Απόκριση στις Βλάβες DNA. Επιδιόρθωση βλαβών και βιολογική σημασία μέσω βιολογίας συστημάτων.

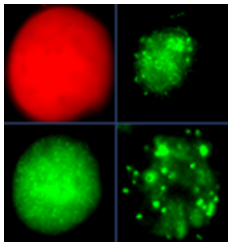
Αλέξανδρος Γ. Γεωργακίλας, Ph.D

Καθηγητής

Τομέας Εφαρμοσμένης Φυσικής

Εθνικό Μετσόβιο Πολυτεχνείο

*e-mail: alexg@mail.ntua.gr



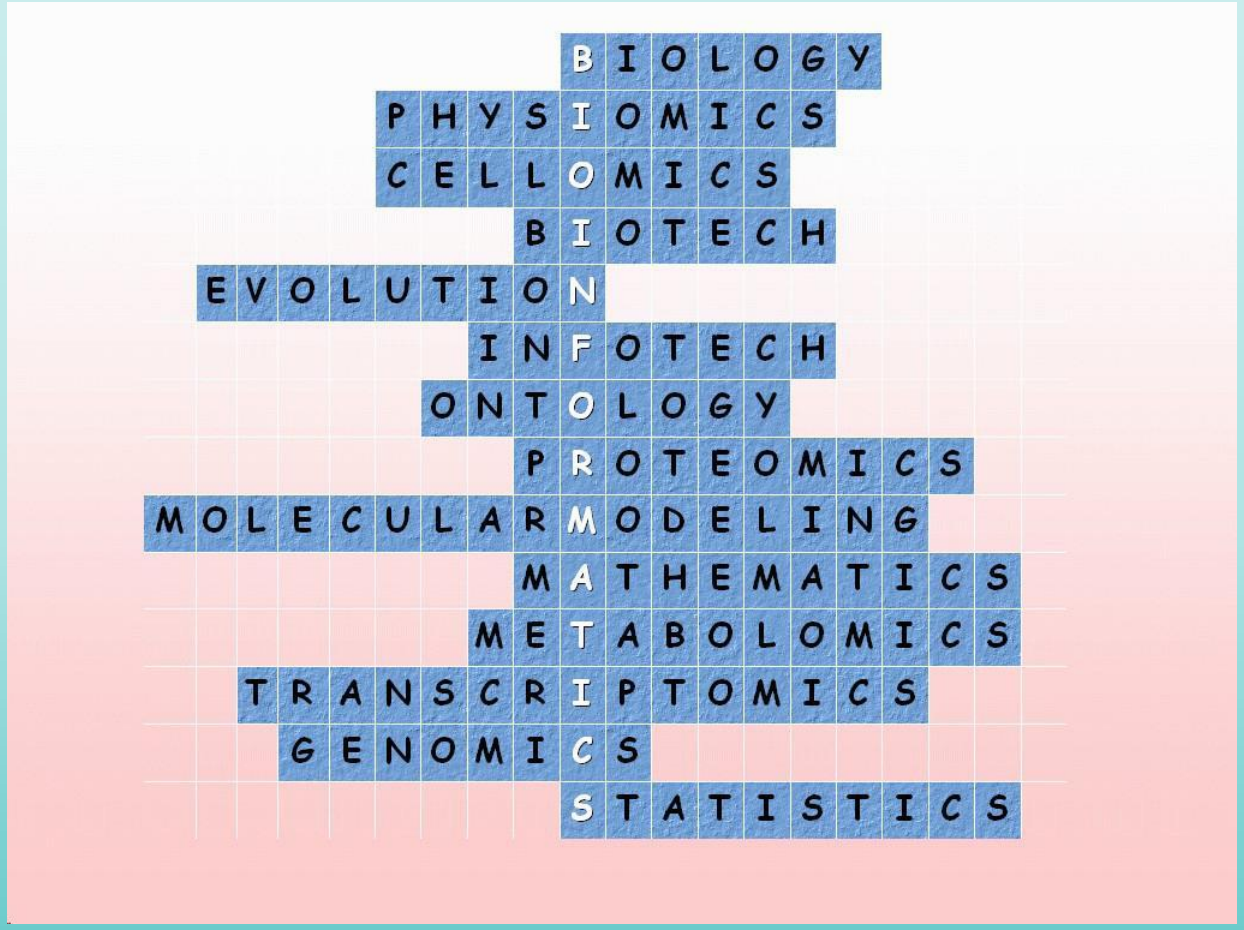
DNA DAMAGE Lab

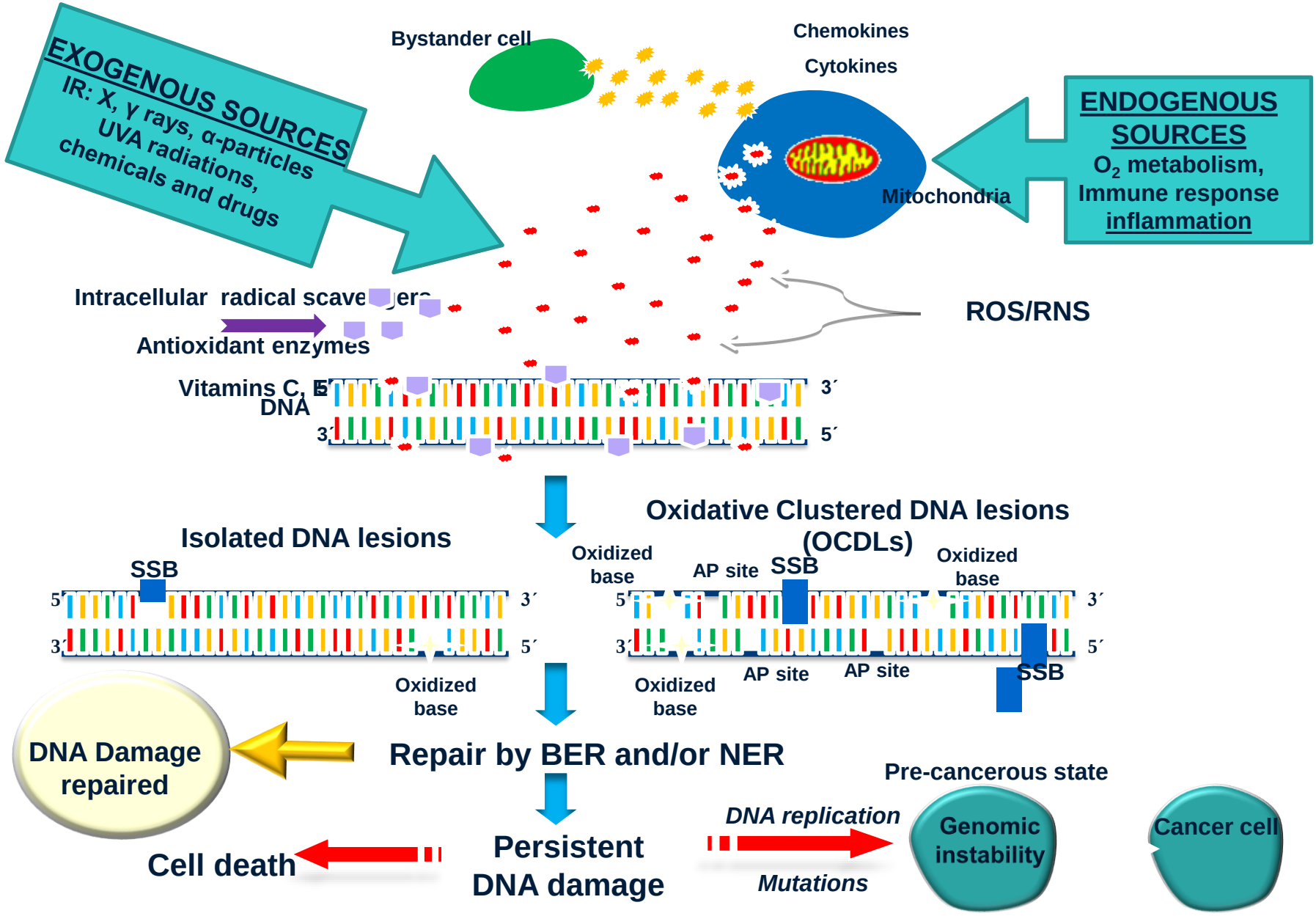
Εργαστήριο Μελέτης Βλαβών DNA

National Technical University of Athens

Η παρουσίαση αυτή χωρίζεται στα παρακάτω τμήματα:

1. Εισαγωγή στην έννοια των βλαβών DNA, μελέτες σε ανθρώπινα κύτταρα.
2. Μηχανισμοί επιδιόρθωσης (DNA repair).
3. Παραδείγματα βιοπληροφορικής προσέγγισης- Ανάγκη συστημικής θεώρησης


BIOLOGY
PHYSIOMICS
CELLOMICS
BIOTECH
EVOLUTION
INFOTECH
ONTOLOGY
PROTEOMICS
MOLECULARMODELING
MATHEMATICS
METABOLOMICS
TRANSCRIPTOMICS
GENOMICS
STATISTICS

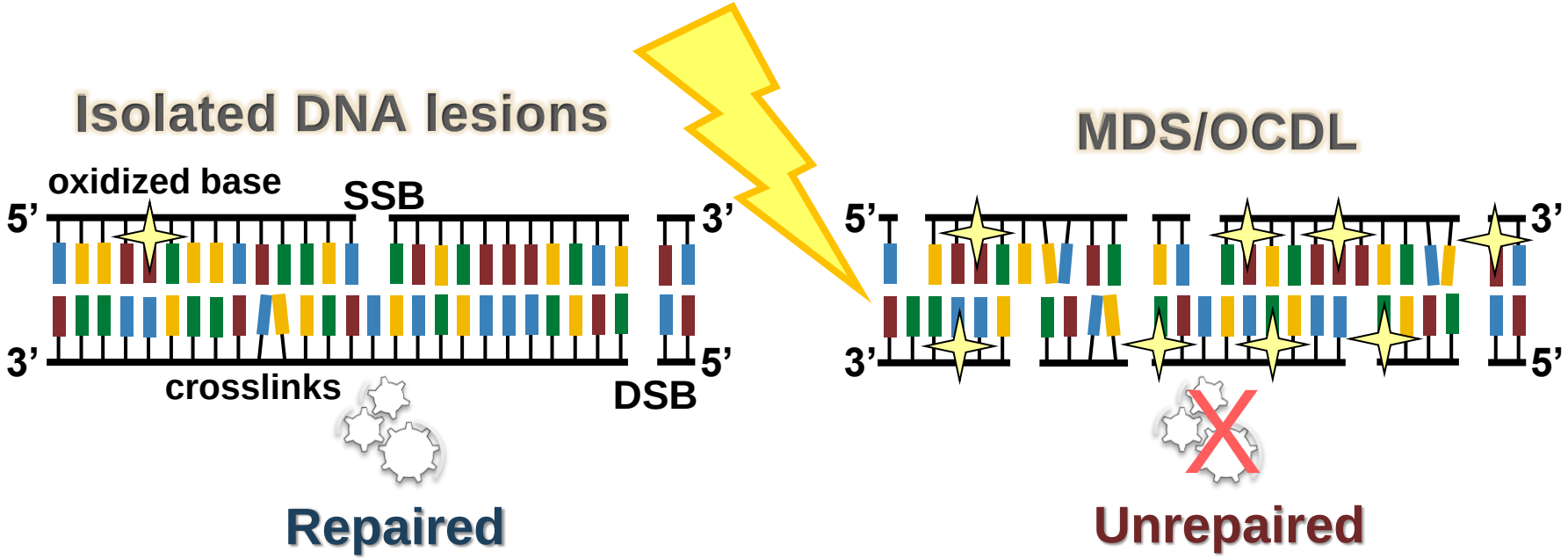


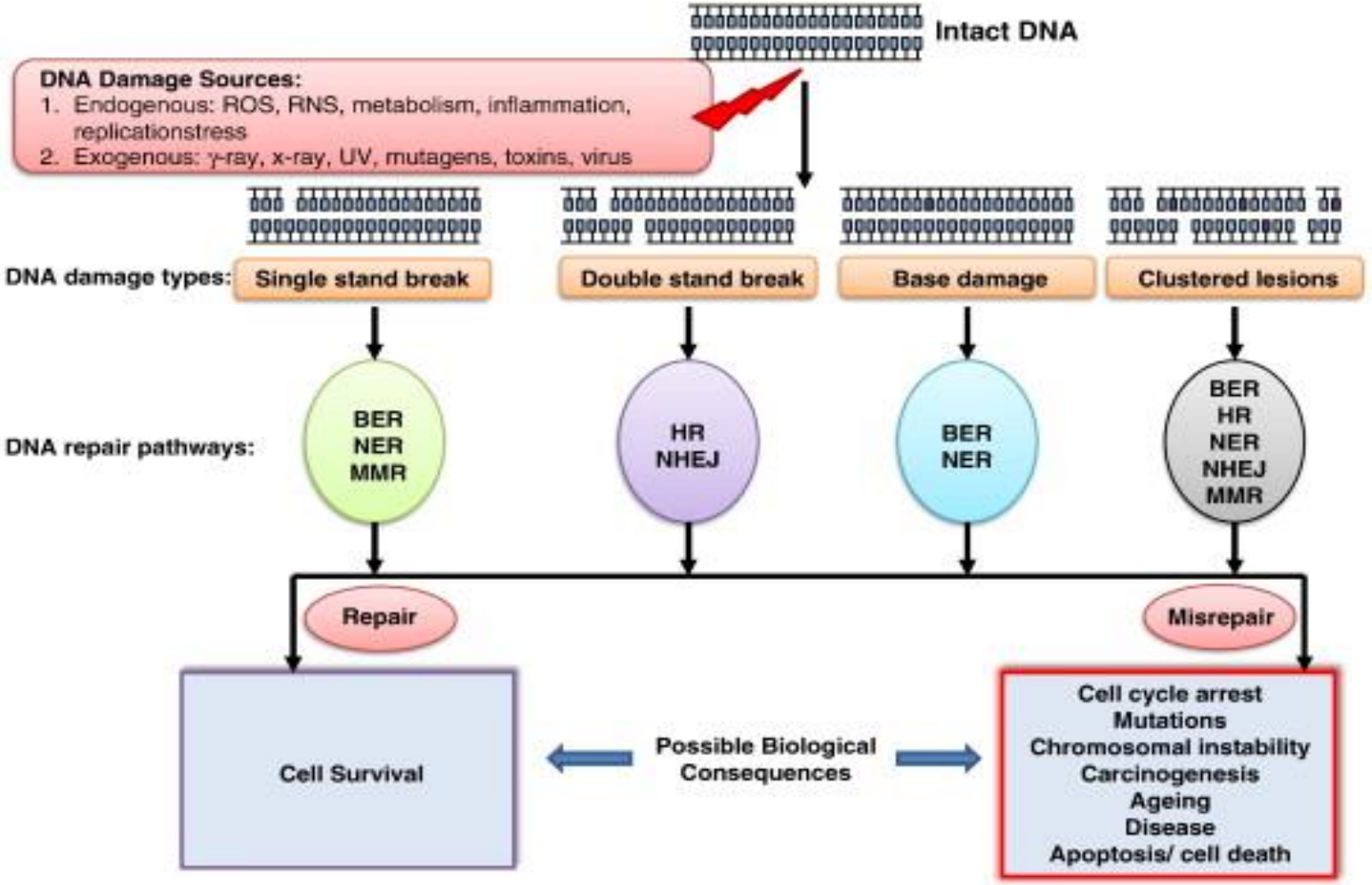
Nowsheen et al. Curr. Mol. Med. 2012; 12:672-680.

Kryston et al. Mutat Res. 2011

Complex DNA damage

IR-induced DNA lesions can be formed either separately or in close vicinity (a few nm), resulting in "clustered DNA lesions" or locally *m*ultiply *d*amaged *s*ites (**MDS**), which is considered the most severe type of genomic damage because of its complexity. This complex DNA damage includes both DSBs and non-DSBs, referred to as *o*xidatively-*c*lustered *D*NA *l*esions (**OCDLs**).





An overview of the different types of DNA damage and the expected damage repair mechanisms. Sources of DNA damage can be divided into endogenous and exogenous (environmental). The DNA lesion pool can consist of a variety of DNA modifications ranging from single-base lesions and single-strand breaks to more complex ones such as double-stranded fragments (DSBs) and clustered DNA lesions (non-DSBs).

