translocations**	– fluorescence in situ hybridization (FISH),	• from 0.25 to 4 Gy	
• **Premature chromosome condensation**	chromosome banding	• from 0.2 to 20 Gy	
• **Complex chromosomal rearrangement**		• NA	
• **Telomere length**	– Flow cytometry, FISH, qPCR	• NA	
• **Micronuclei**		• from 0.2 to 4 Gy	• Months
Gene mutation related			
• **Single nucleotide polymorphisms (SNP)**	– SNP assay/genome wide association studies (GWAS)	• NA	
• **Copy number variants and alterations**	– Comparative genomic hybridization (CGH), FISH, next generation sequencing (NGS)	• NA	• Years
	– Flow cytometer assay for Glycophorin A	• >1 Gy	
• **Induced somatic mutations**	– PCR for hypoxantine-guanine phosphoribosyl transferase mutation	• >90 mGy	
Related to nucleotide pool and DNA damage			
• **Double and/or single strand break**	– Comet assay	• from 0.1 to 8 Gy	• Weeks
• **γH2AX assay**	– Immunofluorescent staining, flow cytometry, high throughput techniques	• from 0.01 to 8 Gy	• Days
• **Extracellular 8-Oxo-deoxyguanosine**	– HPLC-enzyme-linked immunosorbent assay (ELISA), ELISA	• from 1 to 100 mGy	• Weeks
Related to transcriptional and translational changes			
• **Gene expression genes (cell cycle, apoptosis and DNA repair)**	– TaqMan assay, qPCR, microarray, nanostring, NGS	• NA	• Days, Months
• **Serum amylase**	– Serum amylase test	• >1 Gy	• Days
• **C-reactive protein**	– ELISA	• >1 Gy	• Years
• **Cytokine levels**	– ELISA	• >m1 Gy	
• **Protein analysis**	– Western blotting, ELISA, high throughput techniques	• NA	

Mutation Research/Reviews in Mutation Research
Volume 771, January–March 2017, Pages 59-84

Review

Ionizing radiation biomarkers in epidemiological studies – An update

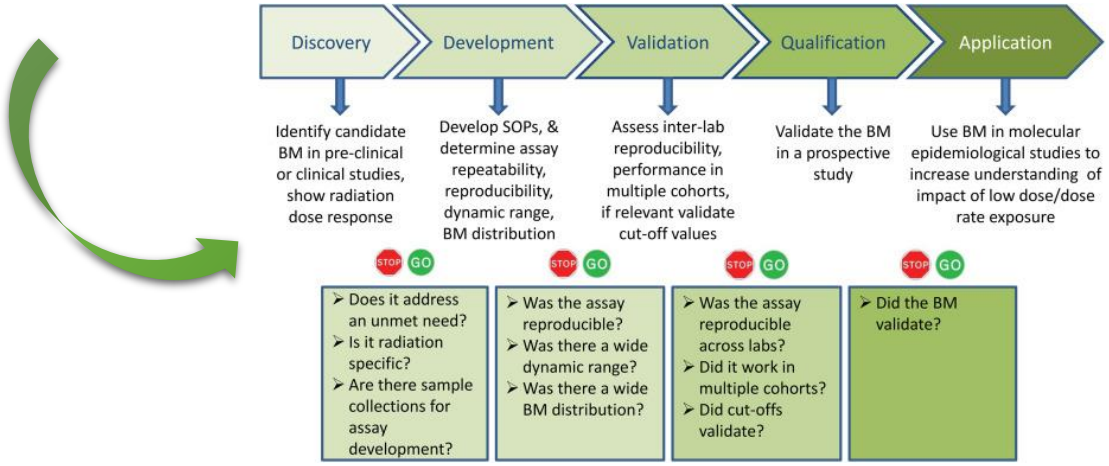
Janet Hall [a], Penny A. Jeggo [b], Catharine West [c], Maria Gomolka [d], Roel Quintens [e], Christophe Badie [f], Olivier Laurent [g], An Aerts [e], Nataša Anastasov [h], Omid Azimzadeh [h], Tamara Azizova [i], Sarah Baatout [e, j], Bjorn Baselet [e, k], Mohammed A. Benotmane [e], Eric Blanchardon [g], Yann Guéguen [g], Siamak Haghdoost [i], Mats Harms-Ringhdahl [i] ... Elisabeth Cardis [q, r, s]

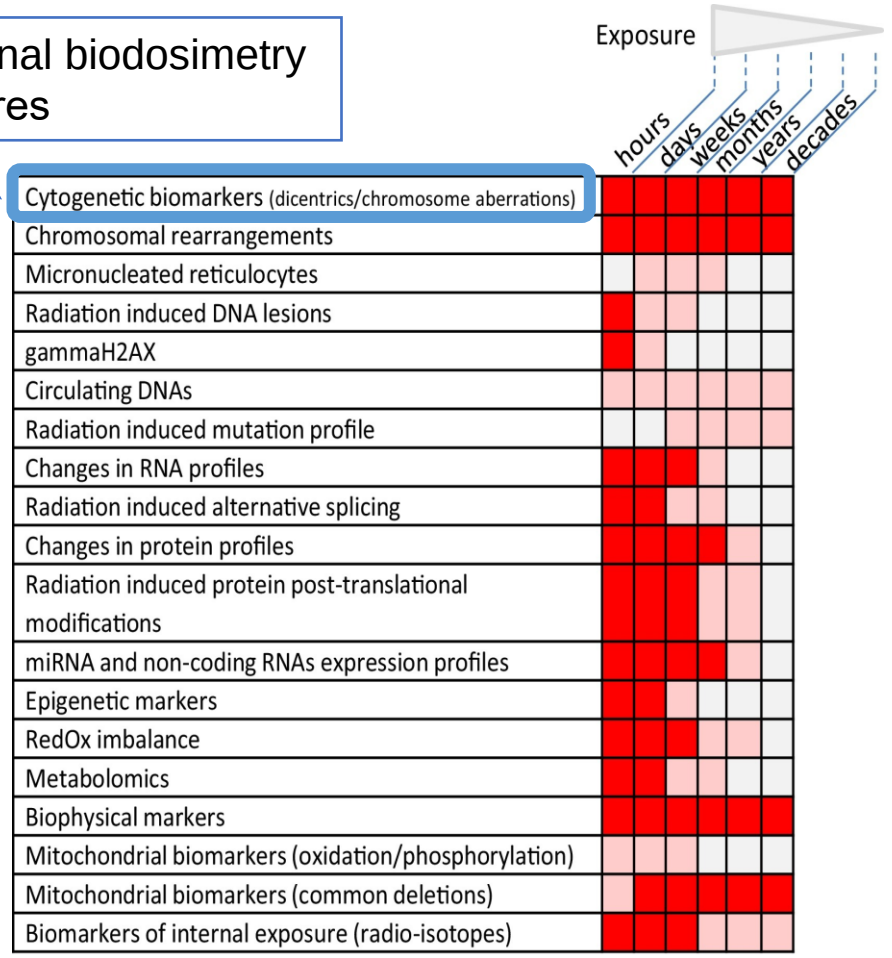
Potential biomarkers of LDIR exposure / effects in epidemiological studies

The extensive information gathered through the different *IR induced biomarker projects* and the rapid development of bioinformatics/system biology should provide the tools to identify the mechanisms underlying the cellular processes induced in response to low dose IR.

The ***dicentric*** assay remains the international biodosimetry "gold standard" for recent radiation exposures

A roadmap has been provided for biomarker development *from discovery to implementation* and used to summarize the current status of biomarkers proposed for epidemiological studies.





