Συσχετισμός μηχανισμών επαγωγής οξειδωτικών βλαβών DNA με καρκινογένεση

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National Technical University

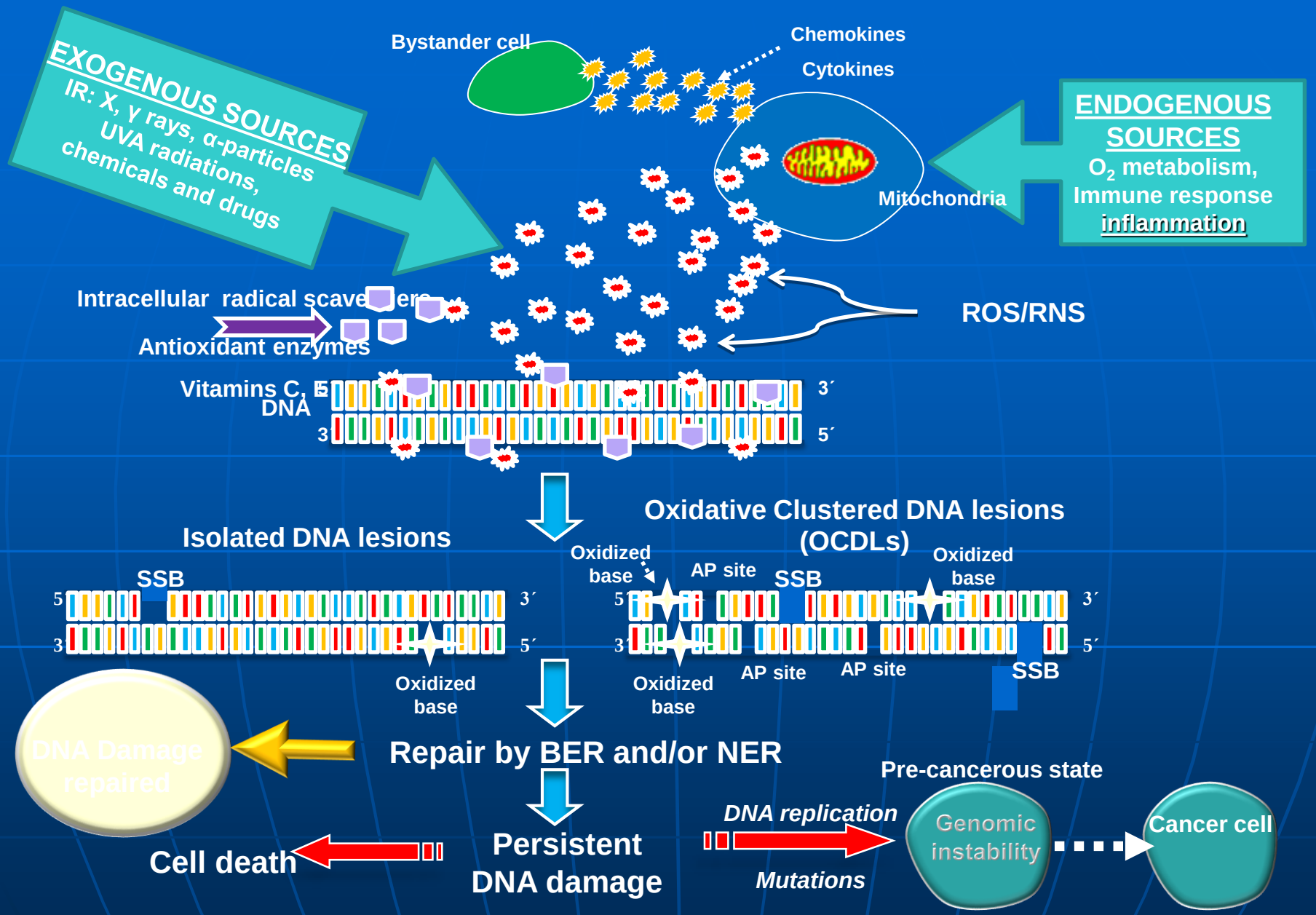
Η παρουσίαση αυτή χωρίζεται στα παρακάτω τμήματα:

1. Εισαγωγή στην έννοια των βλαβών DNA, μελέτες σε ανθρώπινα κύτταρα.
2. Μηχανισμοί επιδιόρθωσης (DNA repair).
3. Βιολογική σημασία. Συστημική δράση ακτινοβολιών.
4. Βιοπληροφορικές προσεγγίσεις

It is all about stress…..