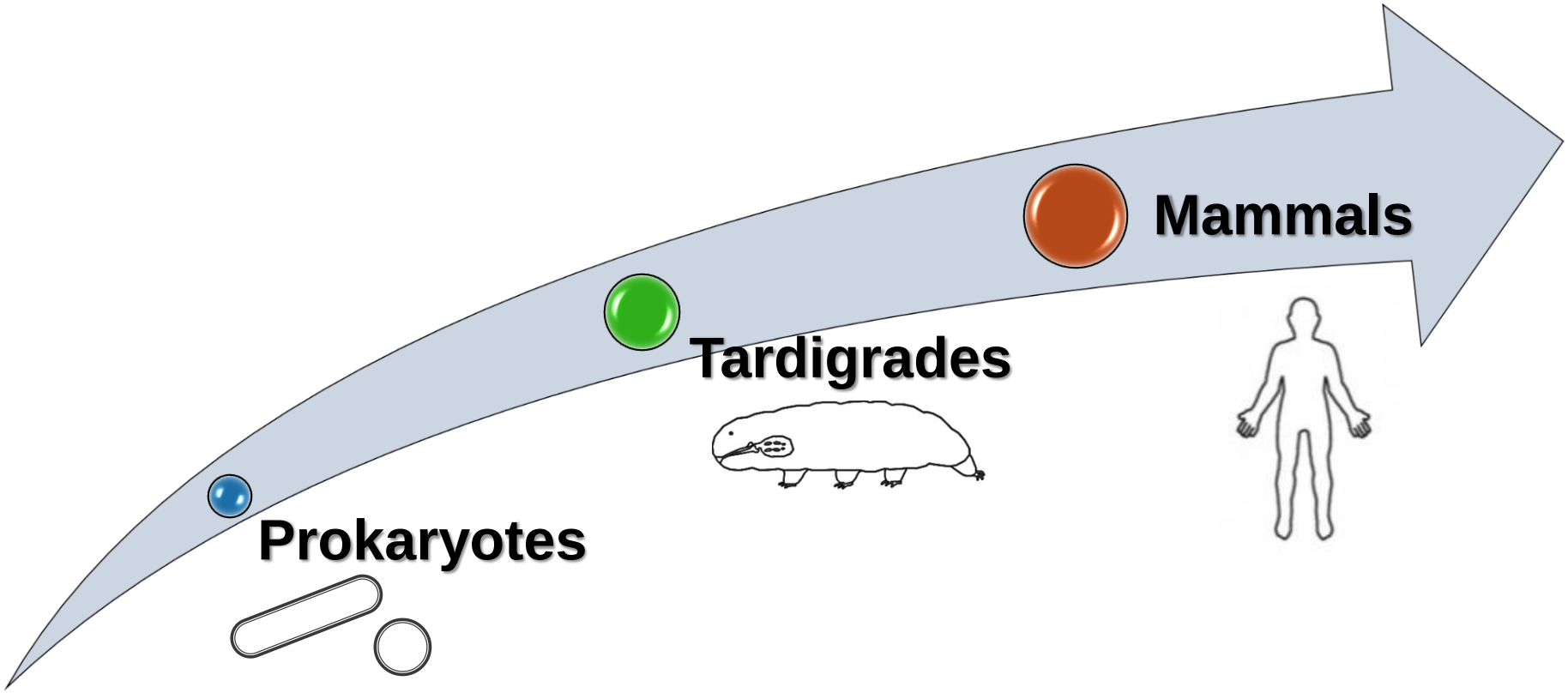
Pharmacology & Therapeutics Volume 133, Issue 3, March 2012, Pages 334-35

Mechanisms of Radiation Response

Universal cellular response(s) against ionizing radiation:

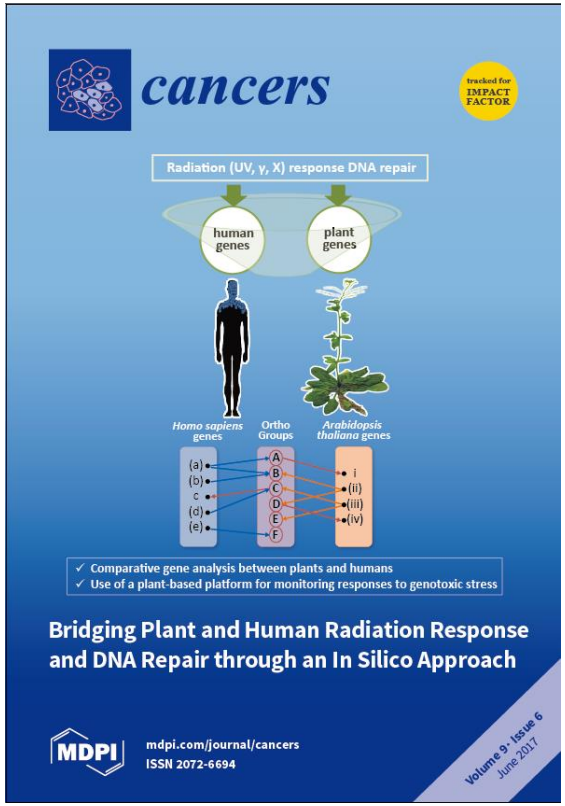
- harnessing of advanced and highly sophisticated DNA Damage Response and Repair (**DDR/R**) mechanisms, in order to preserve genomic integrity
- DDR/R is a complicated process consisting of recognition (or detection, or sensing), signaling, and repair of DNA damage

DNA Damage Response Conservation



Elucidation of <u>evolutionarily conserved</u> mechanisms, ranging from prokaryotes to human, implicated in DNA damage response

Cover story: Application of Bioinformatics and Systems biology



Bridging plant and animal stress responses

The conserved features of the DNA damage response and repair (DDR/R) in plants and animals might facilitate interdisciplinary studies that cross the traditional boundaries between animal and plant biology in order to discover new DNA damage biomarkers, particularly gene transcripts, for radiation exposure monitoring (REM) in environmental and biomedical settings. In this work, we have used a hybrid bioinformatics and experimental analysis, to reveal the common and divergent features of the most relevant DDR/R players in animals and plants focusing on ionizing radiation (IR) and UV-light.

A **plant-based platform for monitoring responses to genotoxic stresses is proposed.**

Nikitaki, Z., Pavlopoulou, A., Hola, M., Dona, M., Michalopoulos, I., Balestrazzi, A., Angelis, K. J., & Georgakilas, A. G. (2017). Bridging Plant and Human Radiation Response and DNA Repair through an In Silico Approach. *Cancers (Basel), 9.*

frontiers in Cell and Developmental Biology

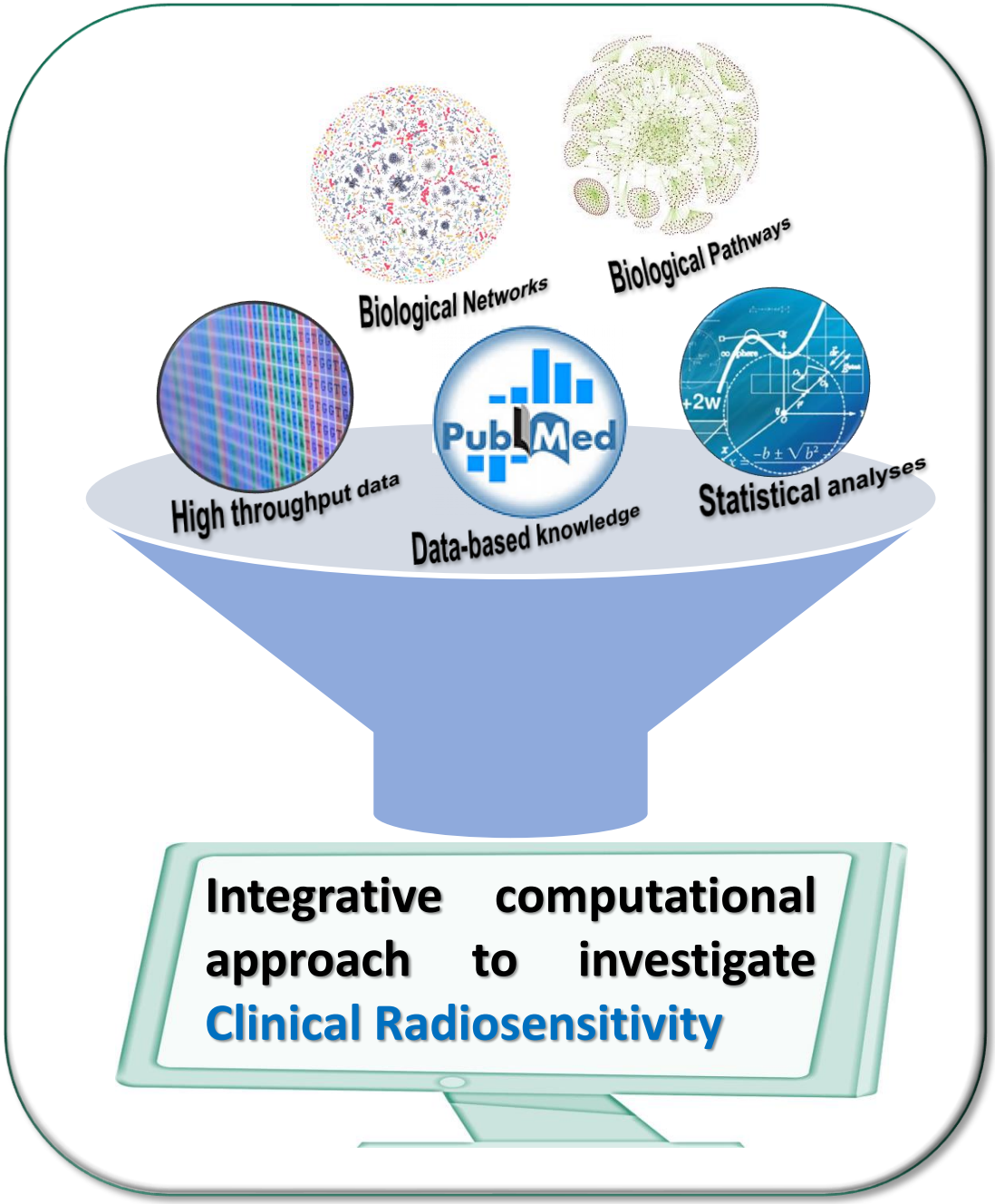
ORIGINAL RESEARCH
published: 07 April 2021
doi: 10.3389/fcell.2021.620248

Check for updates

Investigating Molecular Determinants of Cancer Cell Resistance to Ionizing Radiation Through an Integrative Bioinformatics Approach

Halil Ibrahim Toy[1,2], *Gökhan Karakülah*[1,2], *Panagiota I. Kontou*[3], *Hani Alotaibi*[1,2], *Alexandros G. Georgakilas*[4] *and Athanasia Pavlopoulou*[1,2*]

[1] *Izmir Biomedicine and Genome Center, Izmir, Turkey,* [2] *Izmir International Biomedicine and Genome Institute, Dokuz Eylül University, Izmir, Turkey,* [3] *Department of Computer Science and Biomedical Informatics, University of Thessaly, Lamia, Greece,* [4] *DNA Damage Laboratory, Department of Physics, School of Applied Mathematical and Physical Sciences, Zografou, National Technical University of Athens, Athens, Greece*

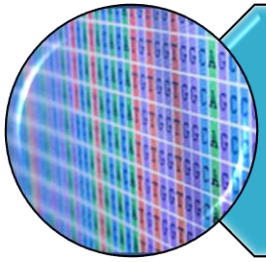


National Technical University of Athens

Bioinformatics Methods

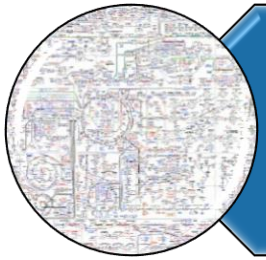
Bibliographic Search

Manual and automated search of biomedical literature for relevant data.



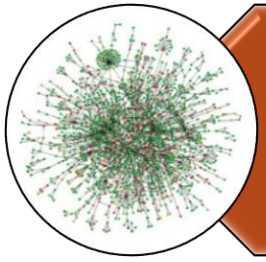
High-throughput data analysis

GWAS (Gene-Wide Association Studies), Microarrays, NGS (Next-Generation Sequencing).



Pathway Enrichment Analysis

Statistically significant over-represented pathways in a set of genes or proteins.



Functional Interaction Networks

Investigation of functional associations, either known or predicted, among genes or proteins.

Cancer Cell Radioresistance

Elucidation of the molecular mechanisms and pathways underlying radioresistance in cancer cells through an integrative bioinformatics approach.

Radioresistant (RR) *vs* **Radiosensitive (RS)**

⇩

Differentially Expressed Genes (DEGs)

⇩

Functionally important DEGs

Transcriptomic Data Analysis

Gene Expression Omnibus

RR and **RS** cell lines from:

- acute lymphoblastic leukemia
- colorectal adenocarcinoma
- breast cancer

Microarray

RNA Sequencing

Identification of DEGs

Βλάβες DNA

- Κάθε αλλαγή στην δομή του DNA και επομένως στο γενετικό κώδικα μπορεί να ερμηνεύσει ποιοτικά τη βιολογική επίδραση των ακτινοβολιών. Οι πιθανές βλάβες του DNA που προέρχονται από ακτινοβόληση με ιοντίζουσα ακτινοβολία παρατίθενται πάρα κάτω:

1. Σπάσιμο ενός κλώνου της αλυσίδας (Single Strand Break-SSB)

2. Διπλό σπάσιμο της αλυσίδας (σπάσιμο και των δύο κλώνων; Double Strand Break-DSB). Εάν η ακτινοβολία προσβάλει και τους δύο κλώνους ταυτόχρονα και μάλιστα στην ίδια θέση τότε οι μηχανισμοί επιδιόρθωσης του κυττάρου δεν μπορούν να λειτουργήσουν με ακρίβεια. Τέτοιου είδους θραύσεις και ακολουθούμενες με λανθασμένη αντικατάσταση βάσεων μπορούν να οδηγήσουν σε μεταλλαγές που μεταφέρονται στους απογόνους (αν γίνονται σε γενετικά κύτταρα) ή προκαλούν καρκινογένεση στο ίδιο το άτομο (αν γίνονται σε σωματικά κύτταρα).

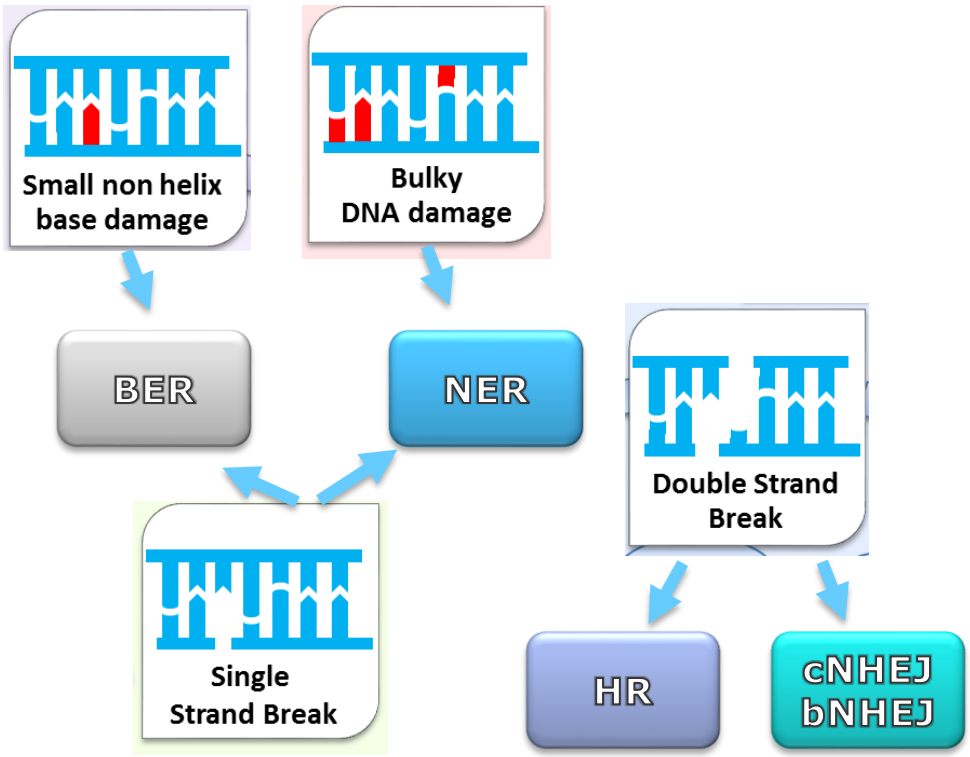
3. Αλλοίωση μιας βάσης (οξειδώσεις, μεθυλιώσεις, αποπουρινώσεις, απαμινώσεις)

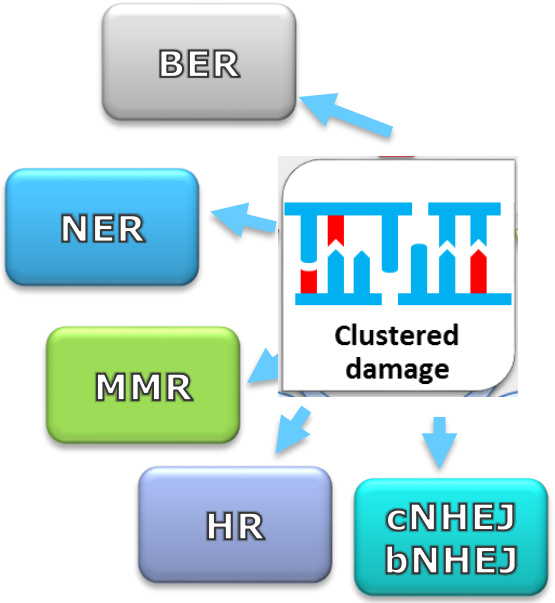
4. Απώλεια μιας βάσης (αβασικά σημεία-AP sites)

5. Σπάσιμο δεσμού υδρογόνου μεταξύ των δύο αλυσίδων

6. Εγκάρσιες συνδέσεις μεταξύ των ελικών (διαδεσμοί-crosslinks)

Τα μονοπάτια επιδιόρθωσης του DNA





Επιδιορθωτικοί Μηχανισμοί DNA

- **Mismatch Repair (MMR)**

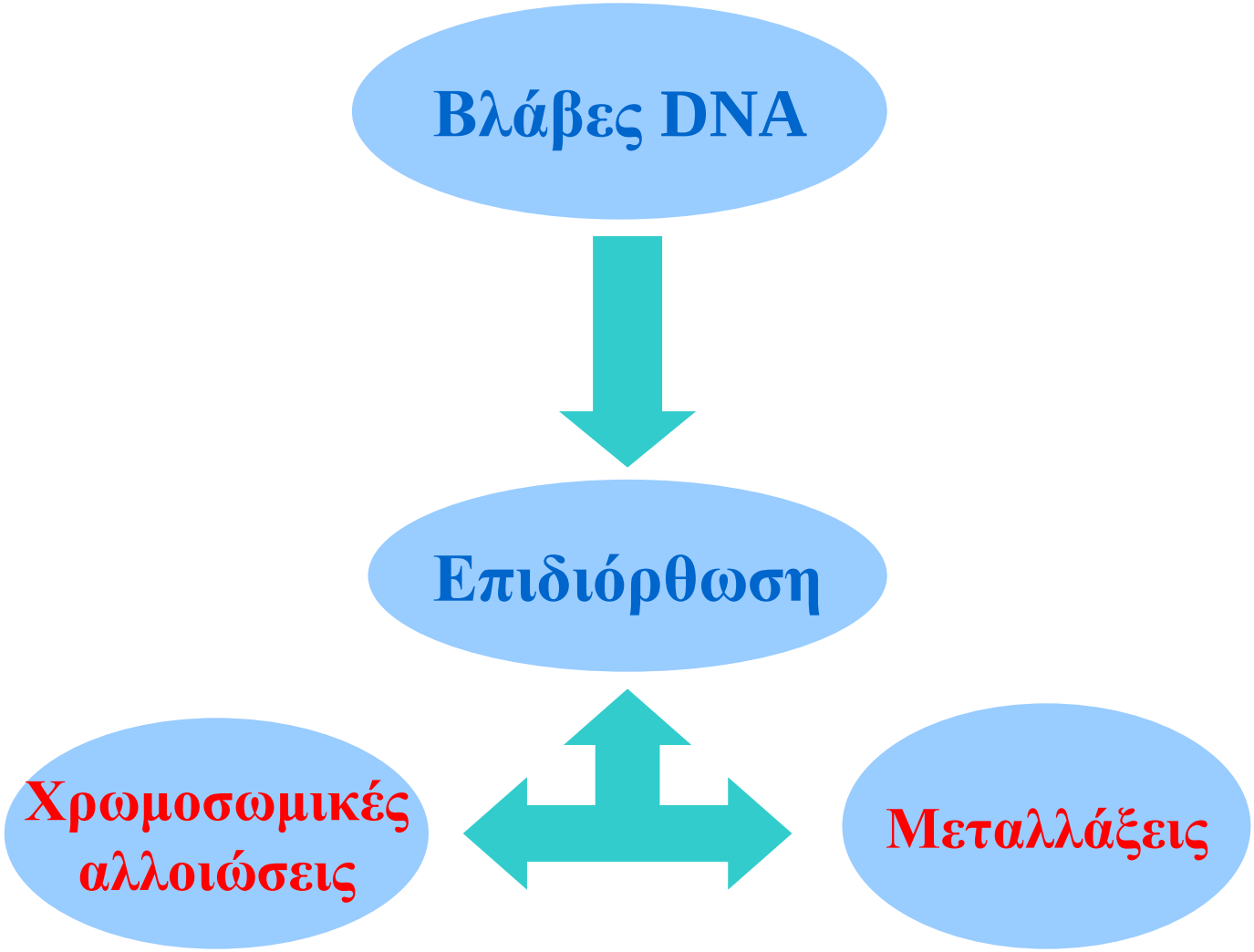
> Διορθώνει τα λεγόμενα λάθη τοποθέτησης ενός νουκλεοτιδίου ή «τυπογραφικά λάθη» που εμφανίζονται κατά την αντιγραφή του DNA (προσθήκη 1-4 βάσεων/ απάλειψη 1-4 βάσεων/ εισδοχή μη συμπληρωματικής βάσης)