Most potential biomarkers remain at the discovery stage and for some there is sufficient evidence that further development is not warranted. One biomarker identified in the final stages of development and as a priority for further research is

«Radiation specific mRNA transcript profiles»

Hall J et al. *Ionizing radiation biomarkers in epidemiological studies - An update.* Mutat Res Rev Mutat Res. 2017 Jan-Mar;771:59-84. doi: 10.1016/j.mrrev.2017.01.001. Epub 2017 Jan 16. PMID: 28342453.

THE DISCOVERY OF SENSITIVE BIOMARKERS REPRESENTS A PRIORITY AREA OF INTEREST

Non/Mini-invasive predictive biomarkers of:

- **Exposure**: estimation or validation of received dose (biodosimetry)
- **Effect**: early detection of a radiation induced health effect or identification of long-term permanent side-effects
- **Susceptibility** during or after exposure that can predict an increased cancer risk.

winning strategy

Liquid biopsy:

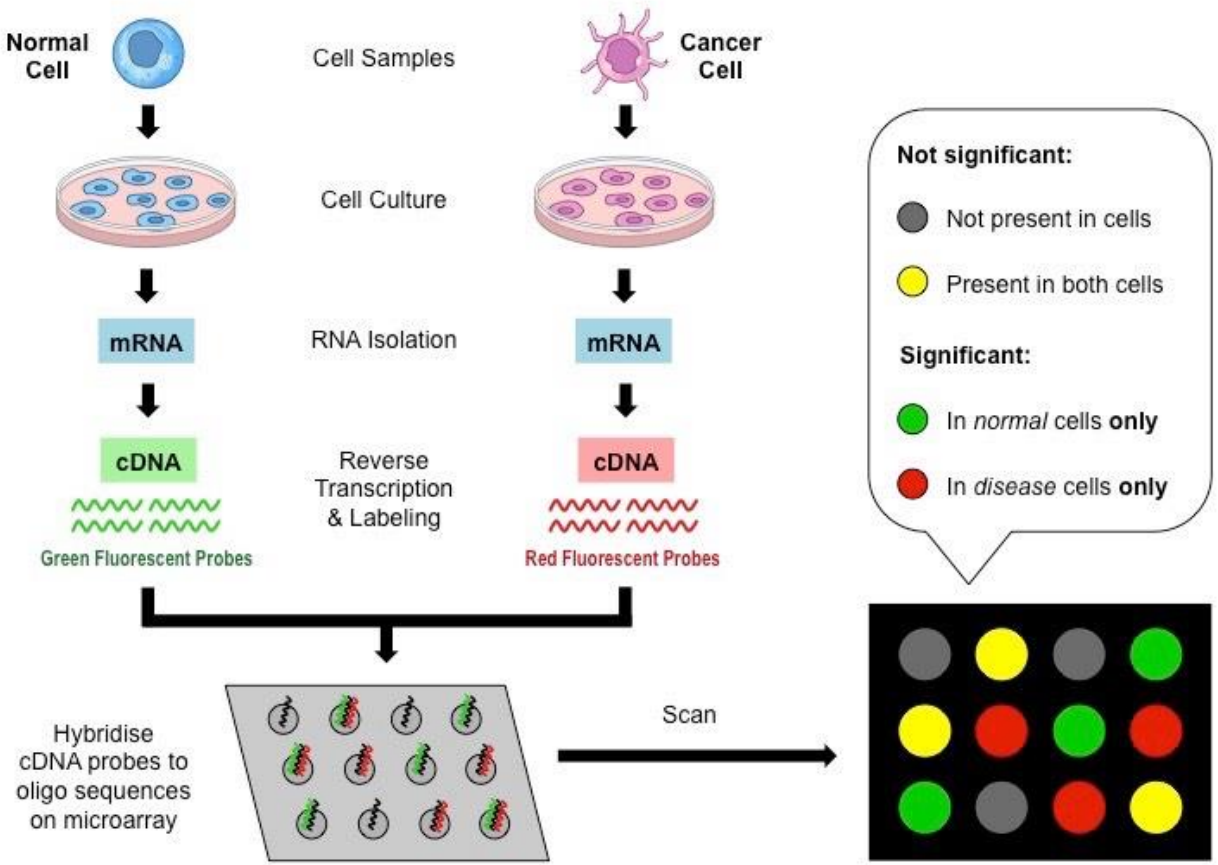
Peripheral Blood Mononuclear Cells (PBMCs) as a source of tumour-derived molecular information

High-throughput technologies

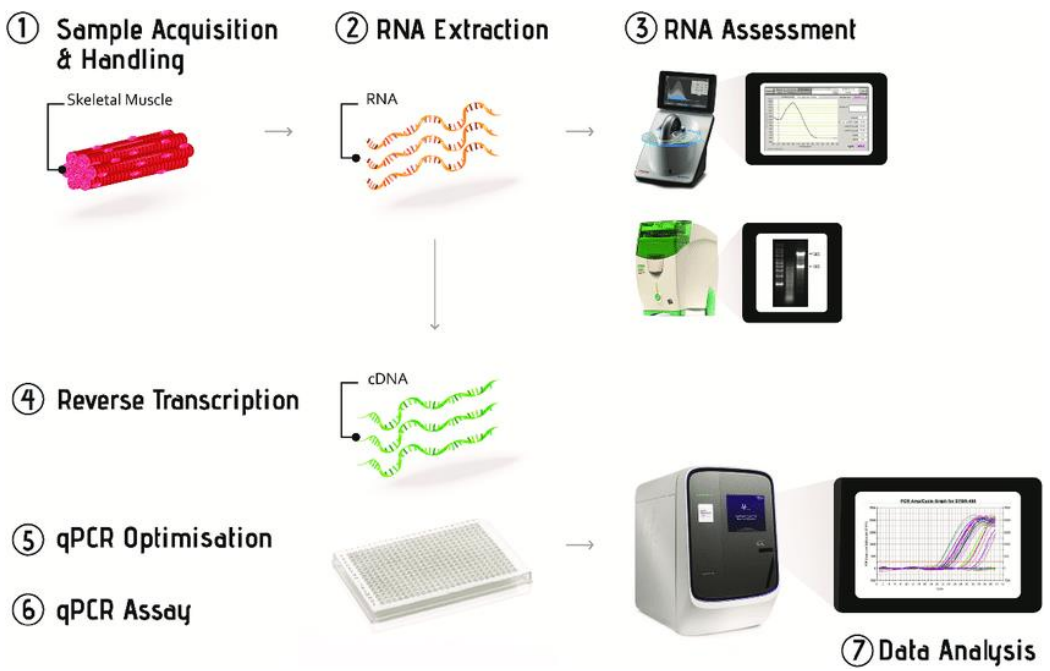
(i.e. gene expression profiles)

Laboratory tests used for gene expression analysis (both in vitro and in vivo studies).

DNA Microarray



Quantitative real-time PCR



“Gene signature”: an appealing strategy for biodosimetry

Several studies have shown that gene expression (GE) is modulated in a dose-dependent manner, suggesting that it could be used as an alternative tool for mini-invasive radiation biodosimetry.
These studies have shown even that LDIR exposure induces a well-defined physiological response that can be determined by gene expression analysis. Low-dose exposure mainly activates stimulatory, inflammatory and pro-survival responses.