- Oxidative stress!
- Radiation stress
- Replications stress

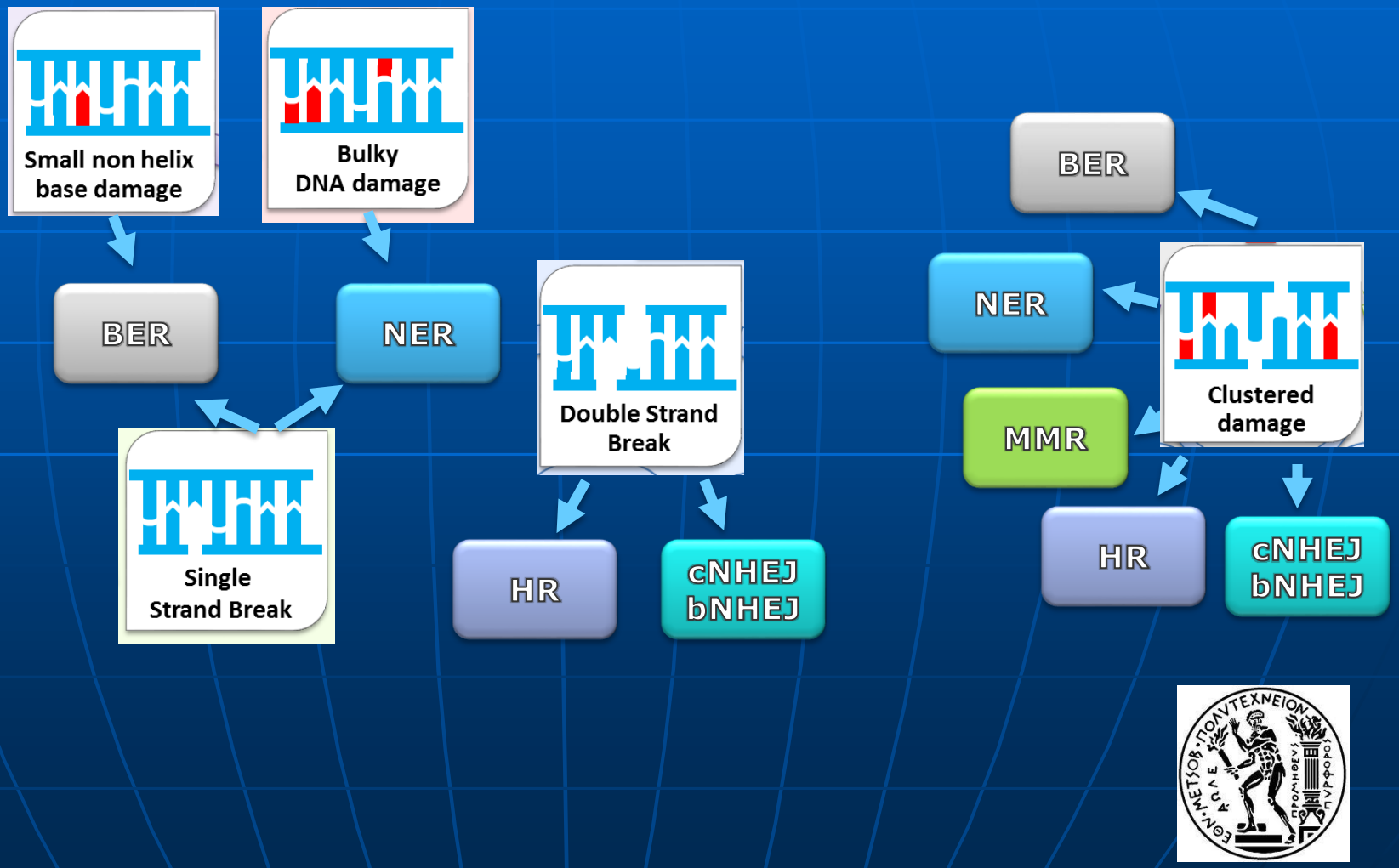
Anti-stress



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

Kryston et al. Mutat Res. 2011

DNA damage and repair

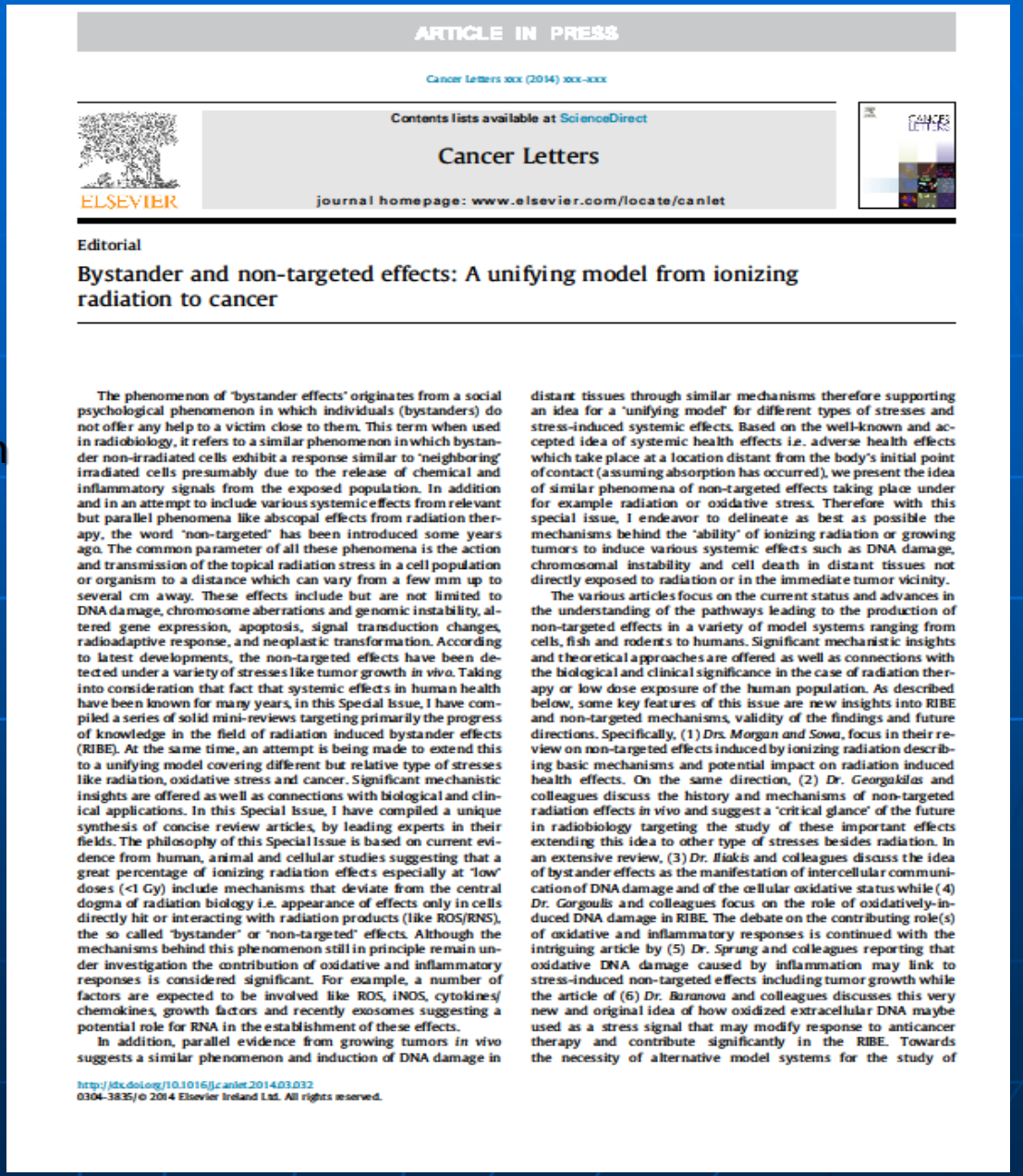


Bystander effects?

Cancer Lett. 2014 Apr 2. pii: S0304-3835(14)00201-8. doi:
Bystander and non-targeted effects: A unifying model from ionizing radiation to cancer.
Georgakilas AG.

Cancer Lett. 2014 Feb 11. pii: S0304-3835(14)00061-5.
The role of oxidative DNA damage in radiation induced bystander effect.

Havaki et al. (Gorgoulis group)



ARTICLE IN PRESS

Cancer Letters xxx (2014) xxx–xxx

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Editorial

Bystander and non-targeted effects: A unifying model from ionizing radiation to cancer

The phenomenon of "bystander effects" originates from a social psychological phenomenon in which individuals (bystanders) do not offer any help to a victim close to them. This term when used in radiobiology, it refers to a similar phenomenon in which bystander non-irradiated cells exhibit a response similar to 'neighboring' irradiated cells presumably due to the release of chemical and inflammatory signals from the exposed population. In addition and in an attempt to include various systemic effects from relevant but parallel phenomena like abscopal effects from radiation therapy, the word "non-targeted" has been introduced some years ago. The common parameter of all these phenomena is the action and transmission of the topical radiation stress in a cell population or organism to a distance which can vary from a few mm up to several cm away. These effects include but are not limited to DNA damage, chromosome aberrations and genomic