- **Nucleotide Excision Repair (NER)**

> Διορθώνει βλάβες οι οποίες παραμορφώνουν (bulk lesions) το σχήμα της διπλής έλικος του DNA, όπως σχηματισμός διμερών πυριμιδινών (pyrimidine dimers) και ομοιοπολική πρόσδεση ογκωδών χημικών ομάδων (συμμετοχή των XP proteins)

- **Base excision repair (BER)**

> Διορθώνει κυρίως αλλοιώσεις μίας μόνο βάσης νουκλεοτιδίου (οξείδωση, μεθυλίωση, αποπουρίνωση ή απαμίνωση) και μονόκλωνες θραύσεις (SSBs; single strand breaks). Κύριος μηχανισμός για ιονίζουσες ακτινοβολίες και ειδικά χαμηλές δόσεις (<1 Gy)


Βλάβες DNA
Επιδιόρθωση
Χρωμοσωμικές αλλοιώσεις
Μεταλλάξεις

Μηχανισμοί επιδιόρθωσης DSBs

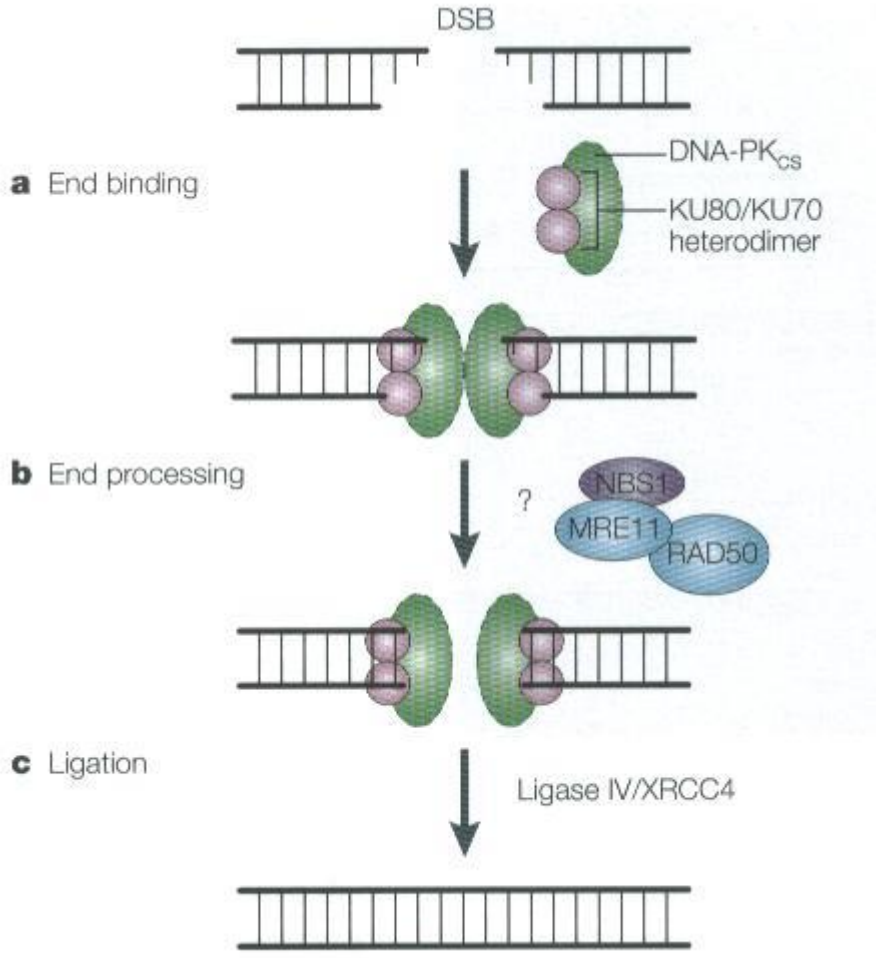
- Οι DSBs απαιτούν λεπτομερή επιδιόρθωση που μπορεί να επιτευχθεί από δύο ανεξάρτητους αλλά όχι αμοιβαία αποκλειόμενους μηχανισμούς:

> την μη ομόλογη ένωση άκρων NHEJ (non-homologous end-joining) ή

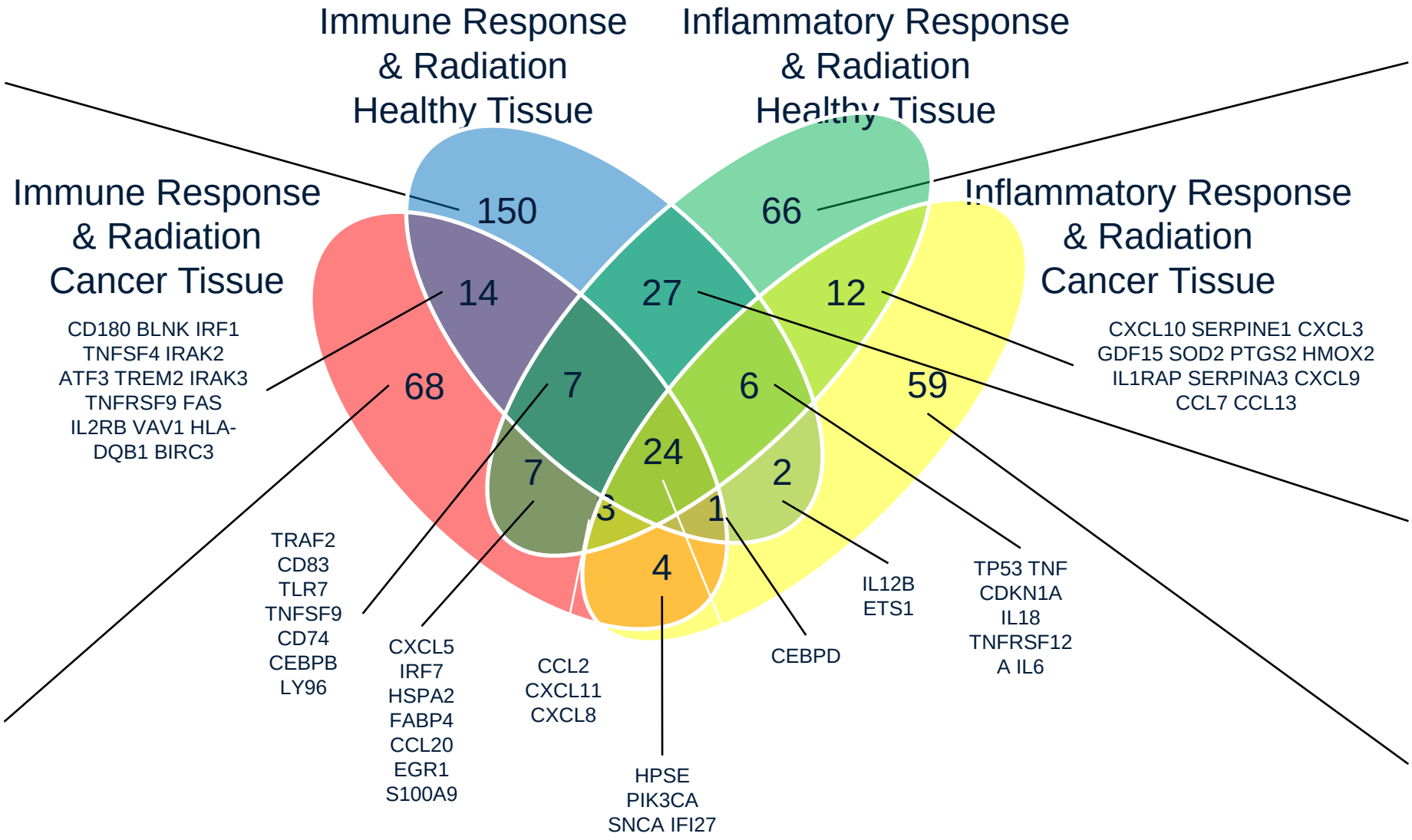
> τον ομόλογο ανασυνδυασμό (homologous recombination-HR).

Επιδιόρθωση DSBs-NHEJ

Η αντίδραση του κυττάρου στις DSBs γίνεται μέσω ενεργοποίησης των ATM και DNA-PK (DNA-dependent protein kinase) κινασών. Η ενεργοποίηση της DNA-PK οδηγεί σε φωσφορυλίωση των καταλοίπων Ser 15 και 37 της p53, αλλά κυρίως προωθεί την επιδιόρθωση των DSBs μέσω NHEJ ειδικά στην περίπτωση έκθεσης σε ιονίζουσες ακτινοβολίες

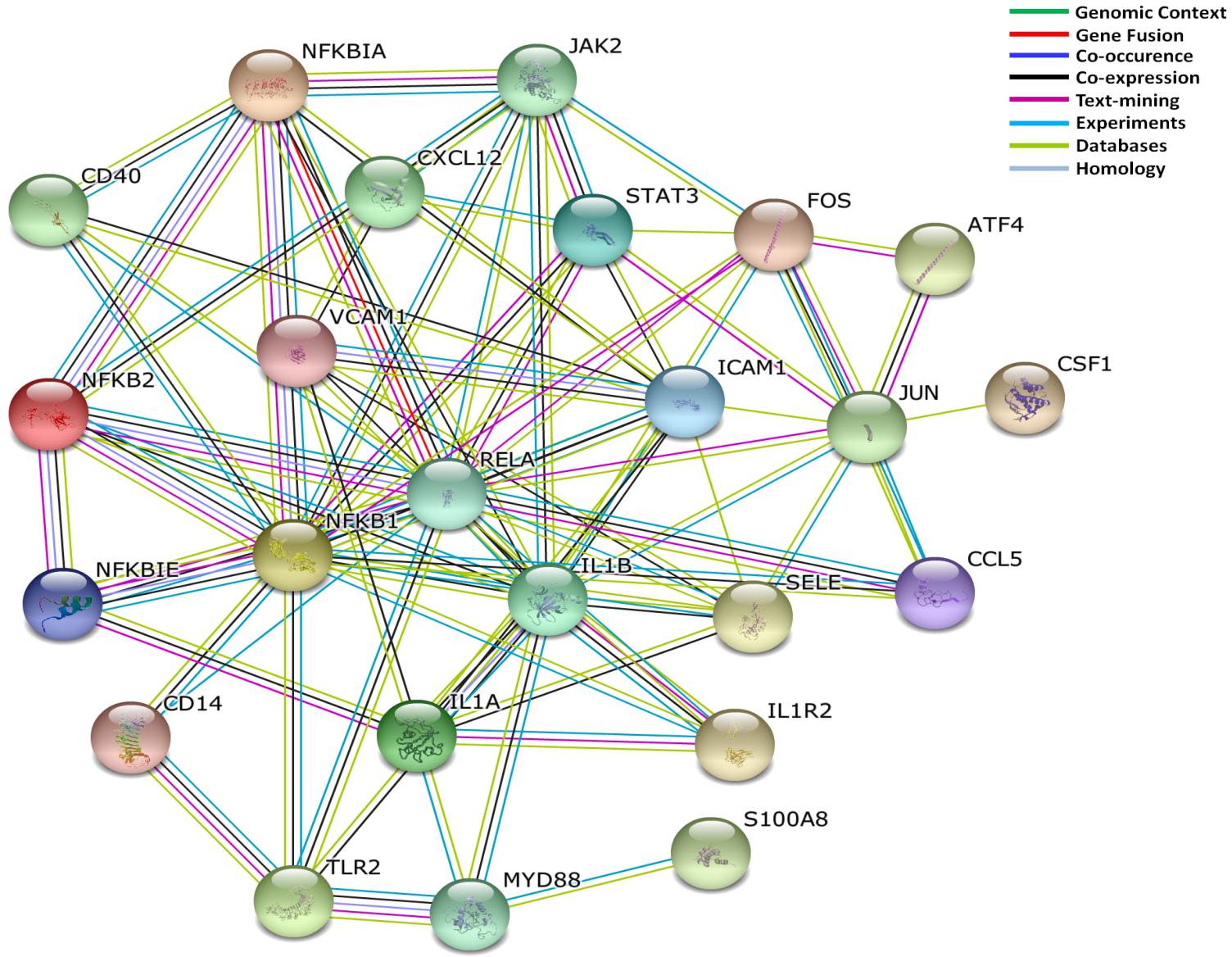


Χρησιμοποιώντας την βιοπληροφορική.....



A.G. Georgakilas et al. Emerging molecular networks common in ionizing radiation, immune and inflammatory responses by employing bioinformatics approaches, Cancer Lett., 368 (2015) 164-172.

Αυτά τα 24 γονίδια συνδέονται ‘στενά’ μεταξύ τους:



Chromosomal regions where the genes implicated in radiation and immune/inflammatory response are located. Gene clusters are underlined.

Cytoband	Genes	adjP
4q21	CXCL1 CXCL2 CXCL3 CXCL9 CXCL10 CXCL11 CXCL13 HPSE SNCA	$2.00 \cdot 10^{-04}$
6p21	C2 CDKN1A CFB CRIP3 FKBP5 HLA-DMA HLA-DMB HLA-DQA1 HLA-DQB1 HLA-DRA HLA-DRB1 HLA-E HSPA1A HSPA1B LTB MAPK13 NCR3 NFKBIE POLH PSMB9 TNF TREM2	$5.24 \cdot 10^{-06}$
12p13	C1R C1S KLRC1 KLRC3 KLRD1 KLRF1 KLRG1 LTBR TAPBPL TNFRSF1A VWF WNT5B	$3.00 \cdot 10^{-04}$

Βασικές έννοιες

- Επίπεδα λειτουργικής ανάλυσης-

1. Γονιδιακή Οντολογία (GO)

Βάση δεδομένων της Γονιδιακής Οντολογίας (www.geneontology.org) με τρεις βασικές, ανεξάρτητες μεταξύ τους, κατηγορίες (οντολογίες) : 1. Της κυτταρικής διεργασίας στην οποία συμμετέχουν οι πρωτεΐνες τους. 2. Της μοριακής λειτουργίας των πρωτεϊνικών προϊόντων τους. 3. Του κυτταρικού εντοπισμού των πρωτεϊνών τους.

2. Βιολογικά μονοπάτια

Η KEGG (Kyoto Encyclopedia of Genes and Genomes,

http://www.genome.jp/kegg/pathway.html αποτελεί την παλαιότερη βάση δεδομένων βιολογικών μονοπατιών

3. Δίκτυα πρωτεϊνικών αλληλεπιδράσεων (Protein-Protein Interaction-PPi)

Human Protein Reference Database HPRD http://www.hprd.org/

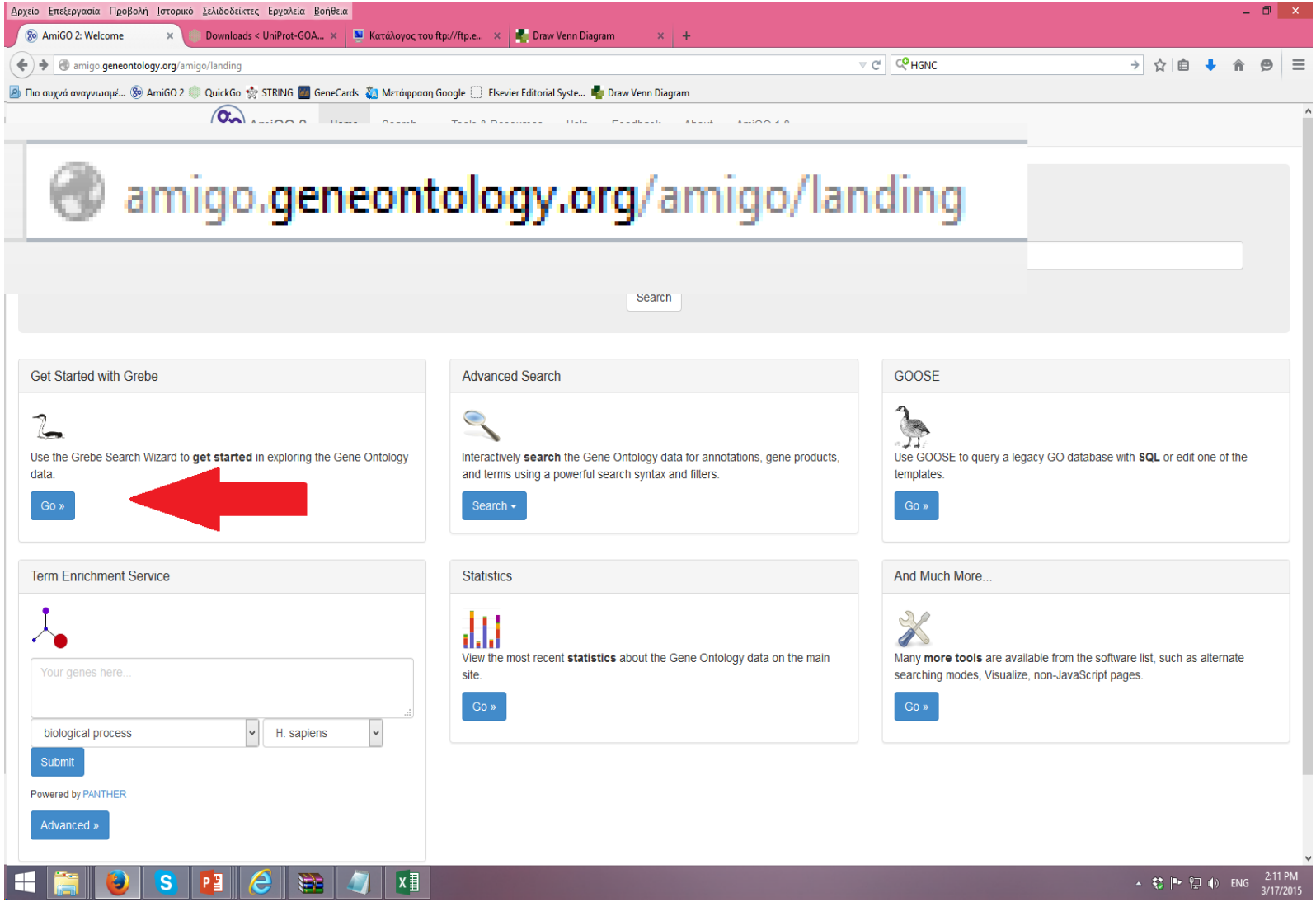
STRINGdb http://string-db.org/

4. Ανάλυση Εμπλουτισμού σε Σύνολα Γονιδίων (Gene Set Enrichment Analysis, GSEA)

Tools for performing GSEA (1. PlantRegMap, Enrichr, DAVID, AmiGO 2, Blast2GO)

How to retrieve common genes among the DNA repair mechanisms

- Firstly, we have to find the official Gene Ontology terms for each mechanism
- Then, from the QuickGO (http://www.ebi.ac.uk/GOA/downloads) download a file with data for the whole Human Genome (488082 entities)
- Data has the following form
- But if copied and pasted to an excel sheet then it looks like
- Using a few lines' code in php we can create .txt files for each GO term, containing its associated proteins.
- Using *Calculate and draw custom Venn diagrams application* from the *Bioinformatics & Evolutionary Genomics* (http://bioinformatics.psb.ugent.be/webtools/Venn/) we can insert the abovementioned .txt files, creating the Venn diagram.