Abend M, et al. 2016. Examining radiation-induced in vivo and in vitro gene expression changes of the peripheral blood in different laboratories for biodosimetry purposes: first RENEB gene expression study. Radiat Res. 185:109–123.

IN VITRO STUDIES

In-vitro studies on human peripheral blood cells exposed to doses between 5 -25 mGy suggest that GE analysis has a sensitivity to LDIR exposure comparable to the DCA method (Knops et al. 2012; Riecke et al. 2012; Manning et al. 2013; Nosel et al. 2013)

Exposure of human lymphocytes to LDIR rather than high dose IR significantly affects biological processes/pathways such as DNA repair and stress response, cell growth and differentiation, metabolism, and transcriptional regulation (Fachin AL, et al 2007)

3 hours after exposure to LDIR of 0.05 Gy, CD4+ T-lymphocytes showed a 10-fold greater gene down-regulation profile than that observed in the other cell subpopulations (T CD8+ and T CD56+), suggesting that the CD4+subpopulation is more sensitive to LDIR. Analysis of down-regulated genes showed that the early response to LDIR alters processes associated with protein biosynthesis and oxidative phosphorylation (Gruel G, et al, 2008)

LDIR (0.05 Gy) → activation of inflammatory genetic patterns, up-regulation of genes associated with innate immunity (HMGB1, TLR4, TLR9, MyD88 and IRAK1).
HDIR → Up-regulation of genes involved in cell cycle arrest (CDKN1A), pro-apoptotic (AEN), and DNA-damage and repair genes (POLH and DDB2)
El-Saghire et al (2013)

EX VIVO STUDIES

GE analysis of PBMCs isolated from prostate cancer patients collected before and after (24 hours) radiotherapy showed that GE allows discrimination of exposure between 0.09-0.017 Gy. The FDXR gene has been identified as a sensitive and reliable tool for radiation dose assessment even after LDIR exposure (Abend et al. 2016).

GE analysis (microarray) of PBMCs isolated from 20 cancer patients revealed the induction of a specific "transcriptional signature" of inflammation-associated genes before radiotherapy last fraction compared with the time of radiotherapy initiation (Cruz-Garcia L, et al 2021)

Cancer patients

78 genes differentially expressed in lymphocytes of 14 healthcare workers exposed for 9.32 ± 5.97 years to LDIR ranging from 0.696 to 39.088 mSv compared with 9 unexposed workers (Fachin et al. 2009)

256 differentially expressed genes in peripheral blood mononuclear cells (PBMCs) isolated from 28 healthcare workers exposed to a persistent comulative dose of 19 +/- 38 mSv (Morandi et al. 2009)

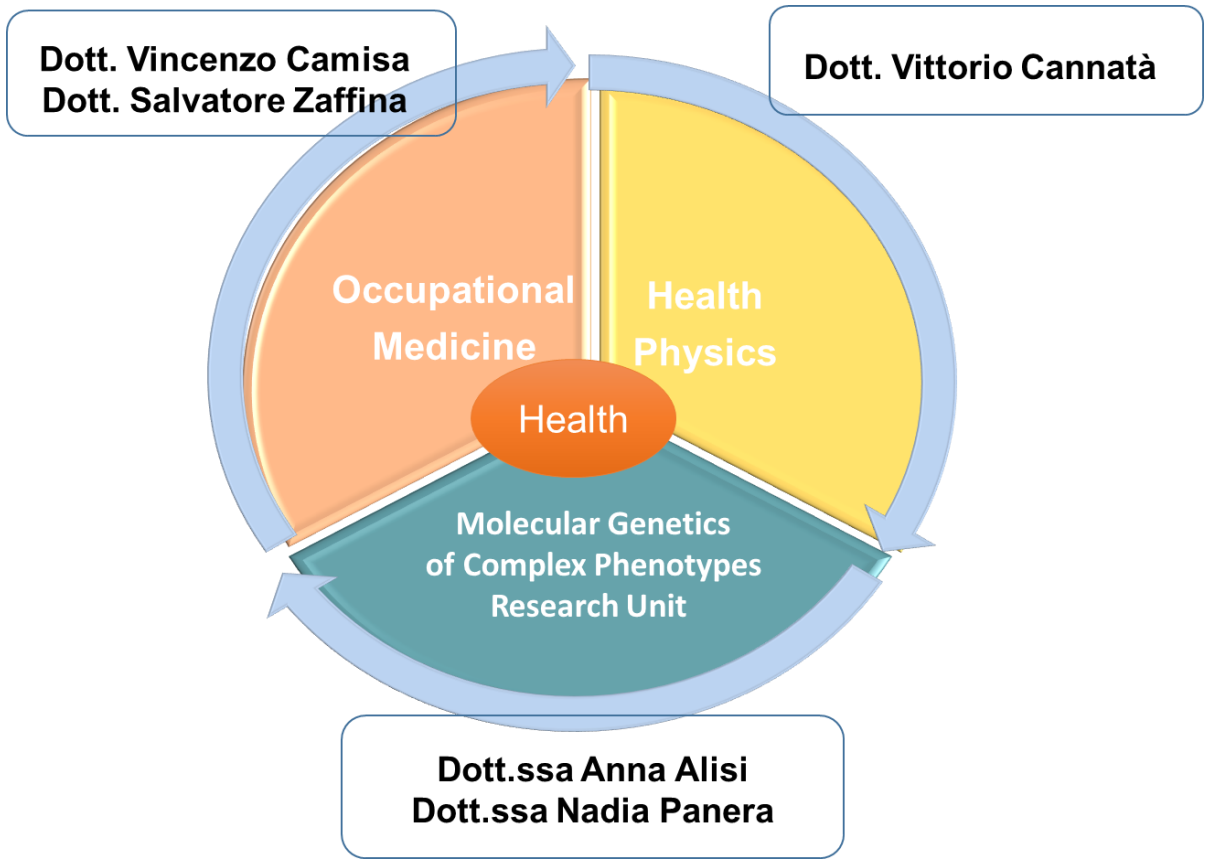
Gene expression analysis (qPCR) showed up-regulation of the hMSH2 gene by about 5-fold in 30 exposed workers compared with the control group (25) and a positive association of hMSH2 expression also with the number of working hours. hMSH2 gene is involved in DNA repair mechanisms, e.g. mismatch repair (Machi et al. 2022)

Physicians, nurses radiological technicians

Patterns of GE analysis as a potentially powerful tool for detection and validation of a dose- and time-dependent panel of genes for **stochastic risk** assessment related to **LDIR (occupational) exposure**.