instability, altered gene expression, apoptosis, signal transduction changes, radioadaptive response, and neoplastic transformation. According to latest developments, the non-targeted effects have been detected under a variety of stresses like tumor growth *in vivo*. Taking into consideration that fact that systemic effects in human health have been known for many years, in this Special Issue, I have compiled a series of solid mini-reviews targeting primarily the progress of knowledge in the field of radiation induced bystander effects (RIBE). At the same time, an attempt is being made to extend this to a unifying model covering different but relative type of stresses like radiation, oxidative stress and cancer. Significant mechanistic insights are offered as well as connections with biological and clinical applications. In this Special Issue, I have compiled a unique synthesis of concise review articles, by leading experts in their fields. The philosophy of this Special Issue is based on current evidence from human, animal and cellular studies suggesting that a great percentage of ionizing radiation effects especially at "low" doses (<1 Gy) include mechanisms that deviate from the central dogma of radiation biology i.e. appearance of effects only in cells directly hit or interacting with radiation products (like ROS/RNS), the so called "bystander" or "non-targeted" effects. Although the mechanisms behind this phenomenon still in principle remain under investigation the contribution of oxidative and inflammatory responses is considered significant. For example, a number of factors are expected to be involved like ROS, iNOS, cytokines/chemokines, growth factors and recently exosomes suggesting a potential role for RNA in the establishment of these effects.