AmiGO 2: Welcome
Downloads < UniProt-GOA...
Κατάλογος του ftp://ftp.e...
Draw Venn Diagram
amigo.geneontology.org/amigo/landing
HGNC
amigo.geneontology.org/amigo/landing
Search
Get Started with Grebe
Use the Grebe Search Wizard to get started in exploring the Gene Ontology data.
Go »
Advanced Search
Interactively search the Gene Ontology data for annotations, gene products, and terms using a powerful search syntax and filters.
Search
GOOSE
Use GOOSE to query a legacy GO database with SQL or edit one of the templates.
Go »
Term Enrichment Service
Your genes here...
biological process
H. sapiens
Submit
Powered by PANTHER
Advanced »
Statistics
View the most recent statistics about the Gene Ontology data on the main site.
Go »
And Much More...
Many more tools are available from the software list, such as alternate searching modes, Visualize, non-JavaScript pages.
Go »
ENG
2:11 PM
3/17/2015

On-line free access tools

- Quertle
- GLAD4U
- AmiGO2 – Gene Ontology Consortium
- STRING v.10

An introduction to effective use of enrichment analysis software: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3525973/

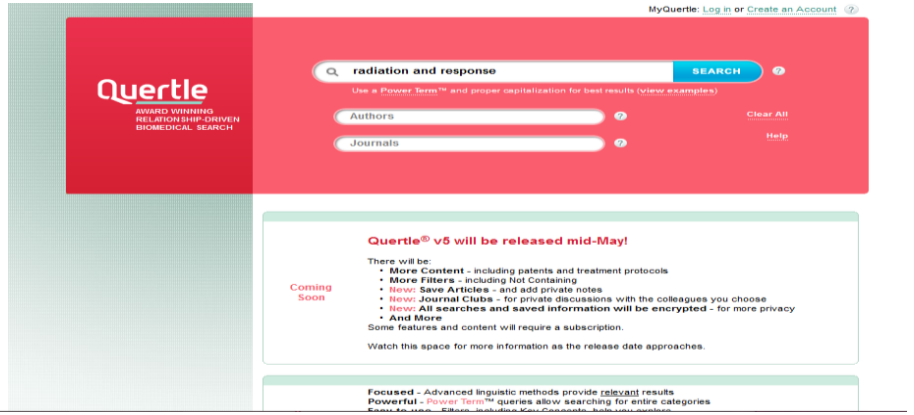
DAVID https://david.ncifcrf.gov/

http://webgestalt.org/

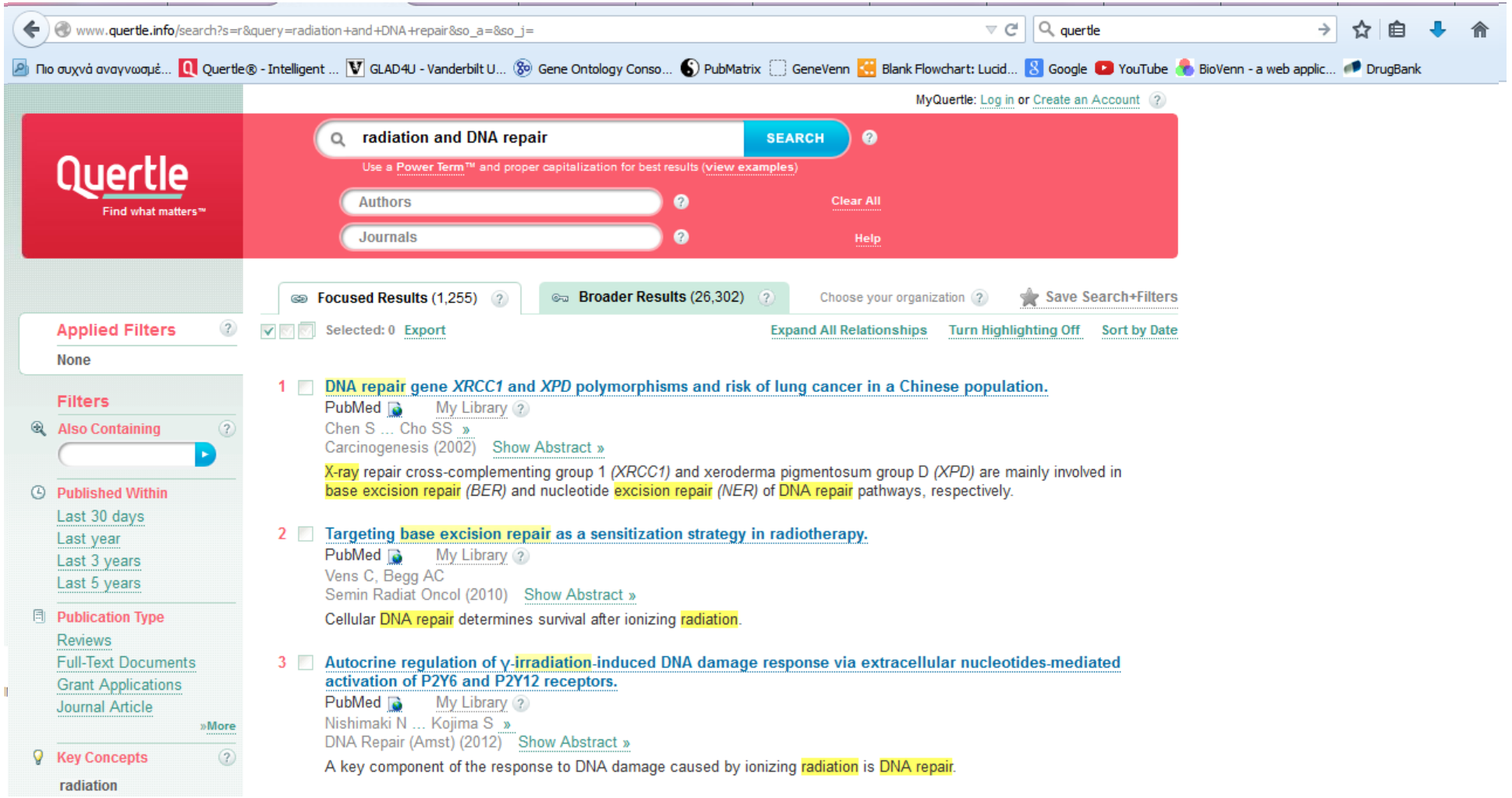
On-line free access tools

- Quertle
- GLAD4U
- AmiGO2 – Gene Ontology Consortium
- STRING v.10

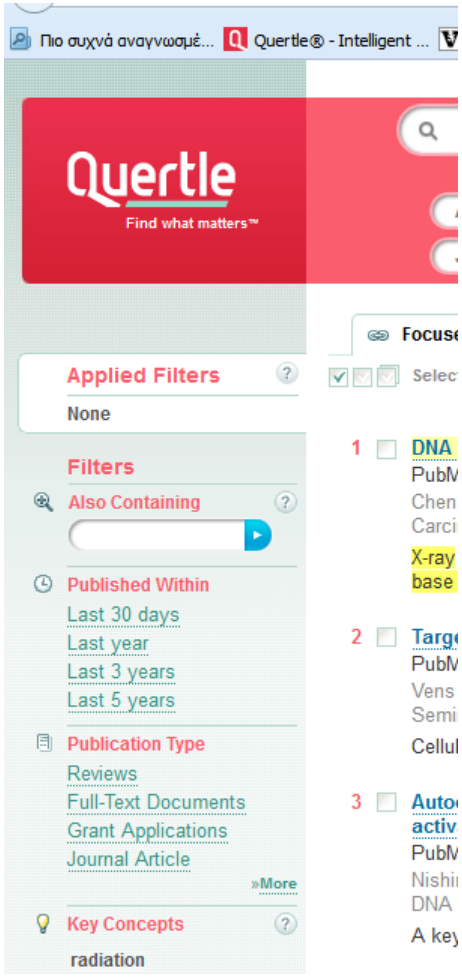
On-line free access tools -- Quertle

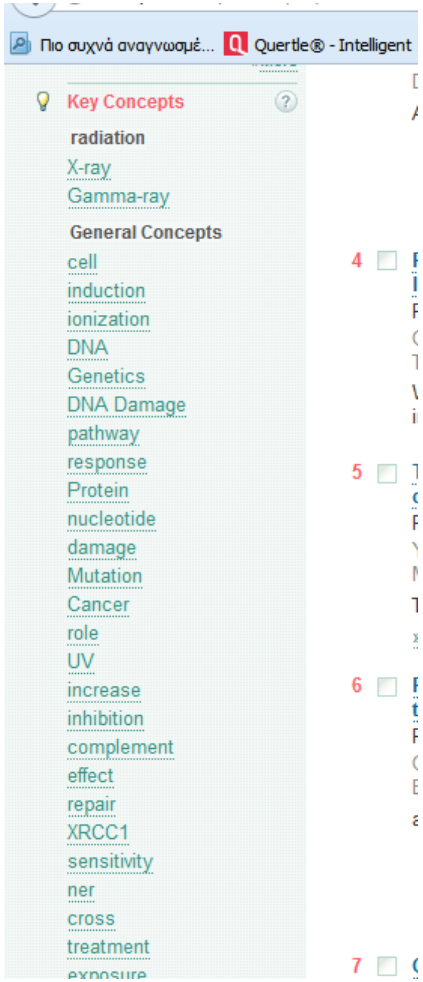


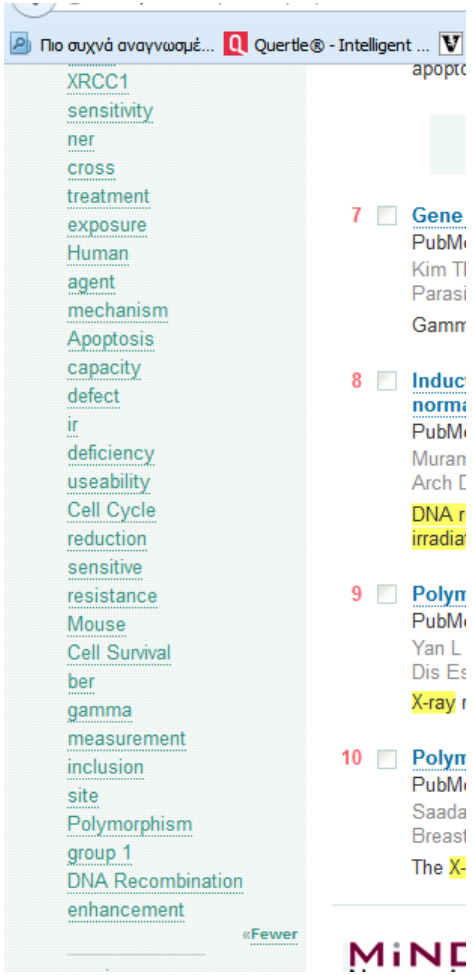
- Quertle is a *semantic* search engine for life and chemical science literature and information. Quertle **simplifies your discovery process** by integrating, organizing, and presenting biomedical literature in the most intuitive, robust framework available.
  - The subject–verb–object relationships are stored in a metadatabase and the user's query is matched against that metadata. This identifies documents based on meaning and context and generally provides fewer, but more relevant, hits than a traditional keyword search.
  - It is enriched with power terms like $Genes, $Proteins, $Diseases and many others,
    to represent entire groups of related objects.
  - It also has available flirters for eliminating the results
  - Content:
    - MEDLINE,
    - full-text articles from BioMed Central
    - PubMed Central (open access subset)
    - NIH grants
    - biomedical news
    - TOXNET database,
    - US National Library of Medicine

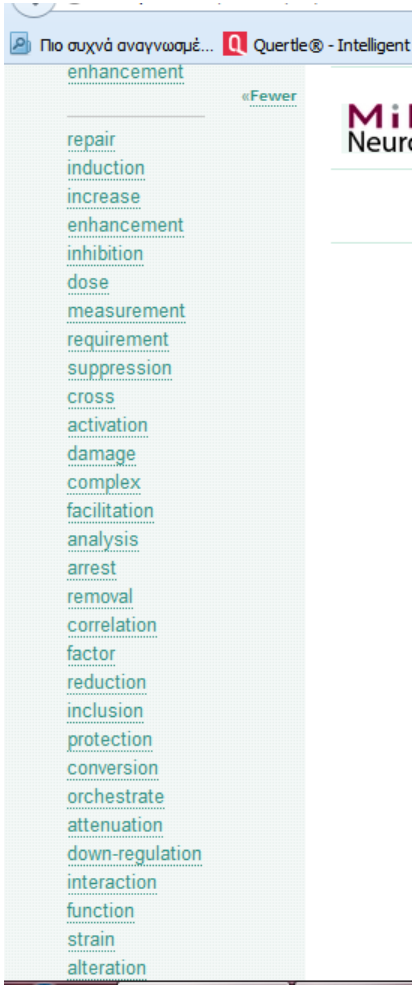

www.quertle.info/search?s=r&query=radiation+and+DNA+repair&so_a=&so_j=
quertle
Πιο συχνά αναγνωσμέ...
Quertle® - Intelligent ...
GLAD4U - Vanderbilt U...
Gene Ontology Conso...
PubMatrix
GeneVenn
Blank Flowchart: Lucid...
Google
YouTube
BioVenn - a web applic...
DrugBank
MyQuertle: Log in or Create an Account
Quertle
Find what matters™
radiation and DNA repair
SEARCH
Use a Power Term™ and proper capitalization for best results (view examples)
Authors
Journals
Clear All
Help
Focused Results (1,255)
Broader Results (26,302)
Choose your organization
Save Search+Filters
Applied Filters
None
Selected: 0 Export
Expand All Relationships
Turn Highlighting Off
Sort by Date
Filters
Also Containing
Published Within
Last 30 days
Last year
Last 3 years
Last 5 years
Publication Type
Reviews
Full-Text Documents
Grant Applications
Journal Article
»More
Key Concepts
radiation
1 DNA repair gene XRCC1 and XPD polymorphisms and risk of lung cancer in a Chinese population.
PubMed My Library
Chen S ... Cho SS »
Carcinogenesis (2002) Show Abstract »
X-ray repair cross-complementing group 1 (XRCC1) and xeroderma pigmentosum group D (XPD) are mainly involved in base excision repair (BER) and nucleotide excision repair (NER) of DNA repair pathways, respectively.
2 Targeting base excision repair as a sensitization strategy in radiotherapy.
PubMed My Library
Vens C, Begg AC
Semin Radiat Oncol (2010) Show Abstract »
Cellular DNA repair determines survival after ionizing radiation.
3 Autocrine regulation of γ-irradiation-induced DNA damage response via extracellular nucleotides-mediated activation of P2Y6 and P2Y12 receptors.
PubMed My Library
Nishimaki N ... Kojima S »
DNA Repair (Amst) (2012) Show Abstract »
A key component of the response to DNA damage caused by ionizing radiation is DNA repair.