Need for further studies to support the possibility of developing an ideal **panel of IR-responsive genes**

OPBG Research Team - PILOT STUDY



We have started with a pilot study on **gene expression profiling** in peripheral blood mononuclear cells (**PBMCs**) to evaluate **LDIR-specific molecular processes**, or pathways, or responses and even to identify (early and late) **possible biomarkers of LDIR exposure** in a small sample of HCW of Bambino Gesù Children's Hospital (OPBG)

STUDY DESIGN

18 Health care workers

♀10 ♂8

Three groups

Exposed category **B** (N=5; ♀3 ♂2) effective dose (1-6 mSv/year)

Exposed category **A** (N=8; ♀4 ♂4) effective dose (6-20 mSv/year)

Subgroup **A+T** (Thyroid tumor *) (N=4; ♀3 ♂1)

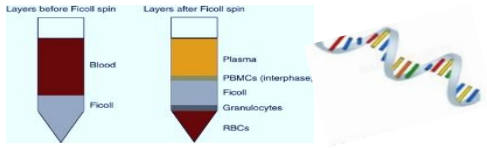
Unexposed **CTRL** group (N=5; ♀3 ♂2)

Exclusion criteria: smoking, previous history of malignancy, medications in the last 6 months

* New diagnosis

Sample Preparation

PBMC Isolation and RNA extraction



Reverse Transcription

cDNA synthesis

Sample Loading

OpenArray Human Cancer Plate (624 genes)

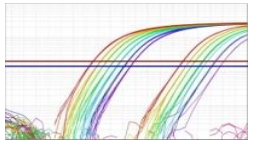
AccuFill™ System

Real-time PCR

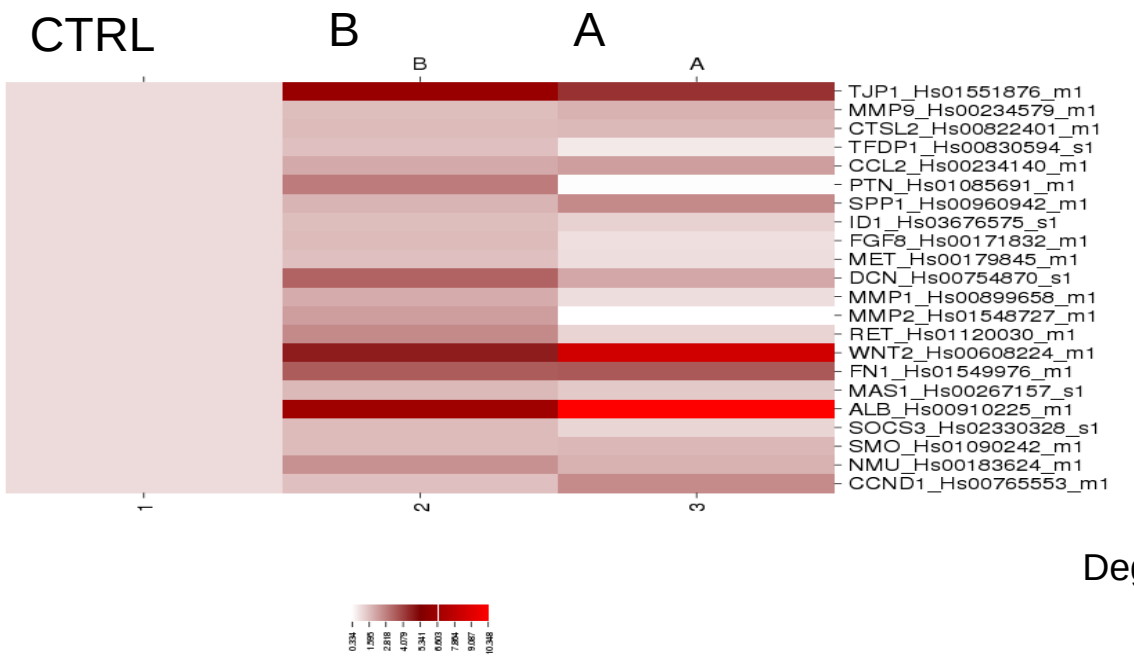
QuantStudio 12K Flex Real-Time PCR System

Data Analysis

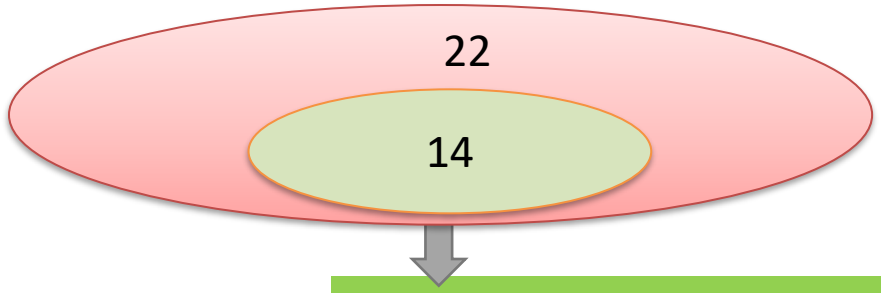
Open source Cloud platform



UP-REGULATED GENES IN RADIATION WORKERS

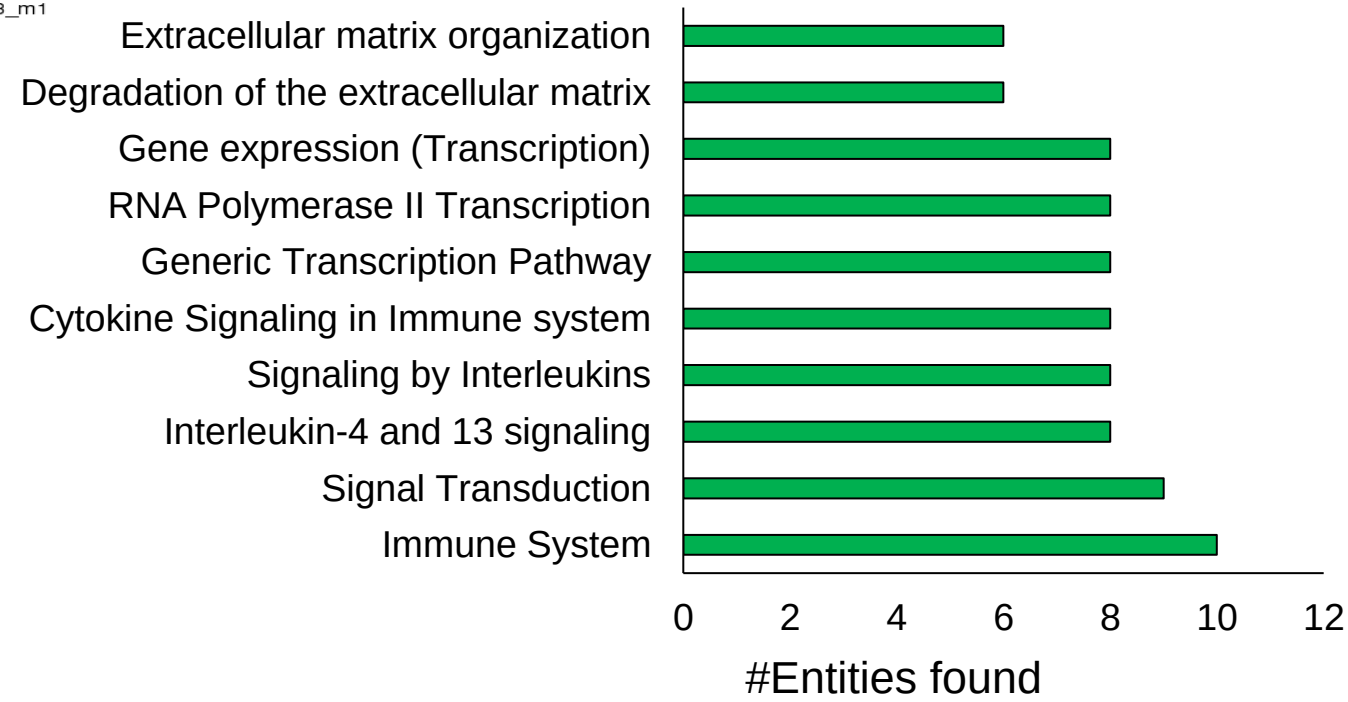


Genes up-regulated in B (22 in total)