In addition, parallel evidence from growing tumors *in vivo* suggests a similar phenomenon and induction of DNA damage in distant tissues through similar mechanisms therefore supporting an idea for a 'unifying model' for different types of stresses and stress-induced systemic effects. Based on the well-known and accepted idea of systemic health effects i.e. adverse health effects which take place at a location distant from the body's initial point of contact (assuming absorption has occurred), we present the idea of similar phenomena of non-targeted effects taking place under for example radiation or oxidative stress. Therefore with this special issue, I endeavor to delineate as best as possible the mechanisms behind the "ability" of ionizing radiation or growing tumors to induce various systemic effects such as DNA damage, chromosomal instability and cell death in distant tissues not directly exposed to radiation or in the immediate tumor vicinity.

The various articles focus on the current status and advances in the understanding of the pathways leading to the production of non-targeted effects in a variety of model systems ranging from cells, fish and rodents to humans. Significant mechanistic insights and theoretical approaches are offered as well as connections with the biological and clinical significance in the case of radiation therapy or low dose exposure of the human population. As described below, some key features of this issue are new insights into RIBE and non-targeted mechanisms, validity of the findings and future directions. Specifically, (1) *Drs. Morgan and Sowa*, focus in their review on non-targeted effects induced by ionizing radiation describing basic mechanisms and potential impact on radiation induced health effects. On the same direction, (2) *Dr. Georgakilas* and colleagues discuss the history and mechanisms of non-targeted radiation effects *in vivo* and suggest a 'critical glance' of the future in radiobiology targeting the study of these important effects extending this idea to other type of stresses besides radiation. In an extensive review, (3) *Dr. Iliakis* and colleagues discuss the idea of bystander effects as the manifestation of intercellular communication of DNA damage and of the cellular oxidative status while (4) *Dr. Gorgoulis* and colleagues focus on the role of oxidatively-induced DNA damage in RIBE. The debate on the contributing role(s) of oxidative and inflammatory responses is continued with the intriguing article by (5) *Dr. Sprung* and colleagues reporting that oxidative DNA damage caused by inflammation may link to stress-induced non-targeted effects including tumor growth while the article of (6) *Dr. Baranova* and colleagues discusses this very new and original idea of how oxidized extracellular DNA maybe used as a stress signal that may modify response to anticancer therapy and contribute significantly in the RIBE. Towards the necessity of alternative model systems for the study of

http://dx.doi.org/10.1016/j.canlet.2014.03.032

Bystander effects:

- The phenomenon of 'bystander effects' originates from a social psychological phenomenon in which individuals (bystanders) do not offer any help to a victim close to them (1968).

Συστημική δράση……

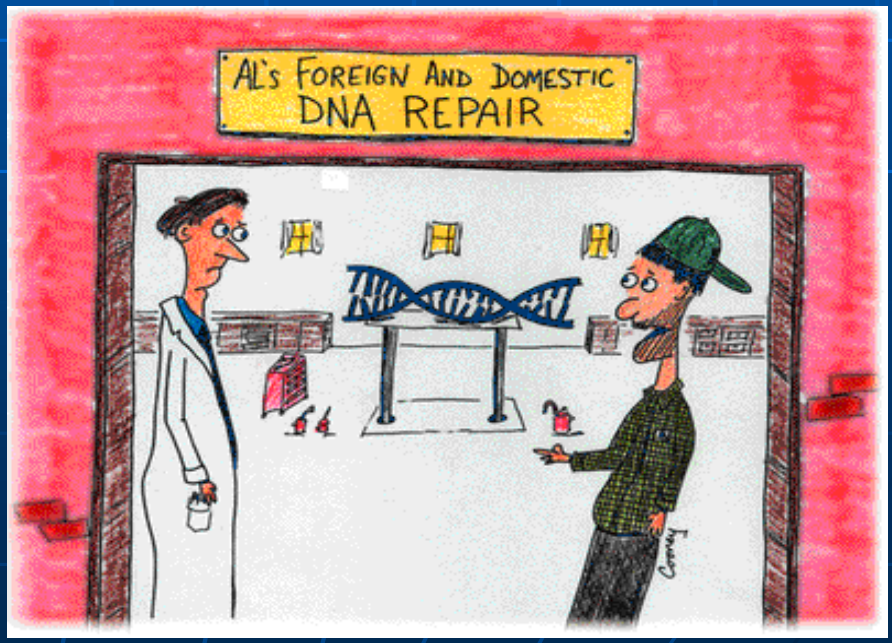
- This term when used in radiobiology, it refers to a similar phenomenon in which bystander non-irradiated cells exhibit a response similar to 'neighboring' irradiated cells presumably due to the release of chemical and inflammatory signals from the exposed population.