Avalilable filters



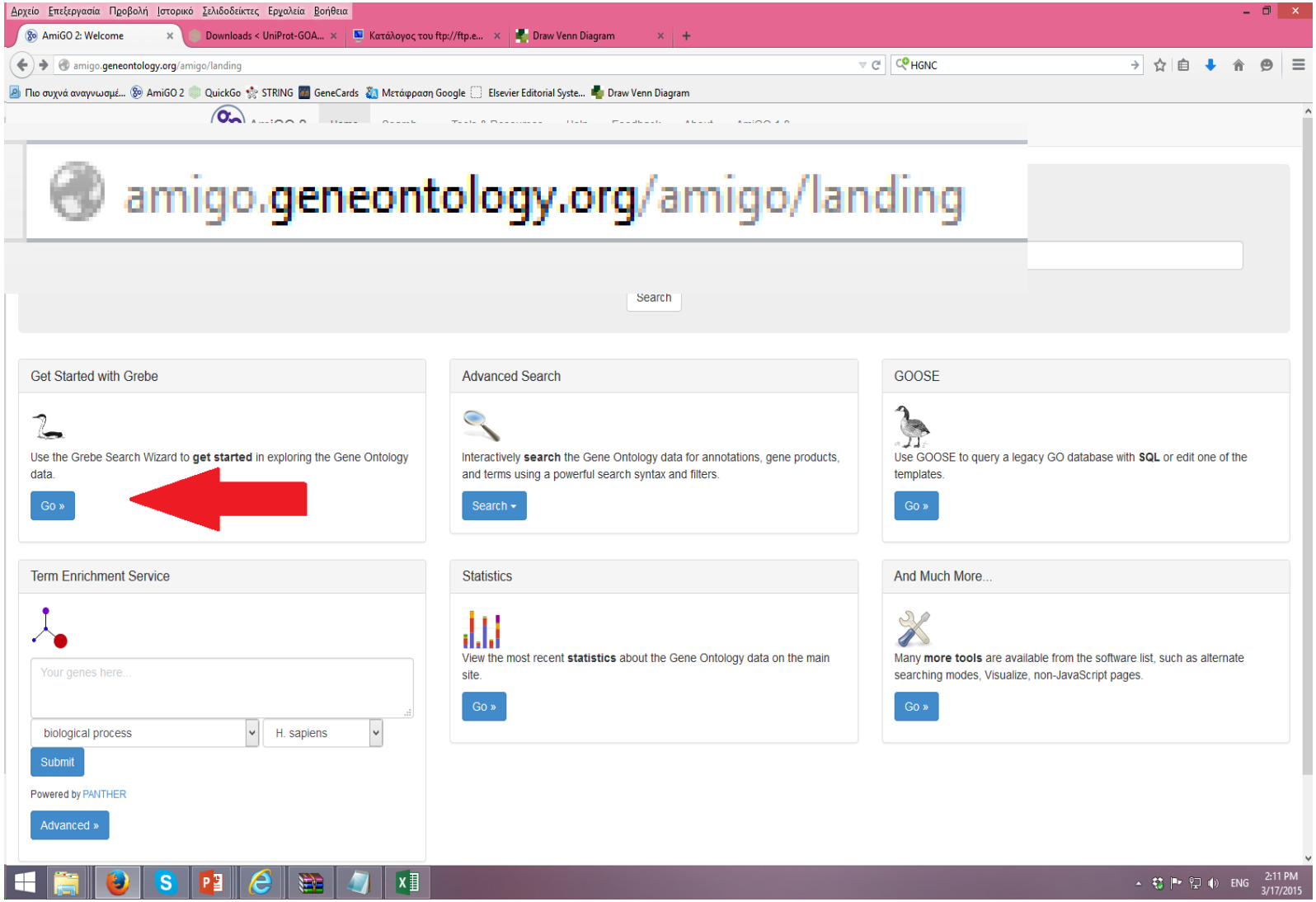




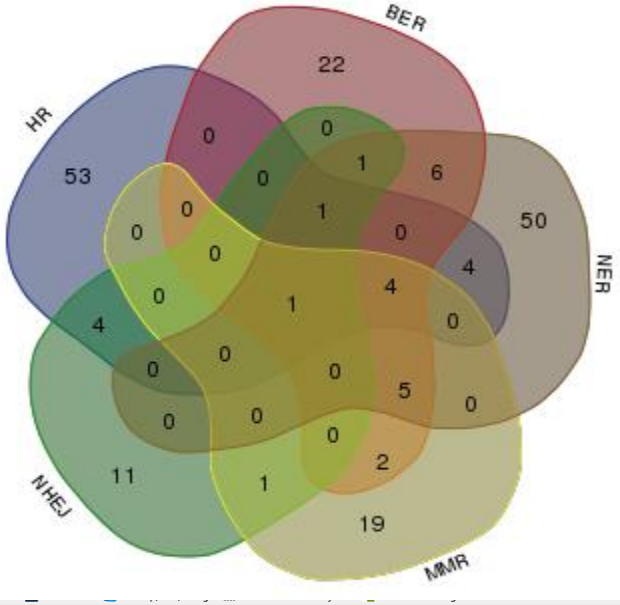


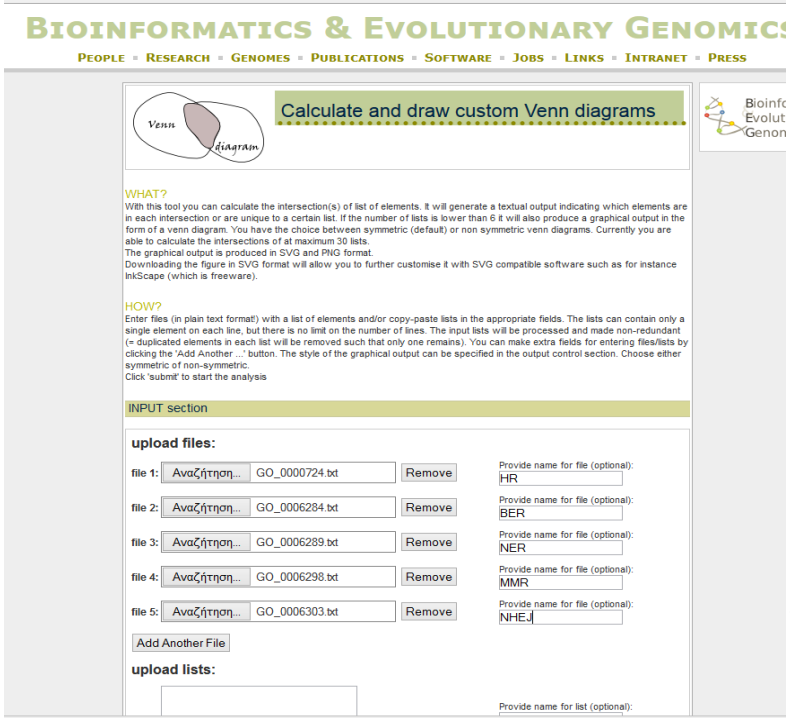
How to retrieve common genes among the DNA repair mechanisms

- Firstly, we have to find the official Gene Ontology terms for each mechanism
- Then, from the QuickGO (http://www.ebi.ac.uk/GOA/downloads) download a file with data for the whole Human Genome (488082 entities)
- Data has the following form
- But if copied and pasted to an excel sheet then it looks like
- Using a few lines' code in php we can create .txt files for each GO term, containing its associated proteins.
- Using *Calculate and draw custom Venn diagrams application* from the *Bioinformatics & Evolutionary Genomics* (http://bioinformatics.psb.ugent.be/webtools/Venn/) we can insert the abovementioned .txt files, creating the Venn diagram.


AmiGO 2: Welcome
Downloads < UniProt-GOA...
Κατάλογος του ftp://ftp.e...
Draw Venn Diagram
amigo.geneontology.org/amigo/landing
HGNC
amigo.geneontology.org/amigo/landing
Search
Get Started with Grebe
Use the Grebe Search Wizard to get started in exploring the Gene Ontology data.
Go »
Advanced Search
Interactively search the Gene Ontology data for annotations, gene products, and terms using a powerful search syntax and filters.
Search
GOOSE
Use GOOSE to query a legacy GO database with SQL or edit one of the templates.
Go »
Term Enrichment Service
Your genes here...
biological process
H. sapiens
Submit
Powered by PANTHER
Advanced »
Statistics
View the most recent statistics about the Gene Ontology data on the main site.
Go »
And Much More...
Many more tools are available from the software list, such as alternate searching modes, Visualize, non-JavaScript pages.
Go »
ENG
2:11 PM
3/17/2015

Venn diagrams





Save Image As PNG | Save Image As SVG

Text results:

Save text

Names	total	elements
BER HR MMR NER NHEJ	1	LIG1
BER HR MMR NER	4	RPA2 RPA1 APEX1 RPA3
BER HR NER NHEJ	1	MRE11A
BER MMR NER	5	POLD2 POLD3 PCNA POLD4 POLD1
BER NER NHEJ	1	LIG3
HR NER	4	FAN1 BRCA2 ERCC4 SLX4
HR NHEJ	4	SMC5 NSMCE2 PSMD14 PRKDC
BER NER	6	NEIL3 TP53 NEIL2 NEIL1 OGG1 ERCC6
BER MMR	2	TDG MUTYH
MMR NHEJ	1	MLH1
HR	53	HUS1 YY1 MCM9 MTOR AP5S1 ZSWIM7 AP5Z1 NBN NABP2 TONSL MDC1 MORF4L1 TP53BP1 RBBP8 INO80 RAD51 MMS22L RAD51B RAD51D BLM ATR REC8 H2AFX RAD54L SWSAP1 MCM8 XRCC3 SLX1A BRCA1 GEN1 RAD50 SMG1 RAD52 WDR48 RAD54B POLN SHFM1 CCDC155 PALB2 SPIDR ZFYVE26 RAD51C SWI5 NABP1 SMC6 SFR1 RAD21L1 UBE2N HELQ MEIOB ATM RAD51AP1 XRCC2
BER	22	M0R2N6 NTHL1 PARP2 DNA2 CCNO PRMT6 XRCC1 DKFZp781L1143 USP47 FEN1 HMGA1 MPG MBD4 UNG POLB WRN HMGA2 E9PQ18 SMUG1 PARP1 APEX2 HUWE1
NER	50	MMS19 ERCC8 SLC30A9 POLR2B ERCC5 POLR2G XPA POLR2L MNAT1 DDB1 XAB2 POLR2I BIVM-ERCC5 RPA4 POLR2J POLR2E ERCC3 ERCC1 GTF2H3 RFC2 RFC1 RFC4 GTF2H1 RFC3 RAD23A CETN2 GTF2H2C RFC5 CDK7 GTF2H5 FANCC TCEA1 XPC POLR2C DDB2 ATXN3 POLR2K POLR2D RAD23B POLL POLR2H GTF2H2 ERCC2 CCNH POLR2A POLR2F POLE2 POLE DCLRE1A GTF2H4
MMR	19	RNASEH2A PMS2P11 MLH3 PMS2P1 SETD2 MSH3 ABL1 TREX1 EXO1 MSH5-SAPCD1 MSH5 TP73 PMS2P3 PMS2P5 PMS2P2 MSH2 PMS2 MSH6 PMS1
NHEJ	11	POLA1 LIG4 PRPF19 XRCC6 NHEJ1 XRCC4 KDM2A SETMAR XRCC6BP1 XRCC5 RNF8

Logo PSB

Contact:
VIB / UGent
Bioinformati
Biology
Technologie
B-9052 Ger
BELGIUM
+32 (0) 9 3
+32 (0) 9 3

Z. Nikitaki, I. Michalopoulos, A.G. Georgakilas, Molecular inhibitors of DNA repair: searching for the ultimate tumor killing weapon, Future medicinal chemistry, (2015) 1-16.

On-line free access tools

- Quertle
- GLAD4U
- AmiGO2 – Gene Ontology Consortium
- STRING v.10

On-line free access tools – GLAD4U

GLAD4U***:*** (Gene List Automatically Derived For You) a web-based gene retrieval and prioritization tool from PubMed literature. (NCBI)

http://glad4u.zhang-lab.org/index.php

How it works:

- it collects the relative to the *query* publications,
- it keeps only those that contain (human) genes.
- For the prioritization of genes the gene-to-publication link table provided by Entrez-Gene is utilized.
- This table contains approx. $3x10^4$ human genes associated with approx. $3x10^5$ publications.
- For prioritization a hypergeometric test is performed. The result is given either as a list (from the more relevant to the less), either classified on tables according to biological processes, cellular components and molecular functions. ***The score for prioritization is given as the negative logarithm of the hypergeometric p-value.***

GLAD4U: Gene List Automatically Derived For You

Query: Search Clear

E-mail:

Please, enter an email address if you want to be updated on the status of your query.

DEFAULT OPTIONS [expand]: *threshold of 0.01, human genes, 100 genes per page, 10 supporting publications per gene, 5 page links per page.*

OR

Ticket number: Retrieve Clear

Please, enter the ticket number for the results that you want to retrieve.

CITATION Jourquin J, Duncan D, Shi Z, Zhang B. GLAD4U: deriving and prioritizing gene lists from PubMed literature. BMC Genomics. 13(Suppl 8):S20, 2012.

USAGE STATISTICS [9082 hits since 11/03/2009]: *1041 local hits (last 03/30/15), 8041 remote hits (last 05/11/15).*

LAST UPDATES: *GLAD4U data last updated on 06/26/2014.*

GLAD4U likes Firefox, Internet Explorer, and Chrome.

Disclaimer: GLAD4U relies on the National Center for Biotechnology Information (NCBI)'s Pubmed data to function. As such, it is important for our users to know that the National Library of abstracts in PubMed; however, journal publishers or authors may. NLM provides no legal advice concerning distribution of copyrighted materials. Please, refer to http://eutils.ncbi.nlm.nih.g disclaimers.

Zhang Lab | Dept. Biomedical Informatics
©2008-2015 J.Jourquin, D.Duncan, B.Zhang

GLAD4U - Vanderbilt University

Department of Biomedical Informatics - *http://bioinfo.vanderbilt.edu/glad4u*

Home | News/Updates | Documentation | Contact Us Search Ticket number: **359a9mte908kdquudmk4ugnc71**

Summary

Generated on: May 11, 2015
Query: Homologous Recombination (Parameters used: threshold of 0.01, search only human genes, 100 genes per page, 10 publications per gene, 5 page links per page
Number of publications retrieved: 28,957
Number of publications containing gene information (among the 28,957): 1,829
Number of genes in these 1,829 publications: 1,993
Number of genes after the score threshold: 613

Send data to Functional Enrichment Analysis (opens a new window)

Visualize genes in a protein-protein interaction network

Pag

Genes identified in your query, from highest to lowest scores:
(all links will open in new windows)
Expand all publications

1. - *[, Entrez-Gene ID:5888]*
   score: 1000, go to Entrez-Gene page, show the first 10 out of the 237 supporting publications
2. - *[, Entrez-Gene ID:641]*
   score: 90.0849, go to Entrez-Gene page, show the first 10 out of the 61 supporting publications
3. - *[, Entrez-Gene ID:7517]*
   score: 88.5195, go to Entrez-Gene page, show the first 10 out of the 69 supporting publications
4. - *[, Entrez-Gene ID:675]*
   score: 78.8392, go to Entrez-Gene page, show the first 10 out of the 91 supporting publications
5. - *[, Entrez-Gene ID:672]*
   score: 63.0743, go to Entrez-Gene page, show the first 10 out of the 94 supporting publications
6. - *[, Entrez-Gene ID:5893]*
   score: 58.3900, go to Entrez-Gene page, show the first 10 out of the 35 supporting publications

WEB-based GEne SeT AnaLysis Toolkit

WebGestalt

Translating gene lists into biological insights...

Your analysis is complete. Thank you for waiting.

Analysis parameters: Data: thirdpartyV3vF67.txt, Organism: hsapiens, Id Type: entrezgene, Ref Set: genome, i.e. entire entrez gene list, Statistic: Hypergeometric, Signficance Level: Top10, MTC: B

View results

Click on this button to visualize significantly enriched GO categories under Biological Process, Molecular Function, and Cellular Component with three separate Directed Acyclic Graphs (DAGs) in one
GO categories in red are the enriched GO categories while the black ones are their non-enriched parents. If the "Top10" option is selected, GO categories in the top 10 that also have a p value < 0
that have a p value > 0.05 are colored brown, and the black ones are the parents of the top 10 categories. The DAG groups related enriched GO categories together and helps the user identify imp
study. Each node shows the name of the GO category, number of genes in the category and the adjusted p value indicating the significance of enrichment. Clicking on an enriched node will open a
included in the GO category. The table will also provide the number of reference genes in the category (C), number of genes in the gene set and also in the category (O), expected number in the ca
hypergeometric test (rawP), and p value adjusted by multiple test adjustment. More information on individual genes can be acquired from external databases by clicking on the Entrez IDs or the En

Export TSV Only

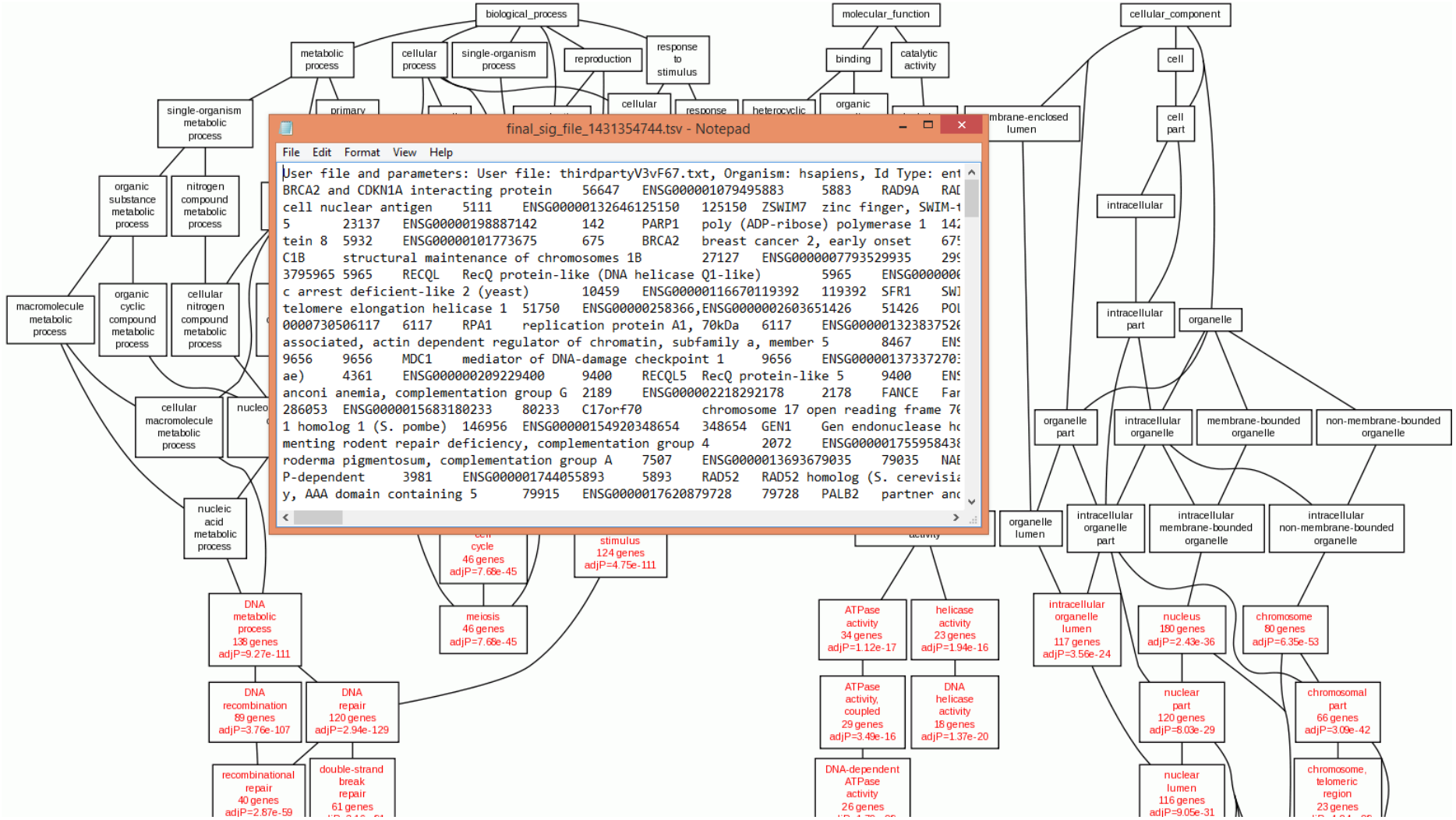
Click on this button to download or view a tab separated list of significant GO categories with corresponding User Uploaded IDs, Entrez IDs, Ensembl Gene Stable IDs, Gene Symbols, and descriptic

Export Complete Results Package

Click on this button to download a .zip file to your desktop. This file can be unzipped and one will find in the directory a html file prefixed with .DAG_. Opening this file in a browser will show you the
results" button. This function is particularly useful for saving analysis results for future reference and sharing results with colleagues.