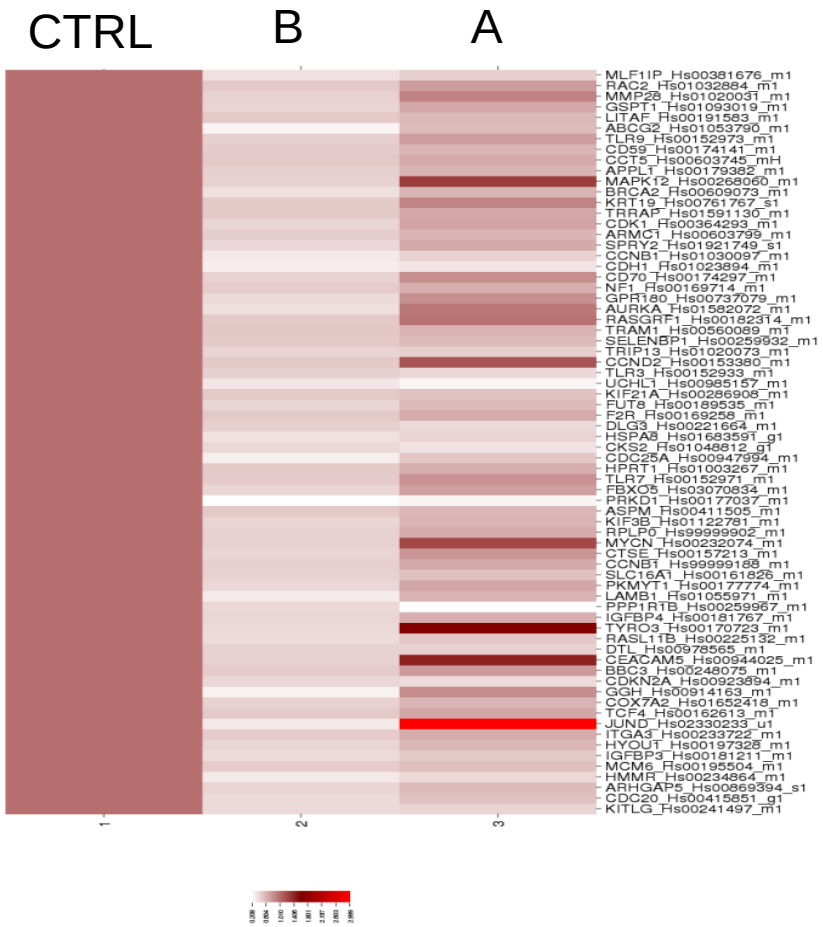
Genes up-regulated in B and A

Reactome Pathways

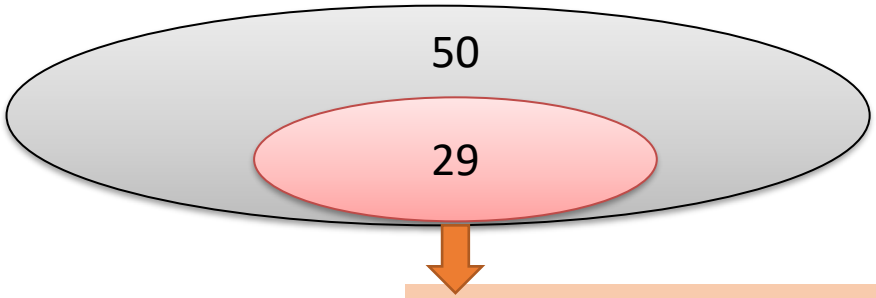


KEGG database
for pathway mapping

DOWN-REGULATED GENES IN RADIATION WORKERS

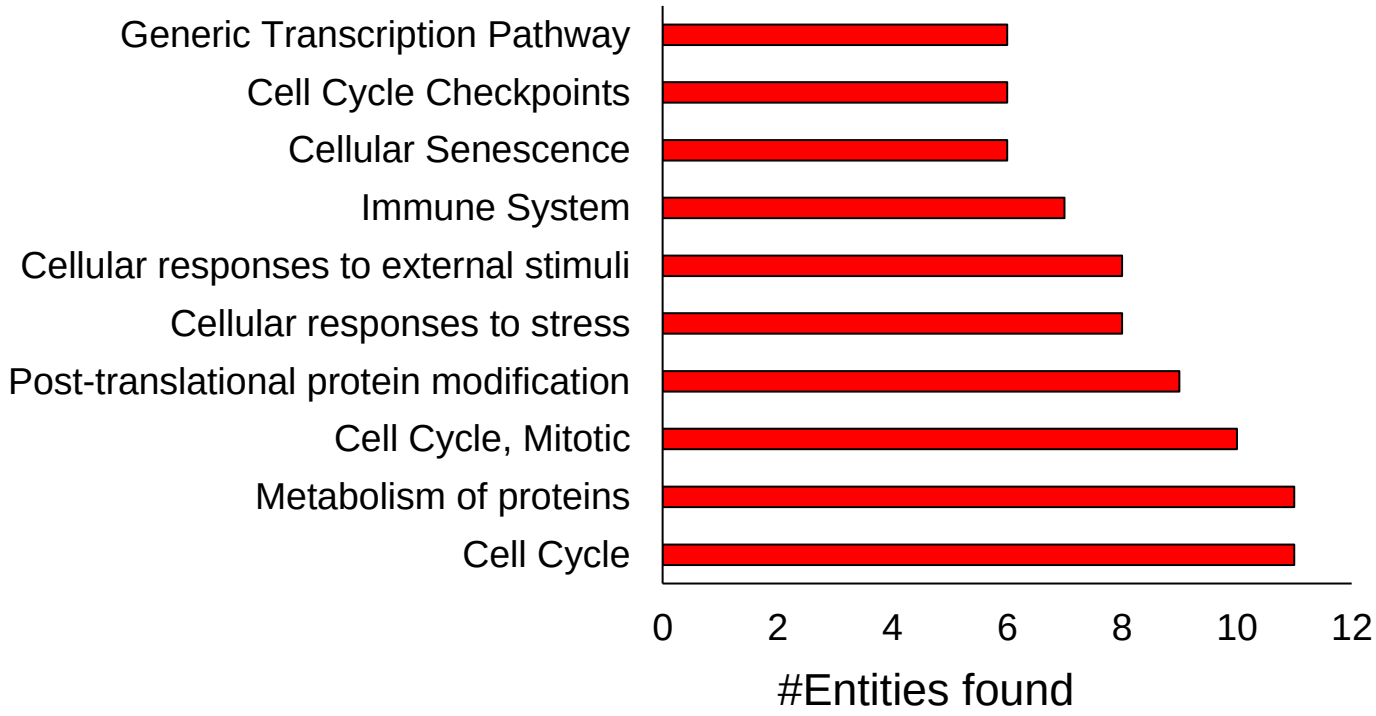


Genes down-regulated in B (50 in total)