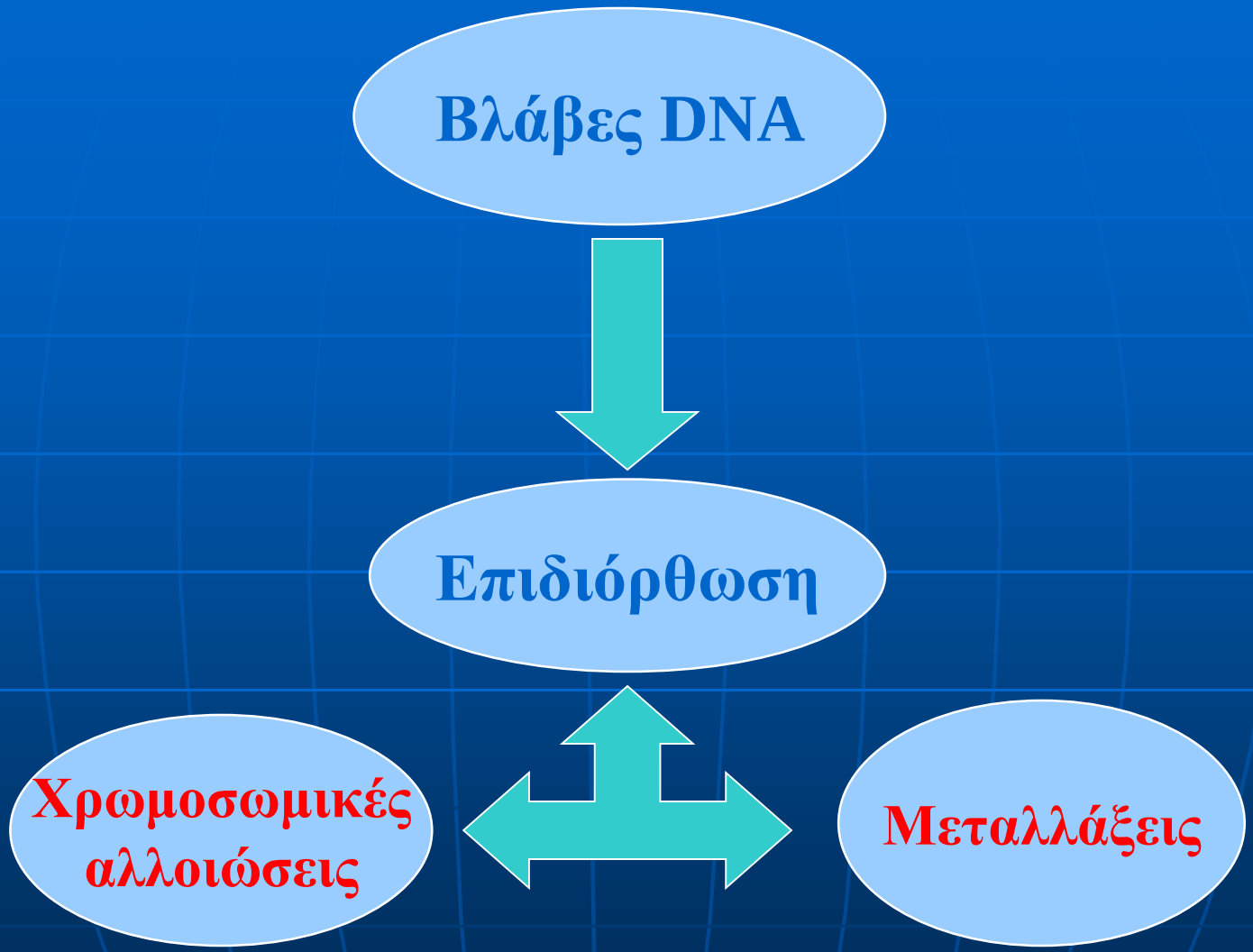
- In addition and in an attempt to include various **systemic health effects** from relevant but parallel phenomena like abscopal effects from radiation therapy, the word 'non-targeted' has been introduced some years ago.

.....ΕΠΙΔΙΟΡΘΩΣΗ DNA

Βιολογικό στάδιο

> Αμέσως μετά το χημικό στάδιο αρχίζει η εμφάνιση ενζυμικών μηχανισμών που δρουν επιδιορθωτικά στους μοριακούς σχηματισμούς που υπέστησαν βλάβη. Η διαδικασία της επιδιόρθωσης διαρκεί κατά το κύριο μέρος της από 15min-3h και ολοκληρώνεται σε 24-48 περίπου ώρες. Στην περίπτωση όπου η βλάβη είναι αδύνατον να επιδιορθωθεί, τα κύτταρα οδηγούνται σε είτε στη δημιουργία μεταλλάξεων η΄/και κυτταρικό θάνατο μέσω απόπτωσης (apoptosis).