WebGestalt is currently developed and maintained by Jing Wang and Bing Zhang at the Zhang Lab. Other people who have made significant contribution to the project include Dexter Duncan, Stefan Kirov, Zhiao Shi,

Funding credits: NIH/NIAAA (U01 AA016662, U01 AA013512); NIH/NIDA (P01 DA015027); NIH/NIMH (P50 MH078028, P50 MH096972); NIH/NCI (U24 CA159988); NIH/NIGMS (R01 GM088822).



final_sig_file_1431354744.tsv - Notepad

File Edit Format View Help

```
User file and parameters: User file: thirdpartyV3vF67.txt, Organism: hsapiens, Id Type: ent
BRCA2 and CDKN1A interacting protein    56647   ENSG000001079495883     5883    RAD9A   RAD
cell nuclear antigen    5111    ENSG00000132646125150   125150  ZSWIM7  zinc finger, SWIM-t
5       23137   ENSG00000198887142      142     PARP1   poly (ADP-ribose) polymerase 1  142
tein 8  5932    ENSG00000101773675      675     BRCA2   breast cancer 2, early onset    675
C1B     structural maintenance of chromosomes 1B        27127   ENSG0000007793529935    295
3795965 5965    RECQL   RecQ protein-like (DNA helicase Q1-like)        5965    ENSG0000006
c arrest deficient-like 2 (yeast)       10459   ENSG00000116670119392   119392  SFR1    SWI
telomere elongation helicase 1  51750   ENSG00000258366,ENSG0000002603651426    51426   POL
0000730506117   6117    RPA1    replication protein A1, 70kDa   6117    ENSG000001323837526
associated, actin dependent regulator of chromatin, subfamily a, member 5       8467    ENS
9656    9656    MDC1    mediator of DNA-damage checkpoint 1     9656    ENSG000001373372703
ae)     4361    ENSG000000209229400     9400    RECQL5  RecQ protein-like 5     9400    ENS
anconi anemia, complementation group G  2189    ENSG000002218292178     2178    FANCE   Fan
286053  ENSG0000015683180233    80233   C17orf70        chromosome 17 open reading frame 76
1 homolog 1 (S. pombe)  146956  ENSG00000154920348654   348654  GEN1    Gen endonuclease ho
menting rodent repair deficiency, complementation group 4       2072    ENSG000001755958438
roderma pigmentosum, complementation group A    7507    ENSG00000013693679035   79035   NAE
P-dependent     3981    ENSG000001744055893     5893    RAD52   RAD52 homolog (S. cerevisia
y, AAA domain containing 5      79915   ENSG0000017620879728    79728   PALB2   partner and
```

Pharmacology & Therapeutics

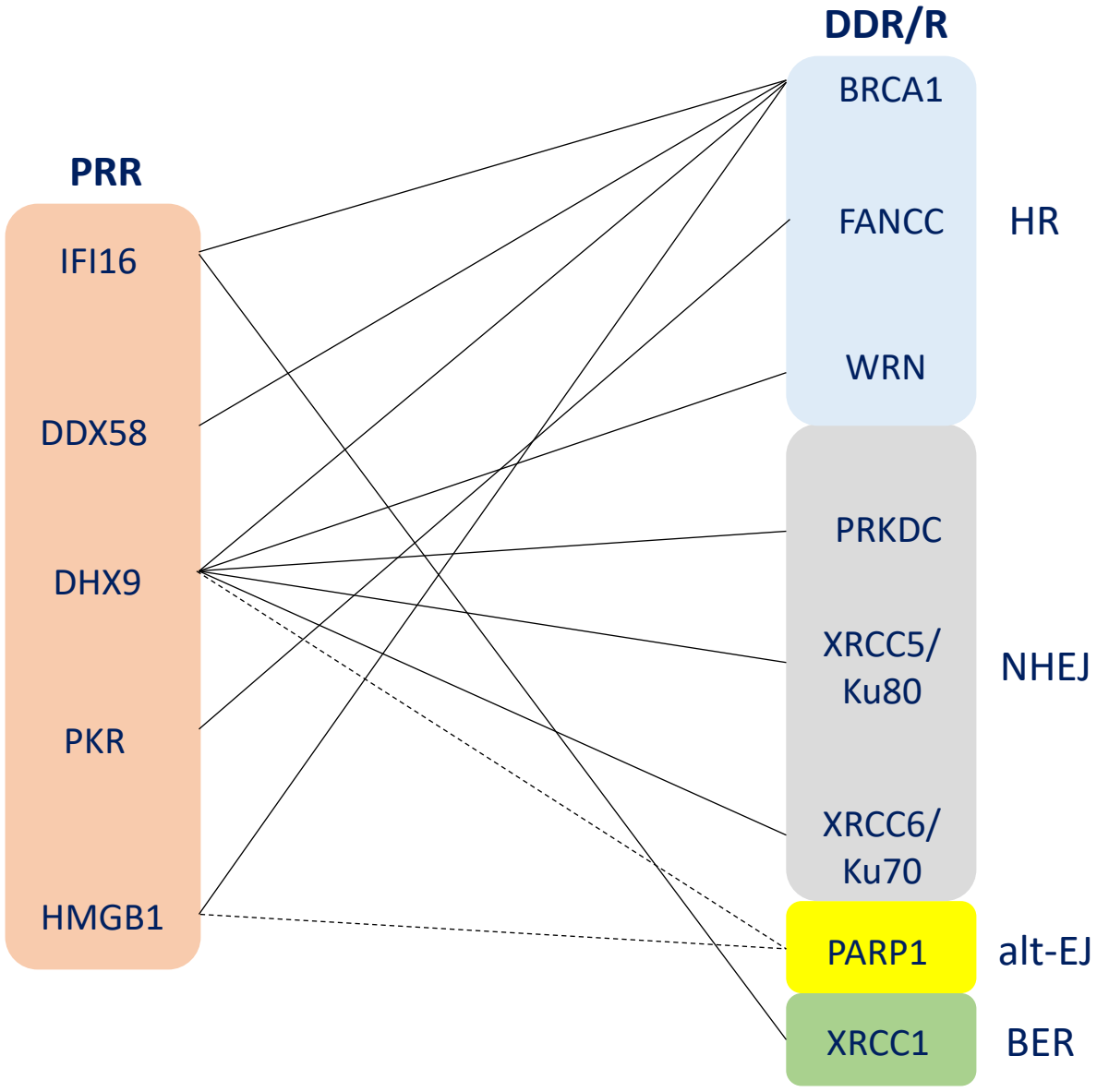
The DNA damage response and immune signaling alliance: Is it good or bad? Nature decides when and where!

Ioannis S. Pateras, Sophia Havaki, Konstantinos Vougas, Paul Townsen, Michalis I. Panayiotidis, Alexandros G. Georgakilas, Vassilis G. Gorgoulis

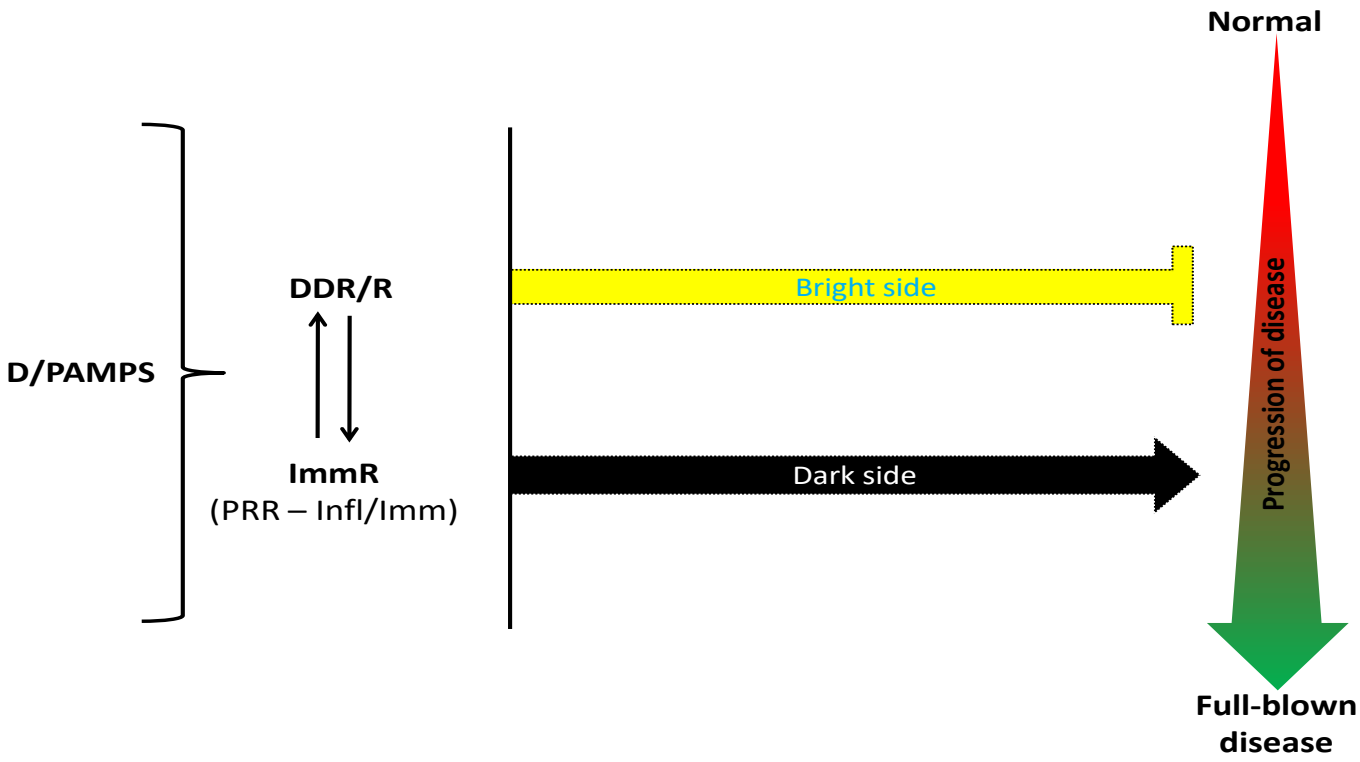
Disruption of DDR/R–ImmR cross talk compromises (multi)cellular integrity, leading to cell-cycle-related and immune defects. The emerging DDR/R–ImmR concept opens up a new avenue of therapeutic options, recalling the Hippocrates quote "everything in excess is opposed by nature."

Pateras, I.S.; Havaki, S.; Nikitopoulou, X.; Vougas, K.; Townsend, P.A.; Panayiotidis, M.I.; Georgakilas, A.G.; Gorgoulis, V.G. The DNA damage response and immune signaling alliance: Is it good or bad? Nature decides when and where. *Pharmacol Ther* ***2015, 154, 36-56.***

Putative interactions between different **Pattern Recognition Receptors (PRRs)** with components of **DNA damage response & repair machinery (DDR/R).** The **Ingenuity Pathway Analysis** Software (Qiagen) along with the underlying Ingenuity Knowledge Base which comprises ~5.1 million relationships was used for the Network Analysis.



Σε συνεργασία με το εργαστήριο του Καθ. Β. Γοργούλη:



I.S. Pateras et al.
The DNA damage response and immune signaling alliance: Is it good or bad? Nature decides when and where,
Pharmacol Ther, 154 (2015) 36-56.

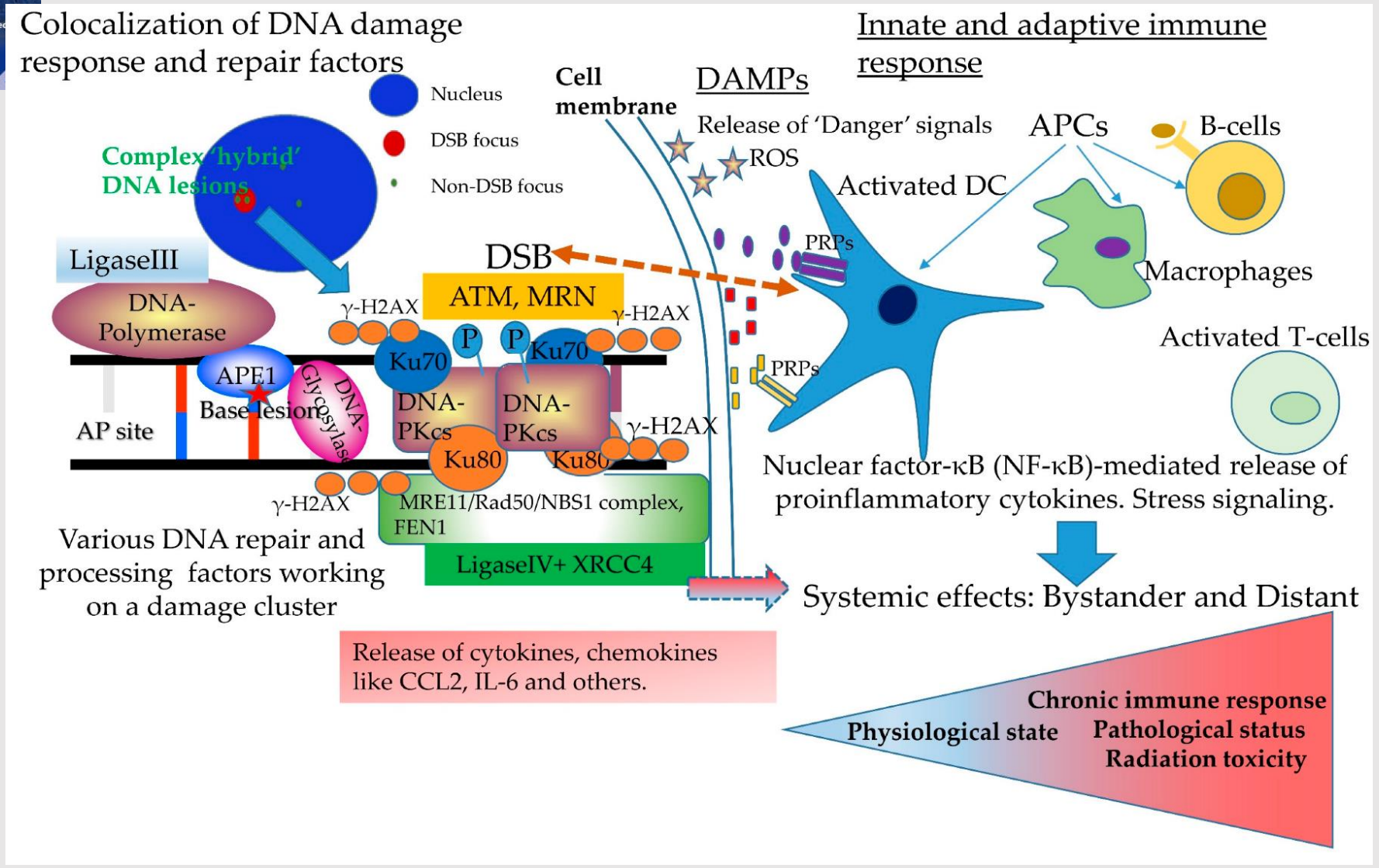
Ένα ενοποιητικό μοντέλο που γεφυρώνει το μηχανισμό απόκρισης DDR/R and ανοσοποιητικό συστημα ImmR (including PRR and Inflammatory/Immune mediators) που ενεργοποιείται όλο μαζί ως μια συμφωνία στην περίπτωση ύπαρξης των λεγόμενων σημάτων κινδύνου DAMPs (Damage Associated Molecular Patterns) ή PAMPs (Pathogen Associated Molecular Patterns). Το δίκτυο DDR-ImmR εμποδίζει την εκδήλωση ασθένειας στα πρώιμα στάδια (early stages bright side), ενώ σε τελευταία στάδειο προωθεί τη λεγόμενη ‘σκοτεινή πλευρά (dark side).