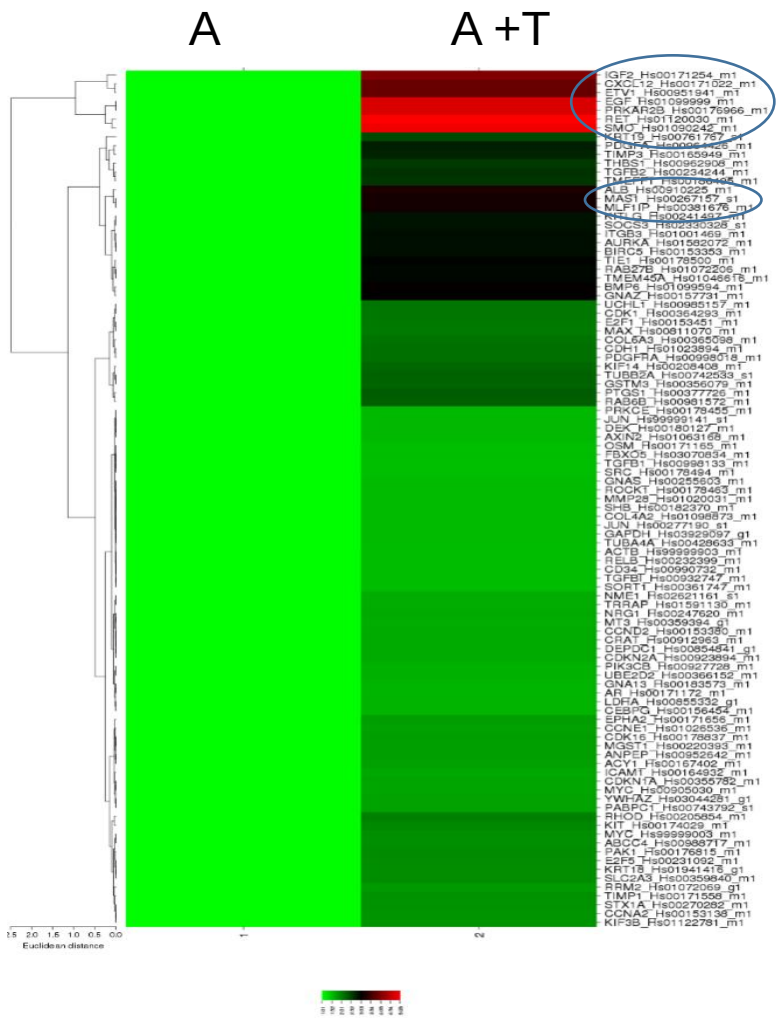


Genes down-regulated in B and A

Reactome Pathways

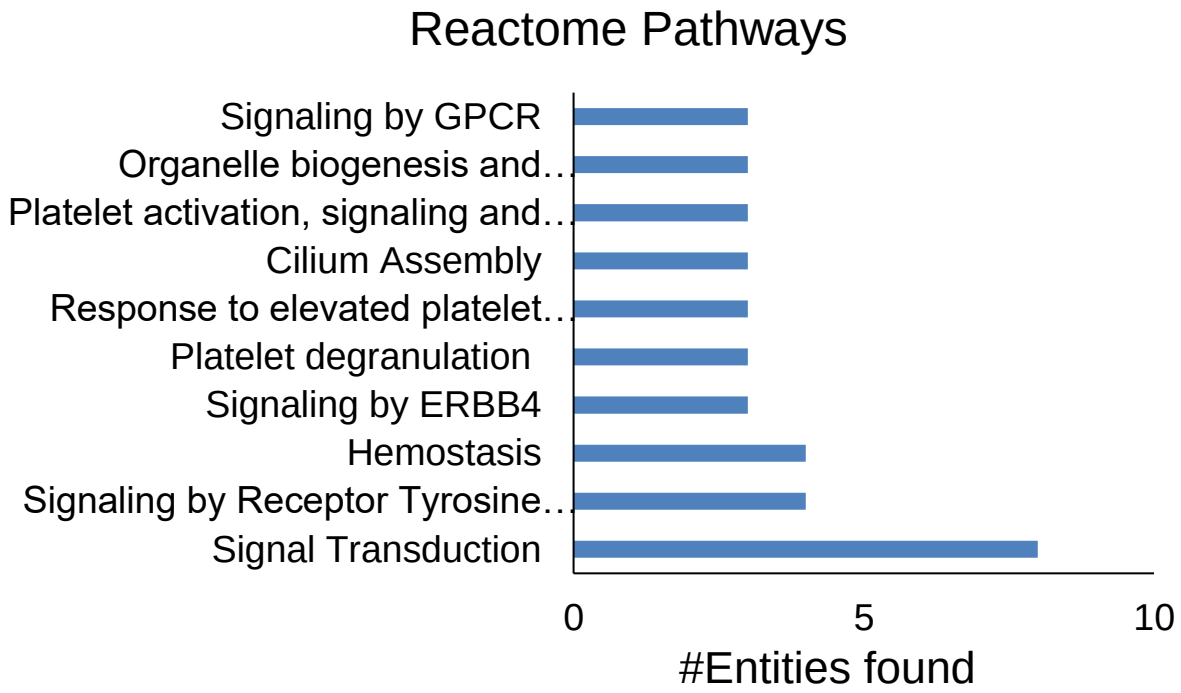


UP-REGULATED GENES IN CATEGORY A+T COMPARED TO CATEGORY A



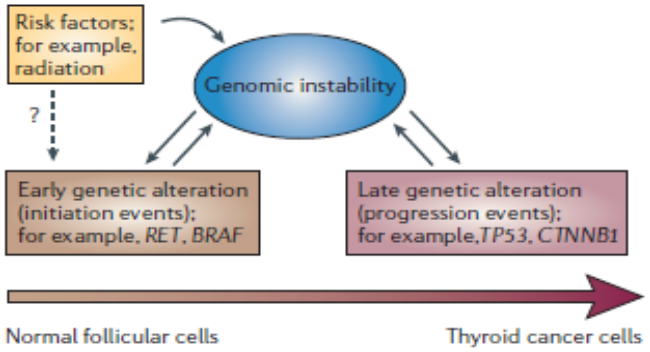
RET ← proto-oncogene
SMO
EGF
PRKAR2B
IGF2
CXCL12
ETV1
ALB
MAS1
MLF1IP

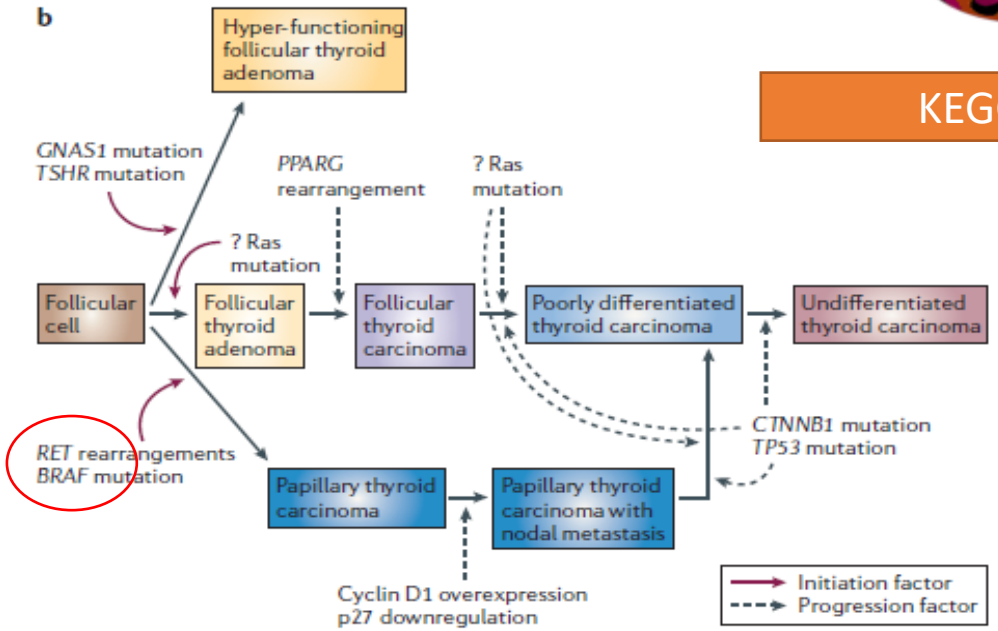
10 genes **up-regulated**



RET GENE: Ionizing Radiation and Thyroyd Cancer

RET was the first activated receptor-tyrosine kinase to be identified in thyroid cancer. Genetic defects that result in activation of RET represent early, frequent initiating events that can be associated with radiation exposure.