Βλάβες DNA
Επιδιόρθωση
Χρωμοσωμικές αλλοιώσεις
Μεταλλάξεις

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)

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)

Μηχανισμοί επιδιόρθωσης DSBs

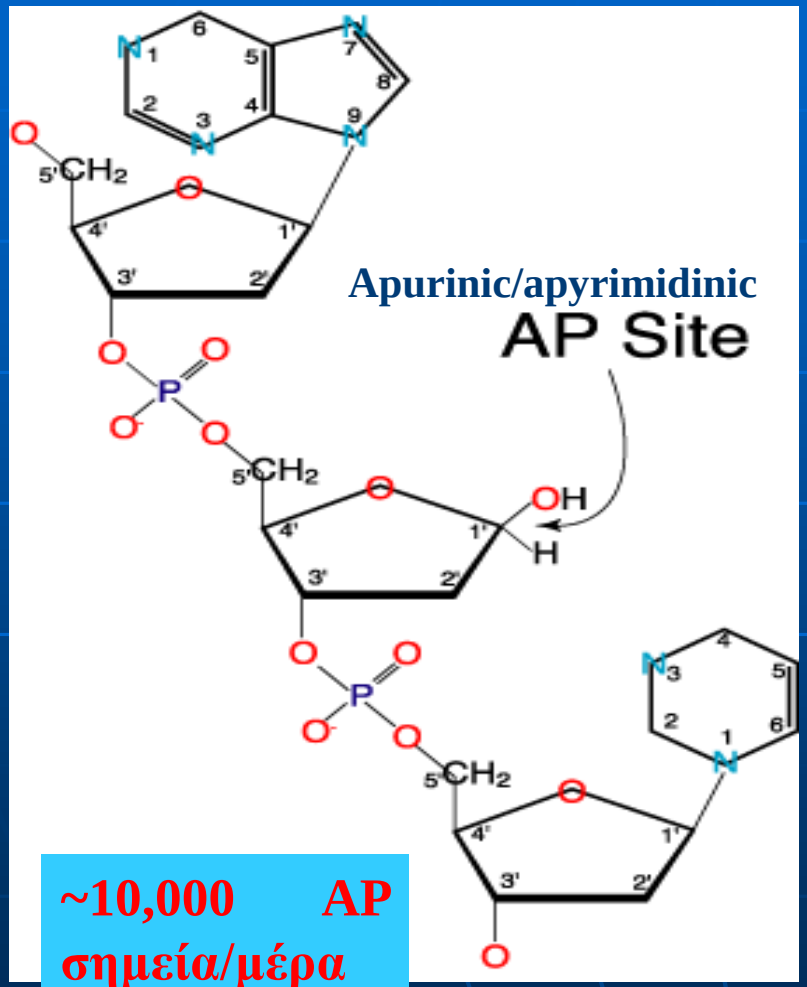
- Οι DSBs απαιτούν λεπτομερή επιδιόρθωση που μπορεί να επιτευχθεί από δύο ανεξάρτητους αλλά όχι αμοιβαία αποκλειόμενους μηχανισμούς:

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

> τον ομόλογο ανασυνδυασμό (homologous recombination-HR).