Cancers 2017, 9(7), 91; doi:10.3390/cancers9070091

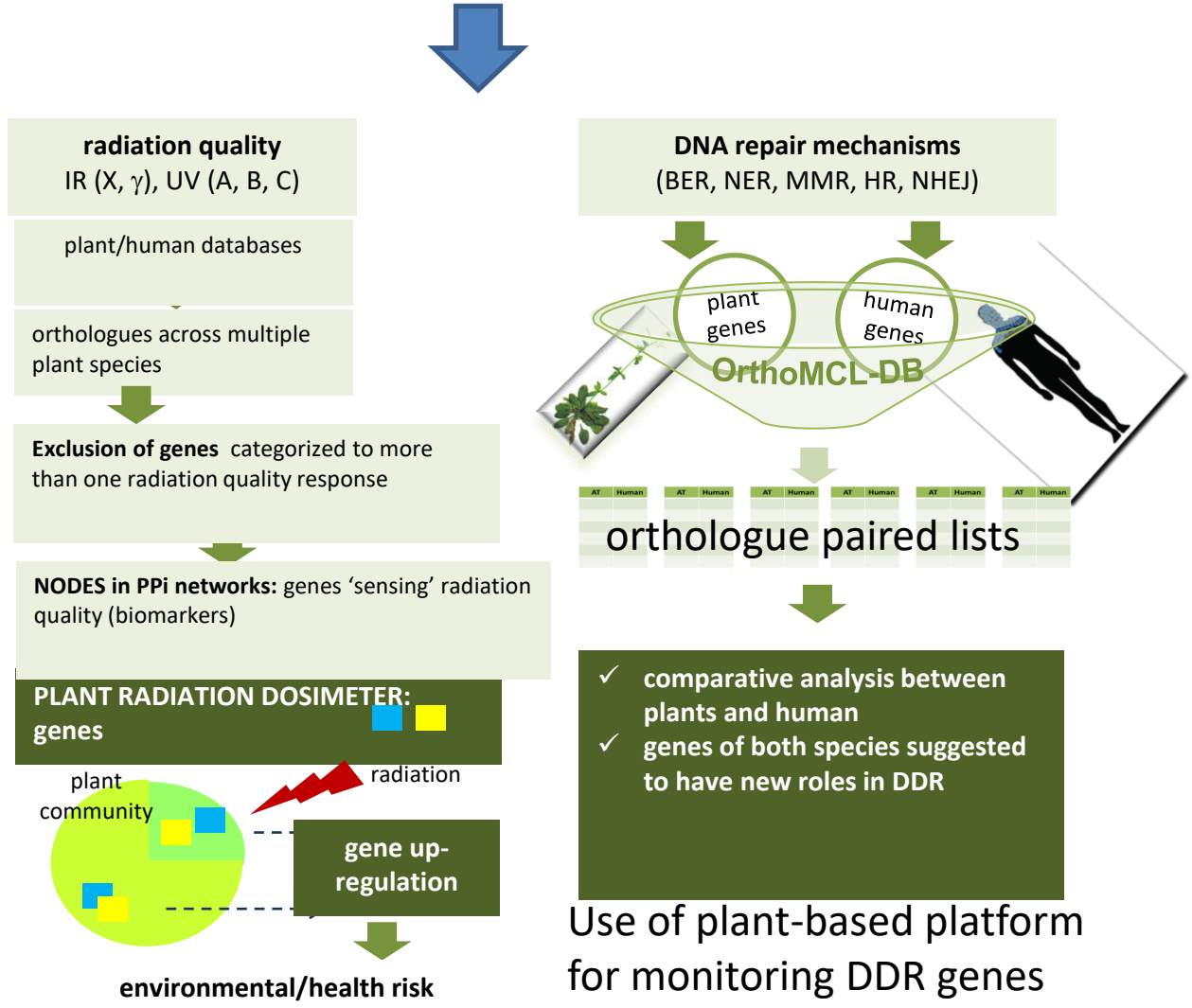
Review

Complex DNA Damage: A Route to Radiation-Induced Genomic Instability and Carcinogenesis

Ifigeneia V. Mavragani [1], *Zacharenia Nikitaki* [1], *Maria P. Souli* [1], *Asef Aziz* [2], *Somaira Nowsheen* [3,4], *Khaled Aziz* [3], *Emmy Rogakou* [5] *and* ***Alexandros G. Georgakilas*** [1,*]



Bridging plant and animal responses



Use of plant-based platform for monitoring DDR genes and genotoxic stress

Nikitaki, Z., Pavlopoulou, A., Hola, M., Dona, M., Michalopoulos, I., Balestrazzi, A., Angelis, K. J., & Georgakilas, A. G. (2017). Bridging Plant and Human Radiation Response and DNA Repair through an In Silico Approach. *Cancers (Basel), 9, E65.*

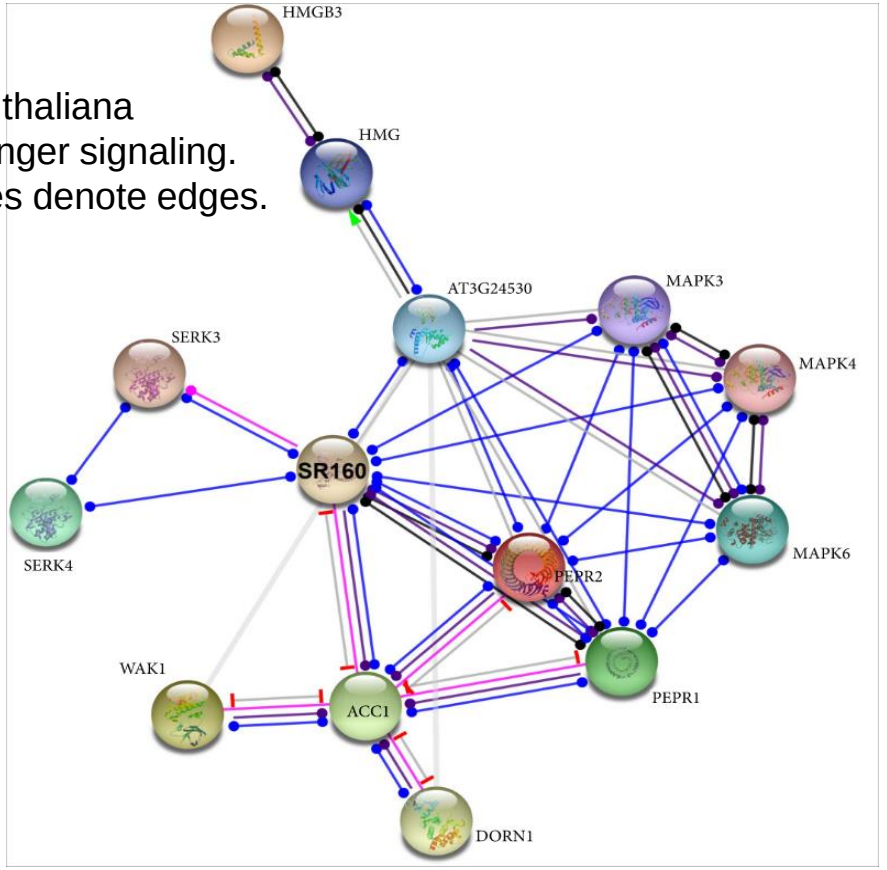
4 *In Silico* Phylogenetic and Structural Analyses of Plant Endogenous Danger Signaling Molecules upon Stress

Athanasia Pavlopoulou , Ezgi Karaca , Alma Balestrazzi , and **Alexandros G. Georgakilas**

https://www.hindawi.com/journals/omcl/2019/8683054/

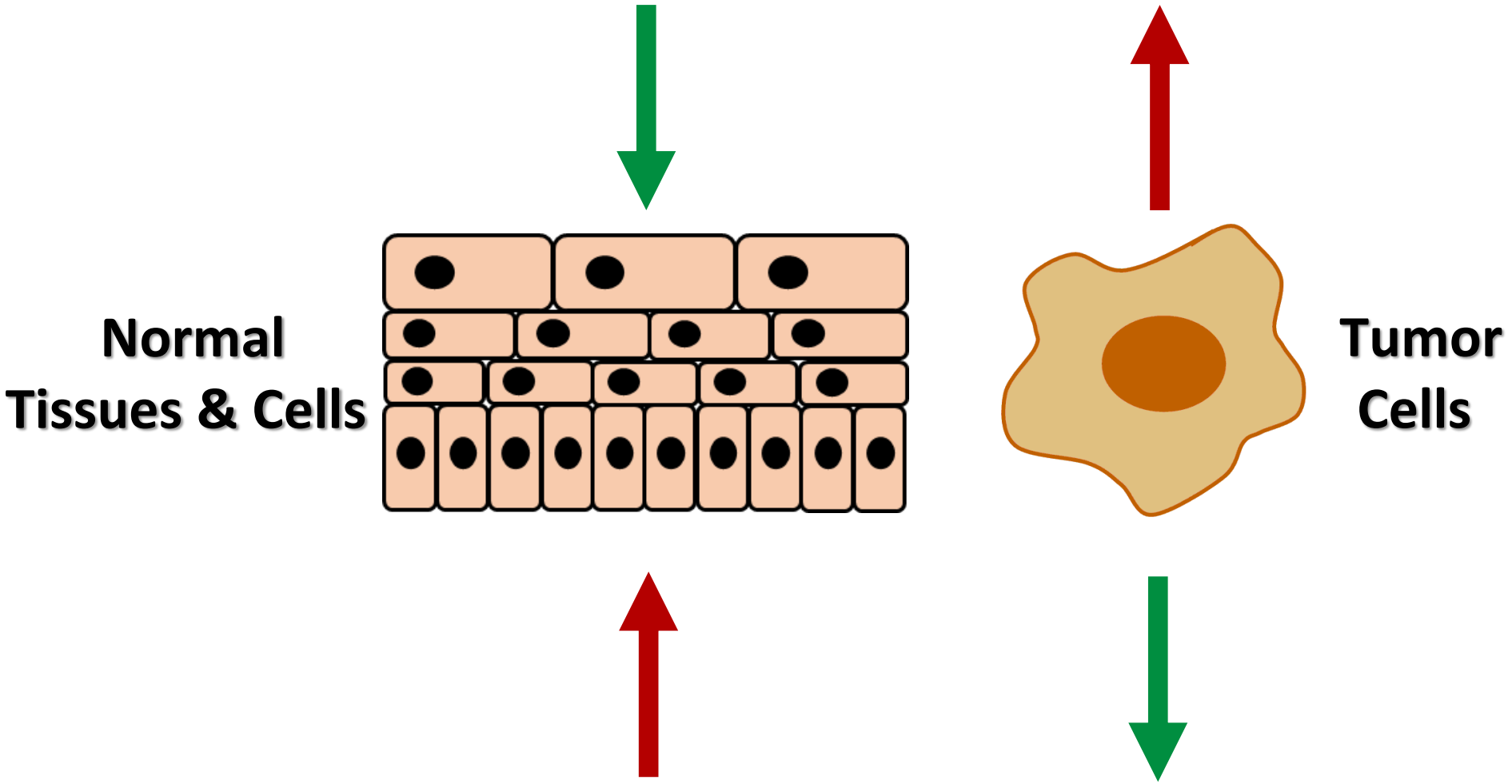
We have performed in silico phylogenetic and structural analyses of the associated biomolecules in taxonomically diverse plant species. On the basis of our results, the defense mechanisms appear to be largely conserved within the plant kingdom. Of note, the sequence and/or function of several components of these mechanisms was found to be conserved in animals, as well. At the same time, the molecules involved in plant defense were found to form a dense protein-protein interaction (PPi) network, suggesting a crosstalk between the various defense mechanisms to a variety of stresses, like oxidative stress.

Functional network PPi of the Arabidopsis thaliana molecules involved in DAMP-mediated danger signaling. The nodes represent proteins, and the lines denote edges.



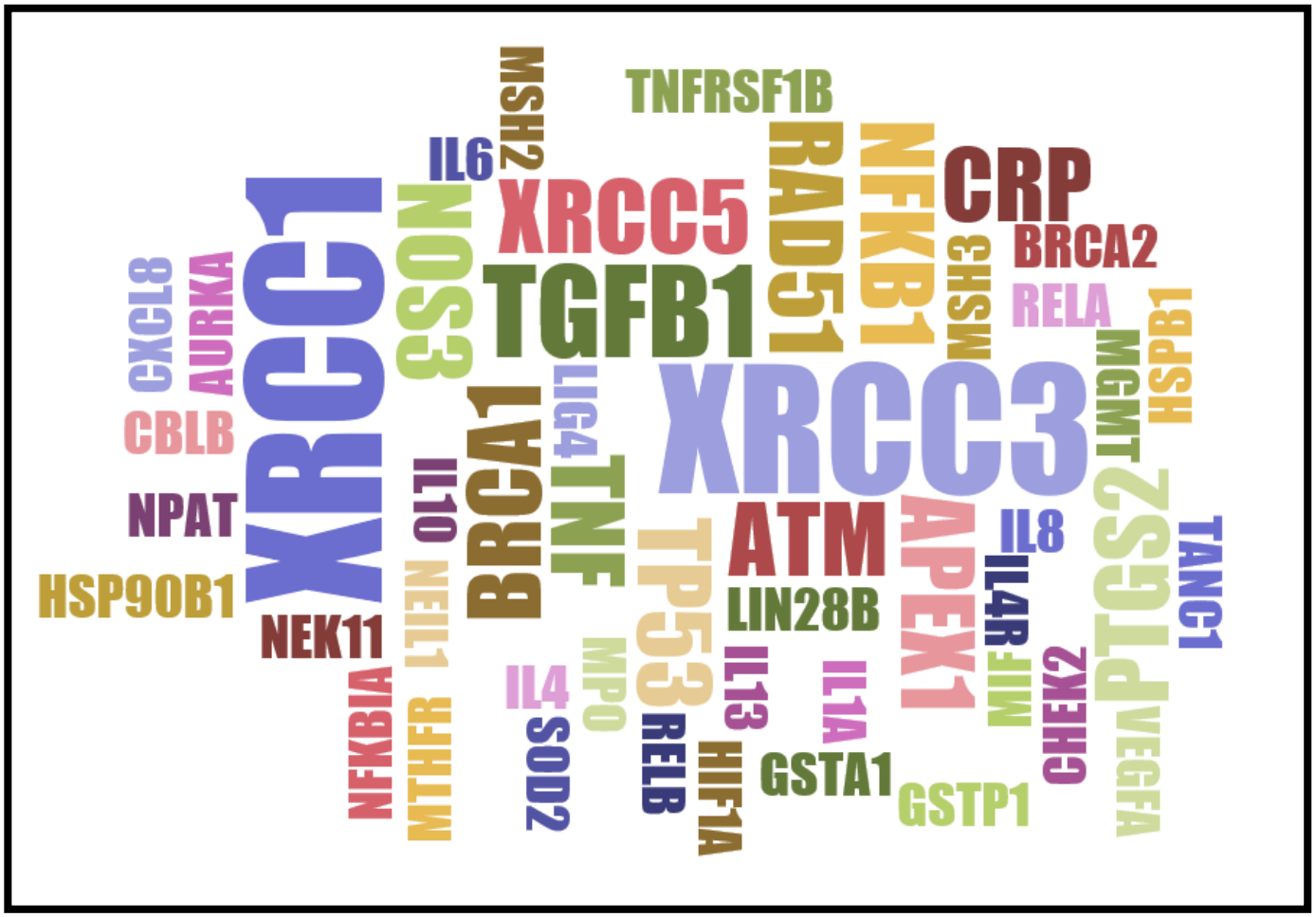
Of importance, based on the finding of this study, it would be tempting to suggest that plants could serve as basal model systems to study the individual signal transduction pathways implicated in danger signaling and further extrapolate this information to more complex organisms like mammals.

“Radiosensitivity” Genes as Therapeutic Targets

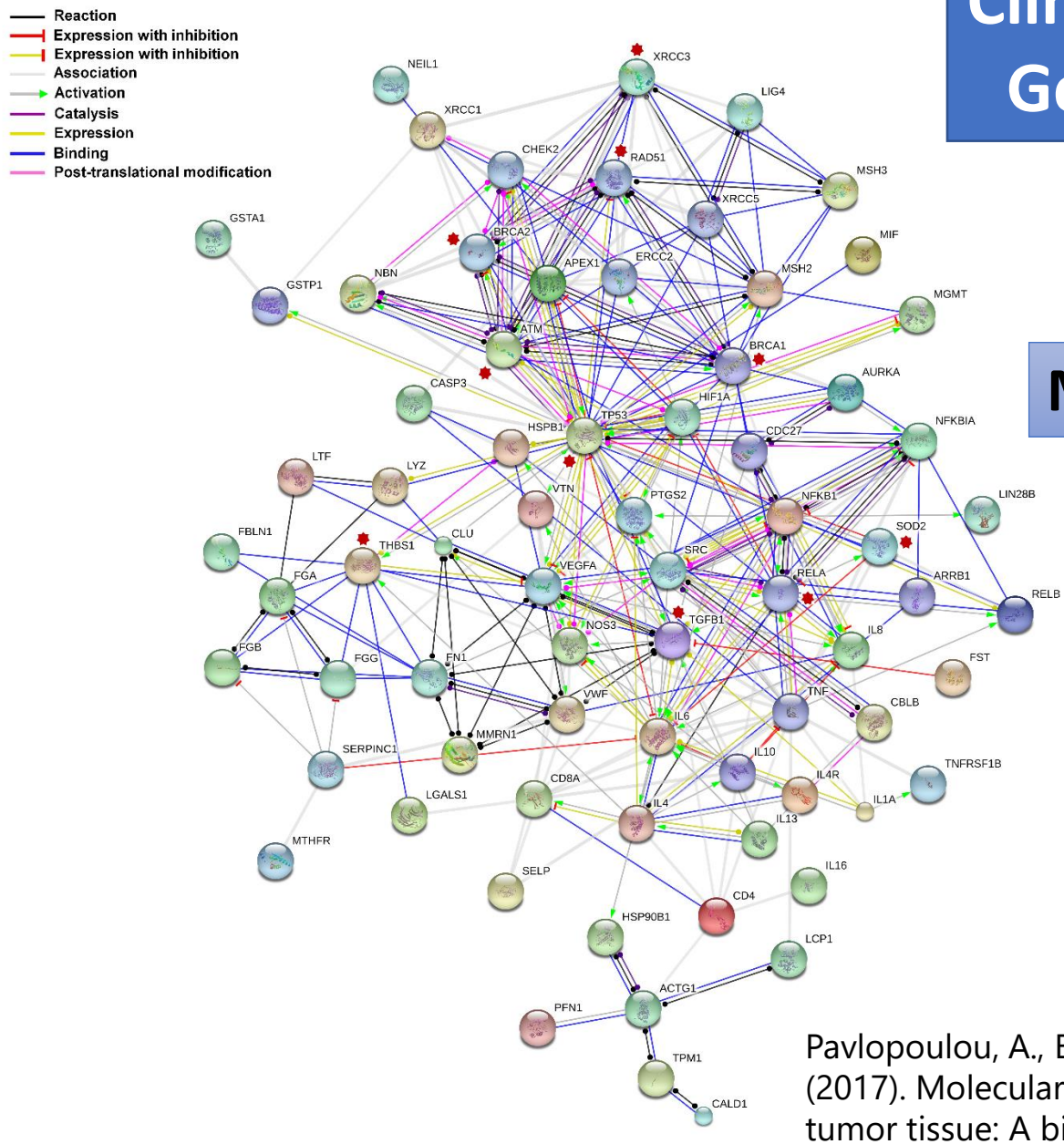


Clinical Radiosensitivity Gene/Gene products

Molecular Signature



Clinical Radiosensitivity Gene/Gene products



Molecular Associations

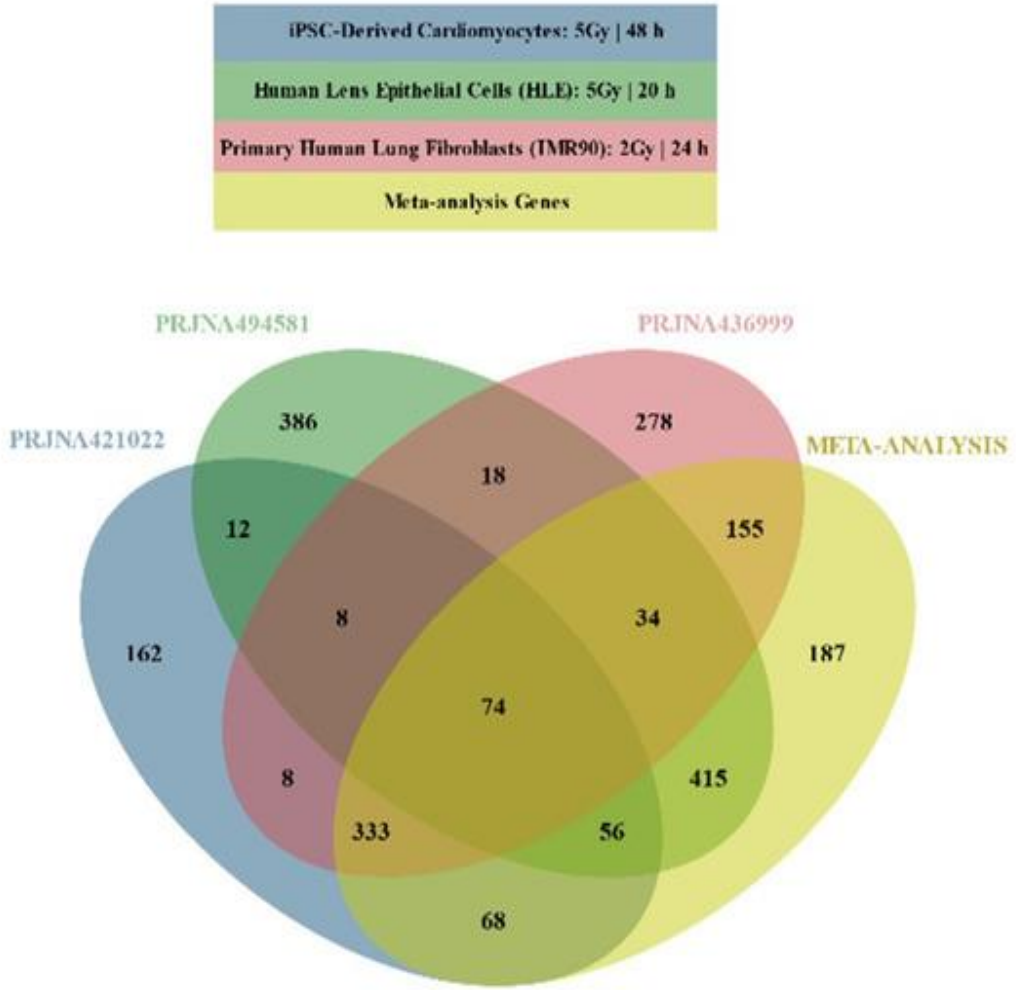
- Molecules associated with clinical, cellular and tumor cell radiosensitivity.