KEGG CANCER

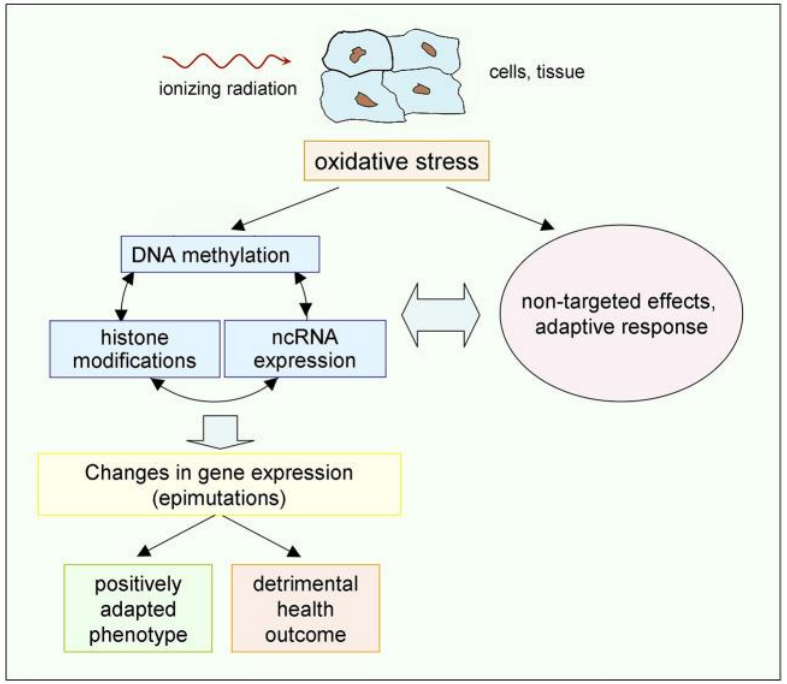
The up-regulation of the protoncogene RET may not be random

The prevalence of RET (RET/PTC) oncogene rearrangements is higher (60-70%) in radio-induced papillary carcinomas than in sporadic thyroid carcinomas (20%)

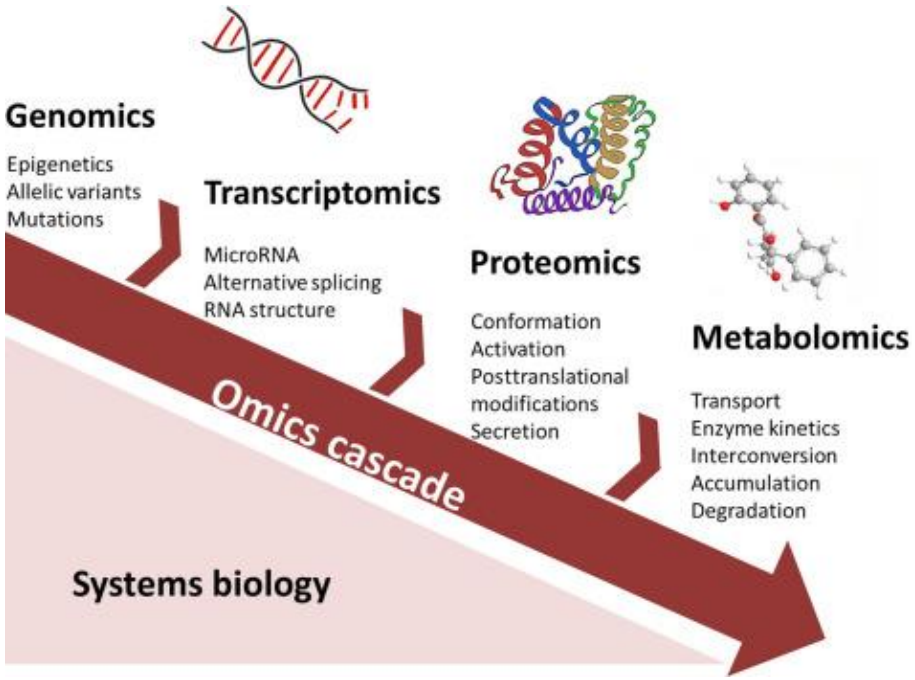
Kondo T., Ezzat S., Asa SL. ***Pathogenetic mechanisms in thyroid follicular-cell neoplasia.*** **Nat Rev Cancer. 2006 Apr;6(4):292-306. Review**

Xing M. ***Molecular pathogenesis and mechanisms of thyroid cancer.*** **Nat Rev Cancer. 2013 Mar;13(3):184-99. doi: 10.1038/nrc3431. PMID: 23429735; PMCID: PMC3791171.**

Suzuki K, Saenko V, Yamashita S, Mitsutake N. Radiation-Induced Thyroid Cancers: Overview of Molecular Signatures. Cancers (Basel). 2019 Sep 2;11(9):1290. doi: 10.3390/cancers11091290. PMID: 31480712; PMCID: PMC6770066.