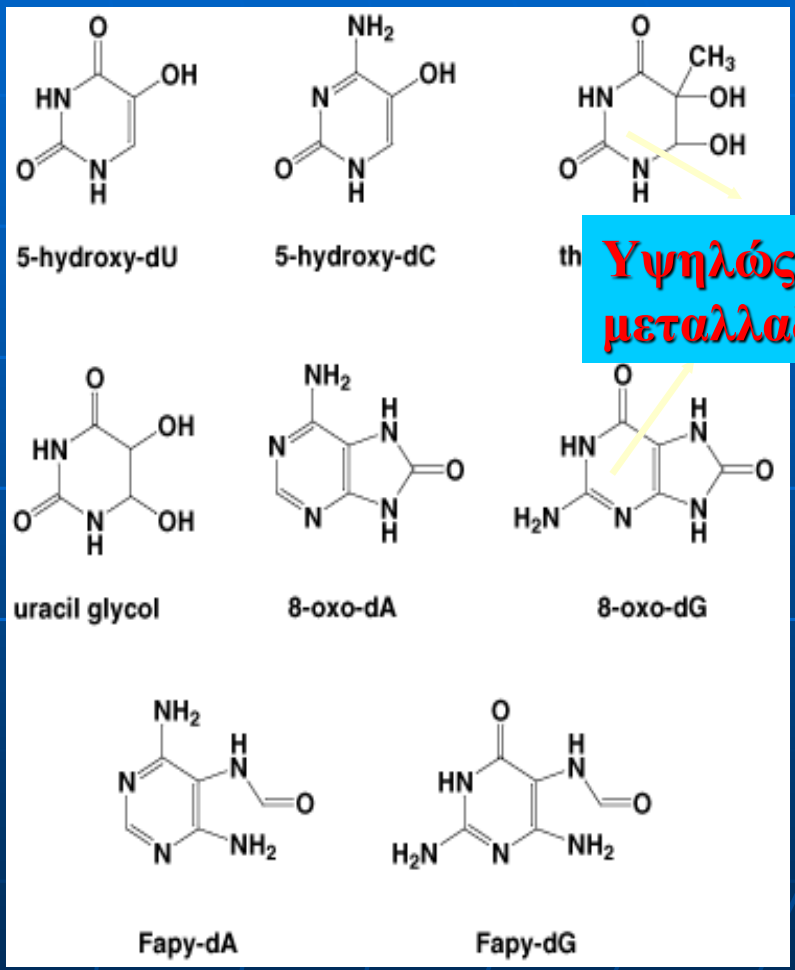
Βασικά είδη οξειδωτικών DNA βλαβών

Αβασικά σημεία (AP)