Pavlopoulou, A., Bagos, P. G., Koutsandrea, V., & Georgakilas, A. G. (2017). Molecular determinants of radiosensitivity in normal and tumor tissue: A bioinformatic approach. *Cancer Lett, 403, 37-47.*

Effects of High-Dose Ionizing Radiation in Human Gene Expression: A Meta-Analysis

Dimitrios S. Kanakoglou,Theodora-Dafni Michalettou, Christina Vasileiou, Evangelos Gioukakis, Dorothea Maneta, Konstantinos V. Kyriakidis, Alexandros G. Georgakilas and Ioannis Michalopoulos

The objective of this work was to investigate the effects of high-dose ionizing radiation on healthy human tissue, utilizing quantitative analysis of gene expression. To this end, publicly available transcriptomics datasets from human samples irradiated with a high dose of radiation and non-irradiated (control) ones were selected, and gene expression was determined using RNA-Seq data analysis.



https://www.mdpi.com/1422-0067/21/6/1938

Investigating Molecular Determinants of Cancer Cell Resistance to Ionizing Radiation Through an Integrative Bioinformatics Approach
https://www.frontiersin.org/articles/10.3389/fcell.2021.620248/full

>Data Retrieval
The public repository NCBI GEO DataSets was searched extensively for gene expression datasets using relevant keywords: ("radiation therapy" or "radiotherapy") and ("cancer" or "tumor") and ("resistance" or "tolerability") and ("sensitivity" or "responsive") and ("human" or "homo sapiens"). A total of three eligible datasets were selected.

>**Microarray-Based Transcriptomic Data Analysis**

>RNA-Seq-Based Transcriptomic Data Analysis

>Pathway Enrichment Analysis
To assign biological role(s) to the genes under study that are associated with biological pathways, gene set enrichment analysis (GSEA), or functional enrichment analysis, was conducted. GSEA is a method to identify biological processes or pathways that are over-represented in a large set of genes. To this end, WebGestalt (WEB-based GEne SeT AnaLysis Toolkit) (Zhang et al., 2005; Liao et al., 2019) was employed to identify statistically significant over-represented WikiPathways (Kutmon et al., 2016) cancer terms in the sets of genes; the threshold for the FDR-corrected *p*-value was set at 10^{-3}, and hypergeometric distribution analysis was used.

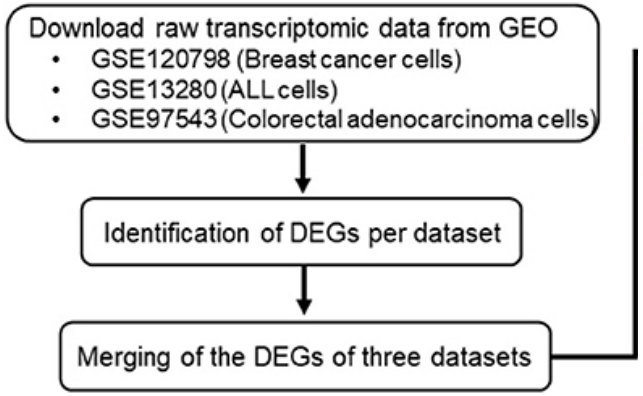
>**Functional Interactions Networks**
The associations among the molecules under study were investigated and visualized with the usage of STRING (Search Tool for Retrieval of Interacting Genes/Proteins) v11.0 (Szklarczyk et al., 2019), a database of either known or predicted, direct or indirect, gene/protein associations derived from diverse resources. The highest confidence interaction score (≥0.9) was chosen to display the associations amongst genes/proteins in the generated network.

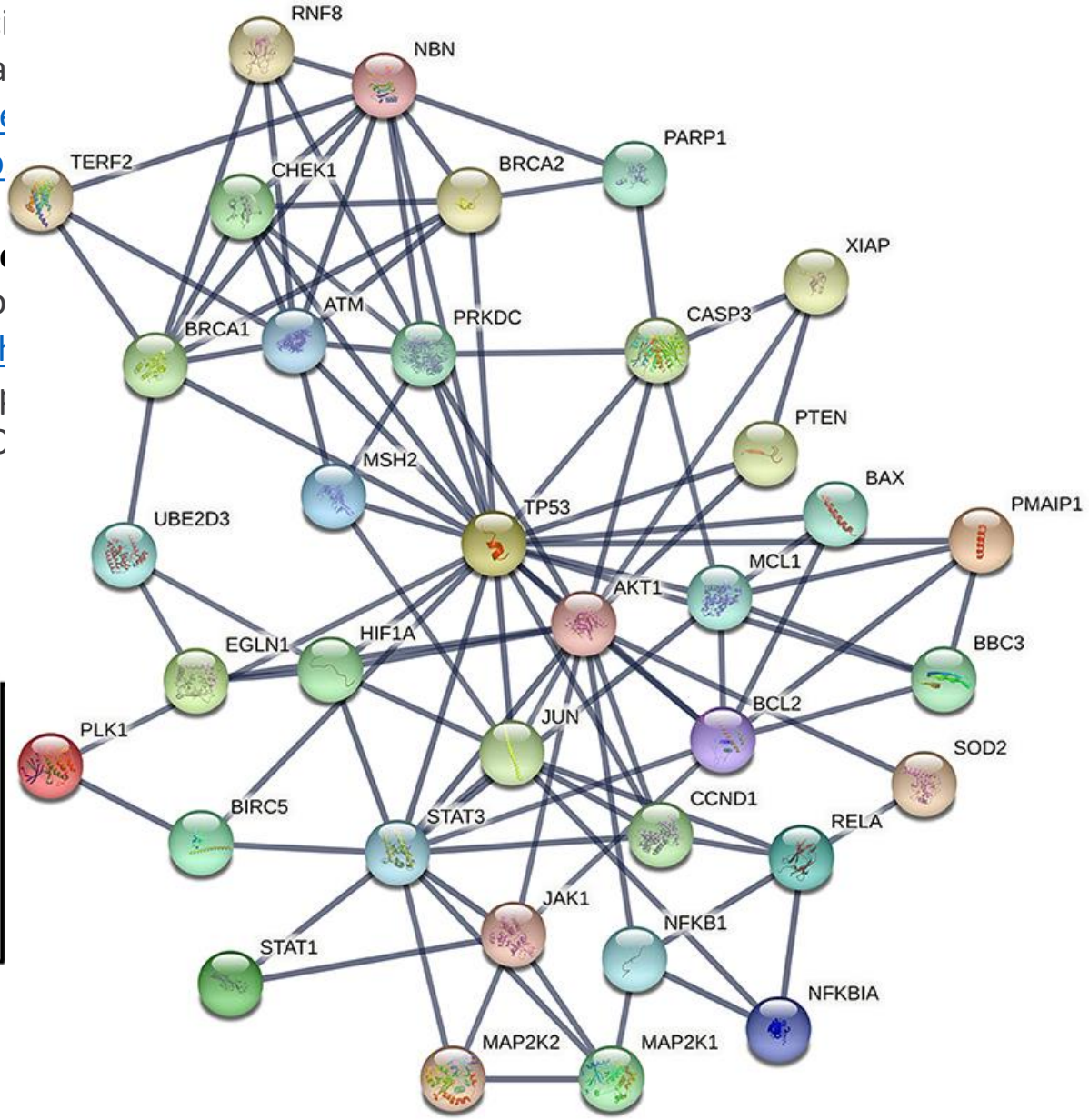
Survival Analysis

The prognostic potential of the 36 radiogenes was investigated in three types of cancers, namely, breast invasive carcinoma (BRCA), colon adenocarci ologic cancer like ALL, through the web-ba t al., 2017) version 2 (http://gepia2.canc Atlas (TCGA) (https://tcga-data.nci.nih.go

Tissue-Wise Differential Gene Expr

GEPIA2 (Tang et al., 2017), which co ssues from TCGA (https://tcga-data.nci.nih (https://gtexportal.org/home/), resp of the radiogenes under study in BRCA, CC -value ≤ 0.05.





Antioxidants (Basel). 2022 Nov; 11(11): 2286.
Published online 2022 Nov 18. doi: 10.3390/antiox11112286
PMCID: PMC9687520
PMID: 36421472

Radiation Type- and Dose-Specific Transcriptional Responses across Healthy and Diseased Mammalian Tissues

Database: http://radbiodb.physics.ntua.gr/

Includes a collection of up-to-date existing data on mammalian genes differentially expressed after exposure to different types (X-rays, γ-rays, protons, carbon ions and α-particles) and doses of radiation in a variety of cell types. This database is a comprehensive tool for correlations of radiation type and/or dose with corresponding transcriptional responses across a variety of tissues. Following an integrated bioinformatics approach that included gene-centric, pathway-oriented and machine learning analyses, we consolidated the IR-induced differential gene expression to biological pathways and human diseases.

Overall, our data suggest that different radiation types and doses can trigger distinct trajectories of cell-intrinsic and cell-extrinsic pathways that hold promise to be manipulated toward improving radiotherapy efficiency and reducing systemic radiotoxicities

➔ SEE next page for method steps:

Data Hybrid Collection and Transcriptomic Analyses

A broad collection of genes was initially obtained by rigorous text mining of the bibliographic database MEDLINE/PubMed 2.0 (https://pubmed.ncbi.nlm.nih.gov/, accessed on 15 March 2021), with the use of keywords related to X-ray, γ-ray, proton, carbon ion and α-particle irradiation, i.e., ((gamma radiation) OR (gamma rays) OR (γ rays)) AND gene expression; ((proton(Title/Abstract)) AND (radiation(Title/Abstract))) AND (gene expression(Title/Abstract)); ((carbon(Title/Abstract)) AND (radiation(Title/Abstract))) AND (gene expression(Title/Abstract)) In this way, a total of 39 studies were selected. Gene symbols were assigned to the extracted human, mouse and rat genes according to the HUGO Gene Nomenclature Committee (HGNC) (https://www.genenames.org/

The following microarray transcriptome datasets were obtained where their respective GEO series and PubMed references are shown in brackets: X-rays (GSE107685 [20], GSE113611 [21], GSE107443 [22], GSE90909 [23], GSE85323 [24], GSE59861 [25], GSE6262 [26]); α particles (GSE12435 [27], GSE21059 [28], GSE18760 [29]); carbon ions (GSE6630 [30]); protons (GSE20629 [31]). The GEO2R interactive web server [19] was employed to detect genes differentially expressed at different conditions. The differentially expressed genes (DEGs) with an absolute log2 fold-change (FC) greater than 1.5 ($|\log2FC| \geq 1.5$), or $FC > 1.5$ and $FC < 0.67$, and FDR-adjusted p-value (q-value) less than 0.05 or p-value < 0.001 (for transcriptomic data) and p-value < 0.05 (for the text mining data) were retained.

Functional Enrichment Analysis

Venn diagrams were constructed using the online tool Draw Venn Diagram (https://bioinformatics.psb.ugent.be/webtools/Venn/ Functional enrichment analysis was conducted with WebGestalt (WEB-based GEne SeT AnaLysis Toolkit) 2019, an online tool used for the identification of statistically significant enriched terms in the given gene sets compared to selected reference sets.

Database Construction

API-based Directus (https://docs.directus.io/, accessed on 10 April 2022), an open-source data platform, was used for content management, and MySQL (https://dev.mysql.com/

Machine Learning Approach

Random Forest is a bagging ensemble algorithm, which uses multiple different algorithms to generate a consensus output. It accepts as input a random sample generated from a given dataset with replacement, and then this sample is fed into the tree classifiers.

Functional Network

The STRING database (version 11.5) (https://string-db.org/

1. Kanakoglou, D.S., Michalettou, T.D., Vasileiou, C., Gioukakis, E., Maneta, D., Kyriakidis, K.V., Georgakilas, A.G. and Michalopoulos, I. (2020) Effects of High-Dose Ionizing Radiation in Human Gene Expression: A Meta-Analysis. *Int J Mol Sci,* ***21.***
2. Dilucca, M., Pavlopoulou, A., Georgakilas, A.G. and Giansanti, A. (2020) Codon usage bias in radioresistant bacteria. *Gene,* ***742, 144554.***
3. Dilucca, M., Forcelloni, S., Georgakilas, G.A., Giansanti, A. and Pavlopoulou, A. (2020) Codon Usage and Phenotypic Divergences of SARS-CoV-2 Genes. *Viruses,* ***12, E498.***
4. de Lastic, H.-X., Liampa, I., G. Georgakilas, A., Zervakis, M. and Chatziioannou, A. (2020) Entropic Ranks: A Methodology for Enhanced, Threshold-Free, Information-Rich Data Partition and Interpretation. *Applied Sciences,* ***10, 7077.***
5. Toy, H.I., Okmen, D., Kontou, P.I., Georgakilas, A.G. and Pavlopoulou, A. (2019) HOTAIR as a Prognostic Predictor for Diverse Human Cancers: A Meta- and Bioinformatics Analysis. *Cancers,* ***11, 778.***
6. Pavlopoulou, A., Karaca, E., Balestrazzi, A. and Georgakilas, A.G. (2019) In Silico Phylogenetic and Structural Analyses of Plant Endogenous Danger Signaling Molecules upon Stress. *Oxidative Medicine and Cellular Longevity,* ***2019, 14.***
7. Düzgün , M.B., Theofilatos, K., Georgakilas, A.G. and Pavlopoulou, A. (2019) A Bioinformatic Approach for the Identification of Molecular Determinants of Resistance/Sensitivity to Cancer Thermotherapy. *Oxidative Medicine and Cellular Longevity,* ***2019, 13.***
8. Nikitaki, Z., Hola, M., Dona, M., Pavlopoulou, A., Michalopoulos, I., Angelis, K.J., Georgakilas, A.G., Macovei, A. and Balestrazzi, A. (2018) Integrating plant and animal biology for the search of novel DNA damage biomarkers. *Mutat Res,* ***775, 21-38.***
9. Yeles, C., Vlachavas, E.-I., Papadodima, O., Pilalis, E., Vorgias, C., Georgakilas, A. and Chatziioannou, A. (2017) Integrative Bioinformatic Analysis of Transcriptomic Data Identifies Conserved Molecular Pathways Underlying Ionizing Radiation-Induced Bystander Effects (RIBE). *Cancers,* ***9, 160.***
10. Pavlopoulou, A., Bagos, P.G., Koutsandrea, V. and Georgakilas, A.G. (2017) Molecular determinants of radiosensitivity in normal and tumor tissue: A bioinformatic approach. *Cancer Lett,* ***403, 37-47.***
11. Nikitaki, Z., Pavlopoulou, A., Hola, M., Dona, M., Michalopoulos, I., Balestrazzi, A., Angelis, K.J. and Georgakilas, A.G. (2017) Bridging Plant and Human Radiation Response and DNA Repair through an In Silico Approach. *Cancers,* ***9, E65.***
12. Nikitaki, Z., Mavragani, I.V., Laskaratou, D.A., Gika, V., Moskvin, V.P., Theofilatos, K., Vougas, K., Stewart, R.D. and Georgakilas, A.G. (2016) Systemic mechanisms and effects of ionizing radiation: A new 'old' paradigm of how the bystanders and distant can become the players. *Semin Cancer Biol,* ***37-38, 77-95.***
13. Pateras, I.S., Havaki, S., Nikitopoulou, X., Vougas, K., Townsend, P.A., Panayiotidis, M.I., Georgakilas, A.G. and Gorgoulis, V.G. (2015) The DNA damage response and immune signaling alliance: Is it good or bad? Nature decides when and where. *Pharmacol Ther,* ***154, 36-56.***
14. Nikitaki, Z., Michalopoulos, I. and Georgakilas, A.G. (2015) Molecular inhibitors of DNA repair: searching for the ultimate tumor killing weapon. *Future medicinal chemistry, 1-16.*
15. Nikitaki, Z., Hellweg, C.E., Georgakilas, A.G. and Ravanat, J.L. (2015) Stress-induced DNA damage biomarkers: applications and limitations. *Frontiers in chemistry,* ***3, 35.***
16. Georgakilas, A.G., Pavlopoulou, A., Louka, M., Nikitaki, Z., Vorgias, C.E., Bagos, P.G. and Michalopoulos, I. (2015) Emerging molecular networks common in ionizing radiation, immune and inflammatory responses by employing bioinformatics approaches. *Cancer Lett.,* ***368, 164-172.***
17. Georgakilas, A.G., Tsantoulis, P., Kotsinas, A., Michalopoulos, I., Townsend, P. and Gorgoulis, V.G. (2014) Are common fragile sites merely structural domains or highly organized "functional" units susceptible to oncogenic stress? *Cellular and molecular life sciences : CMLS,* ***71, 4519-4544.***

Σας ευχαριστώ για τη προσοχή σας!!!!
Ερωτήσεις.....