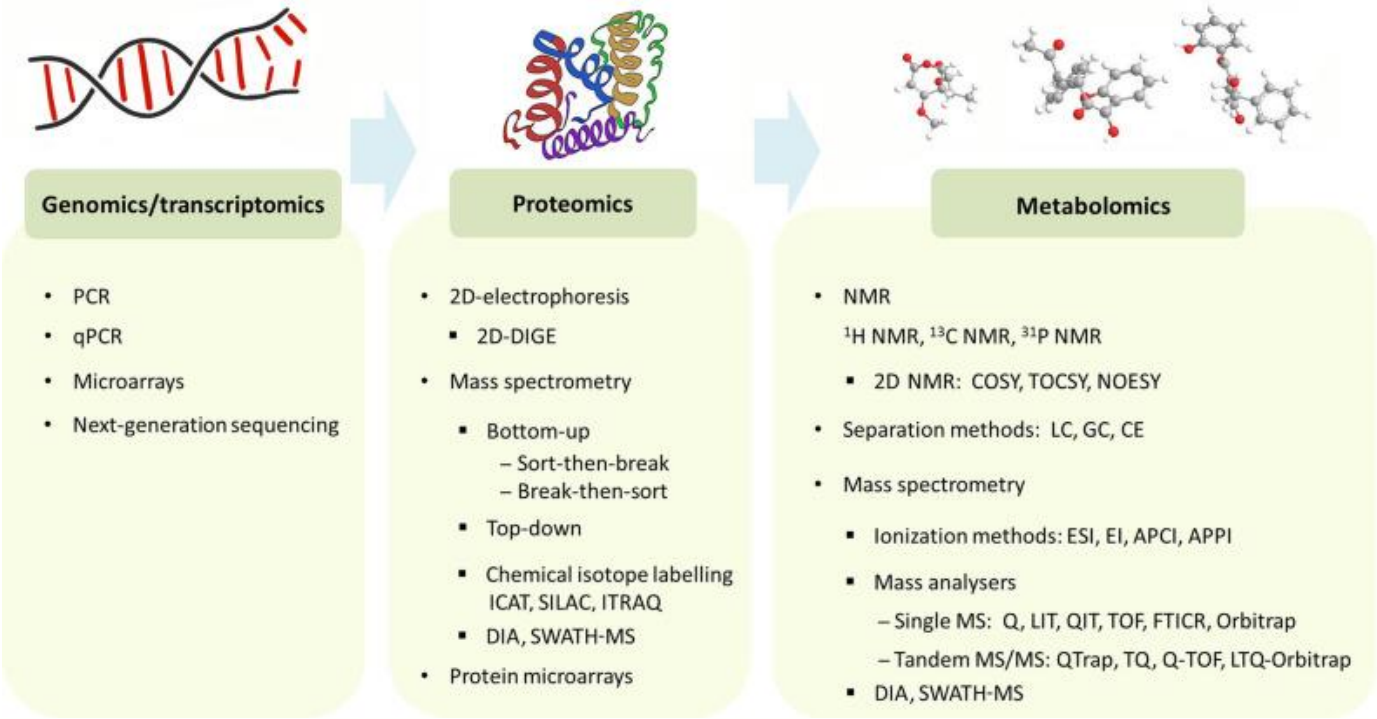


Belli M, Indovina L. The Response of Living Organisms to Low Radiation Environment and Its Implications in Radiation Protection. Front Public Health. 2020 Dec 15;8:601711. doi: 10.3389/fpubh.2020.601711. PMID: 33384980; PMCID: PMC7770185.



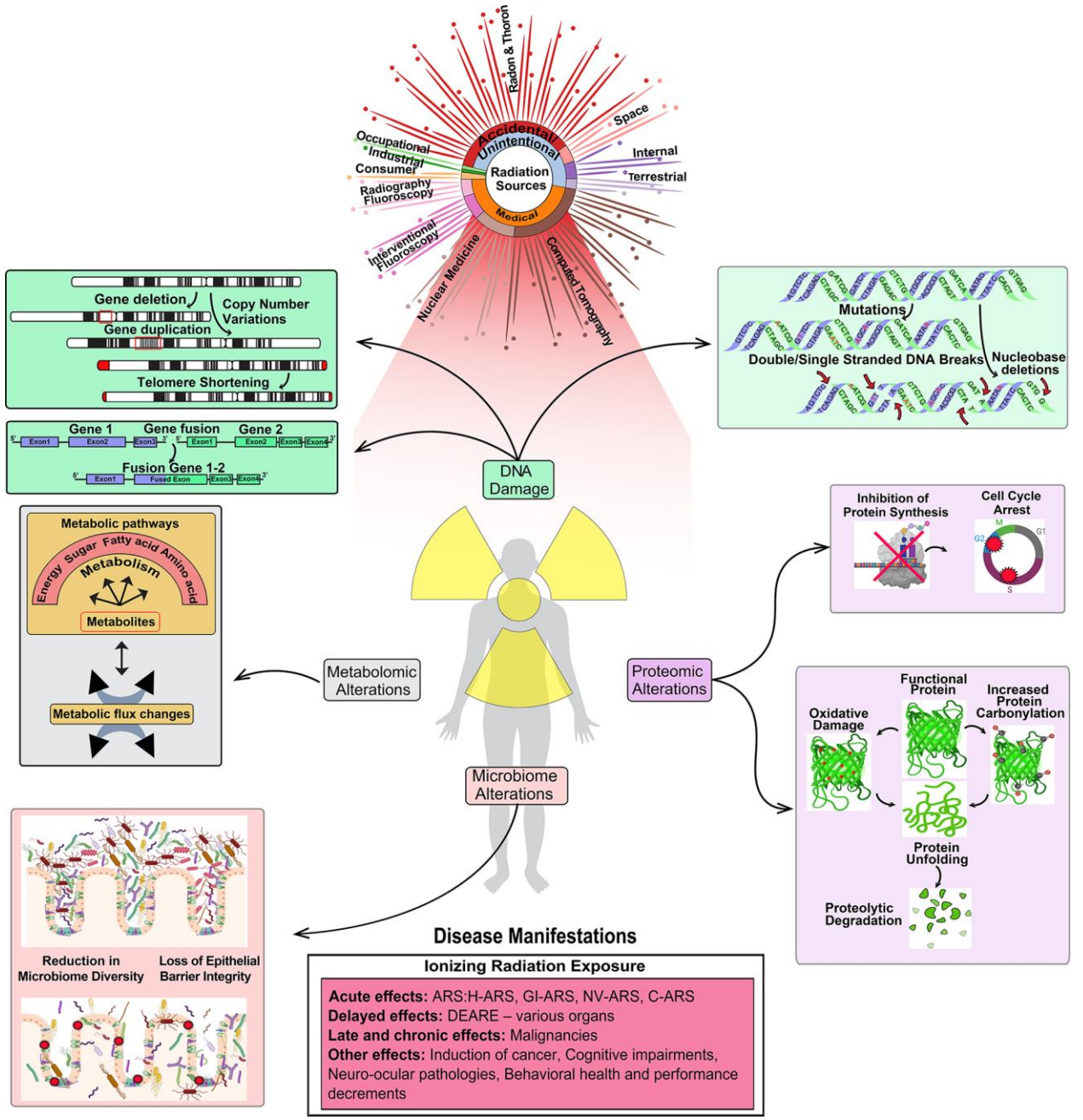
Multi-omic profiles as biomarkers of radiation-induced alterations and radiation injury

https://doi.org/10.1016/bs.coac.2018.07.002



In this review (*Shakyawar SK et al. 2023*), the authors performed a literature search to systematically catalog the radiation-induced alterations from multi-omic studies and the radiation countermeasures. We covered the radiation-induced changes in the *genomic, transcriptomic, proteomic, metabolomic, lipidomic, and microbiome profiles.*

Multi-omic profiles obtained from high-resolution omics platforms offer a holistic approach for identifying reliable biomarkers to predict the radiation injury of organs and tissues resulting from radiation exposures.



A Review of Radiation-Induced Alterations of Multi- Omic Profiles, Radiation Injury Biomarkers, and Countermeasures.

Shakyawar SK, Mishra NK, Vellichirammal NN, Cary L, Helikar T, Powers R, Oberley-Deegan RE, Berkowitz DB, Bayles KW, Singh VK, Guda C.

Radiat Res. 2023 Jan 1;199(1):89-111. doi: 10.1667/RADE-21-00187.1. PMID: 36368026; PMCID: PMC10279411.

CONCLUSIONS

- The results of several research projects might open new scenarios towards the identification of specific tools for assessing early and late effects of LDIR in exposed workers.

- The best scientific evidence currently available suggests that multi-omic profiles obtained from high-resolution omics platforms may help to identify biological response to LDIR.

- The biological effects we observed in our small sample of exposed workers encourage further investigations to assess whether one or more dysregulated genes after response could be used as candidate biomarkers of exposure, or early/late effects, or susceptibility to LDIR, but the limitations of using gene expression profiles must be considered:

- highly dynamic and transient nature of the signals;

- specific response pattern not yet identified;

- partial correlation with radiation exposure in terms of dose or dose-rate

- Further research on the individual IR genetic signature and possible confounding factors is needed to estimate the effective harmful dose and dose-rate in order to create a customized radiation protection model for workers and for patients exposed to LDIR.

- Current research data suggests the necessity of integrated studies of radiobiology and epidemiology at the national and international level in order to collect more systematic and deep information about health effects of low dose ionizing radiation.

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Scientific Committee: Radiation and Work

International Commission on Occupational Health - ICOH
Commission Internationale de la Santé au Travail - CIST

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Thanks for your attention

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