~10,000 AP σημεία/μέρα

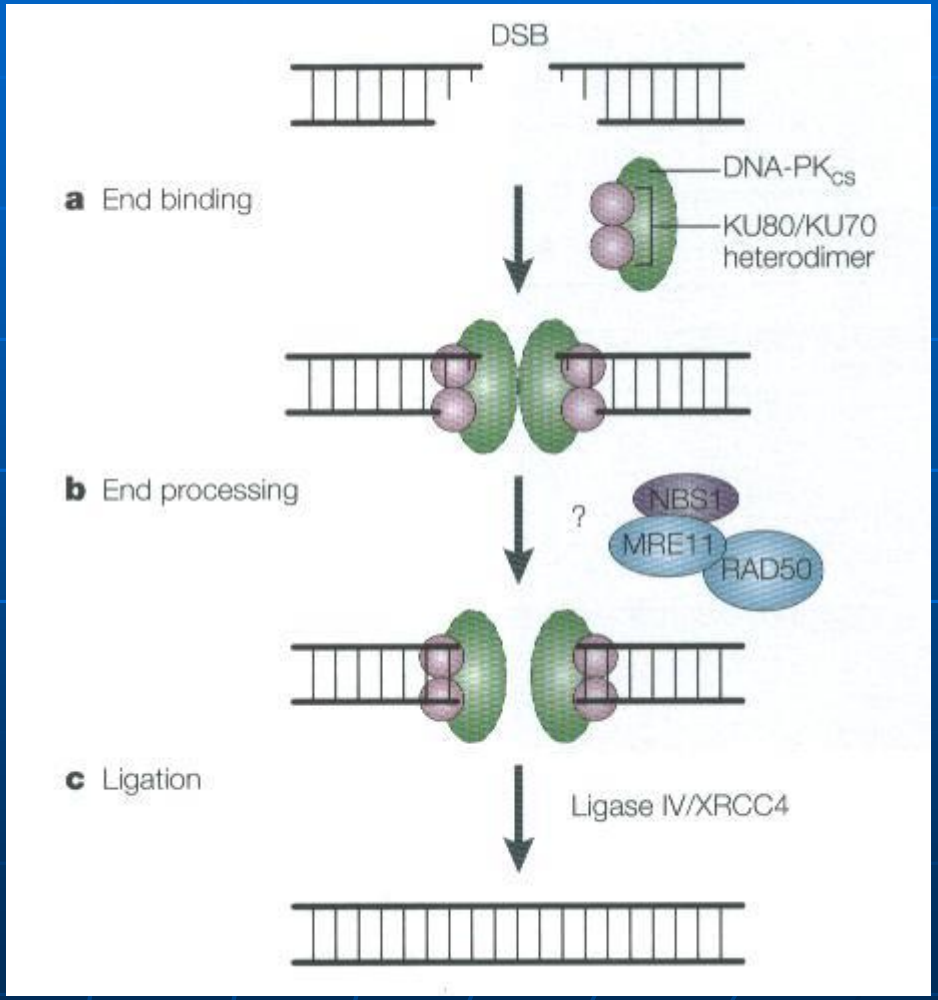
Οξειδωμένες βάσεις



Υψηλώς μεταλλαξογόνες

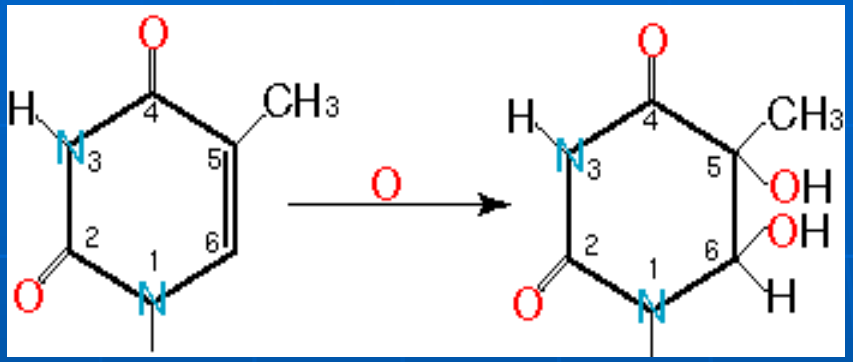
Επιδιόρθωση DSBs

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

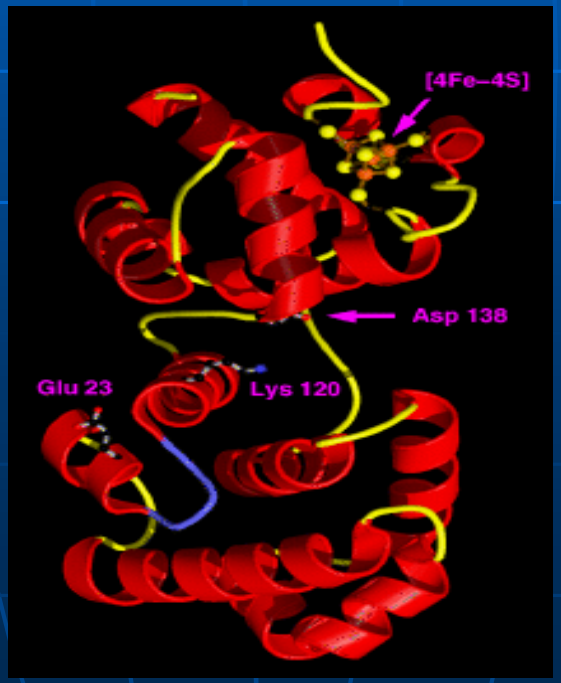


Αλλοιώσεις βάσεων DNA

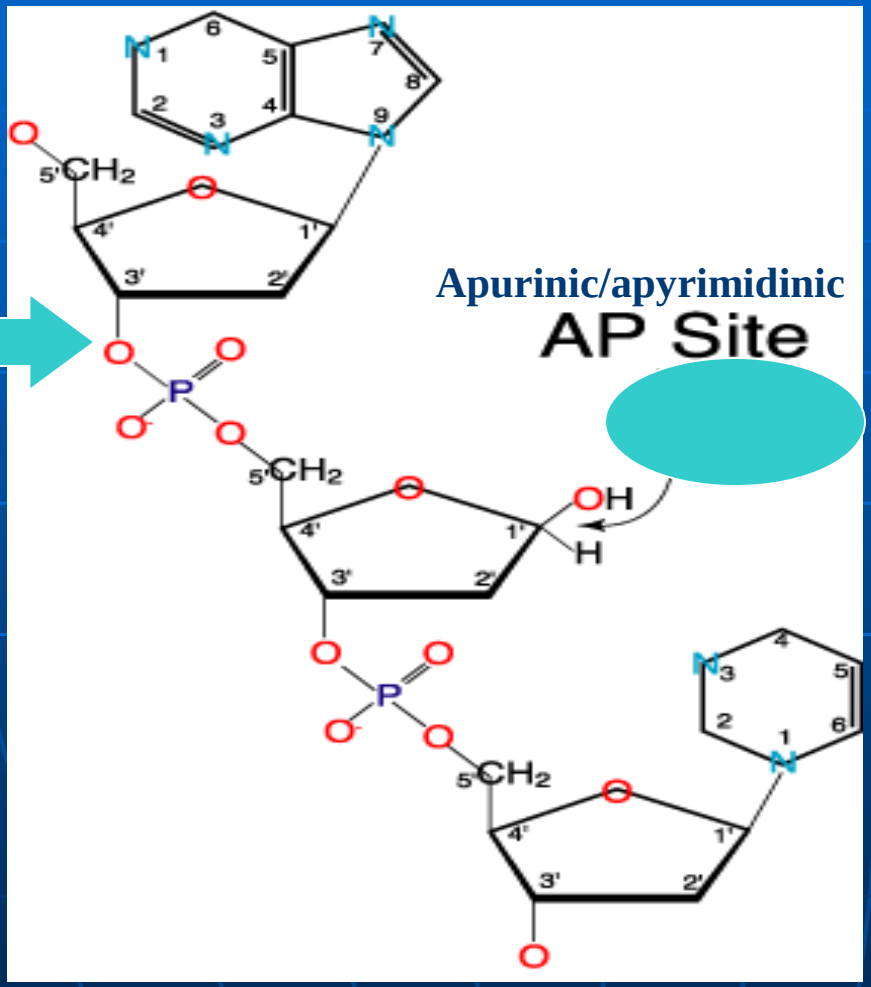
Οξείδωση θυμίνης (γλυκόλη θυμίνης): Tg (thymine glycol)



Ενζυμα επιδιόρθωσης E. Coli Endonuclease III/ human Nth1



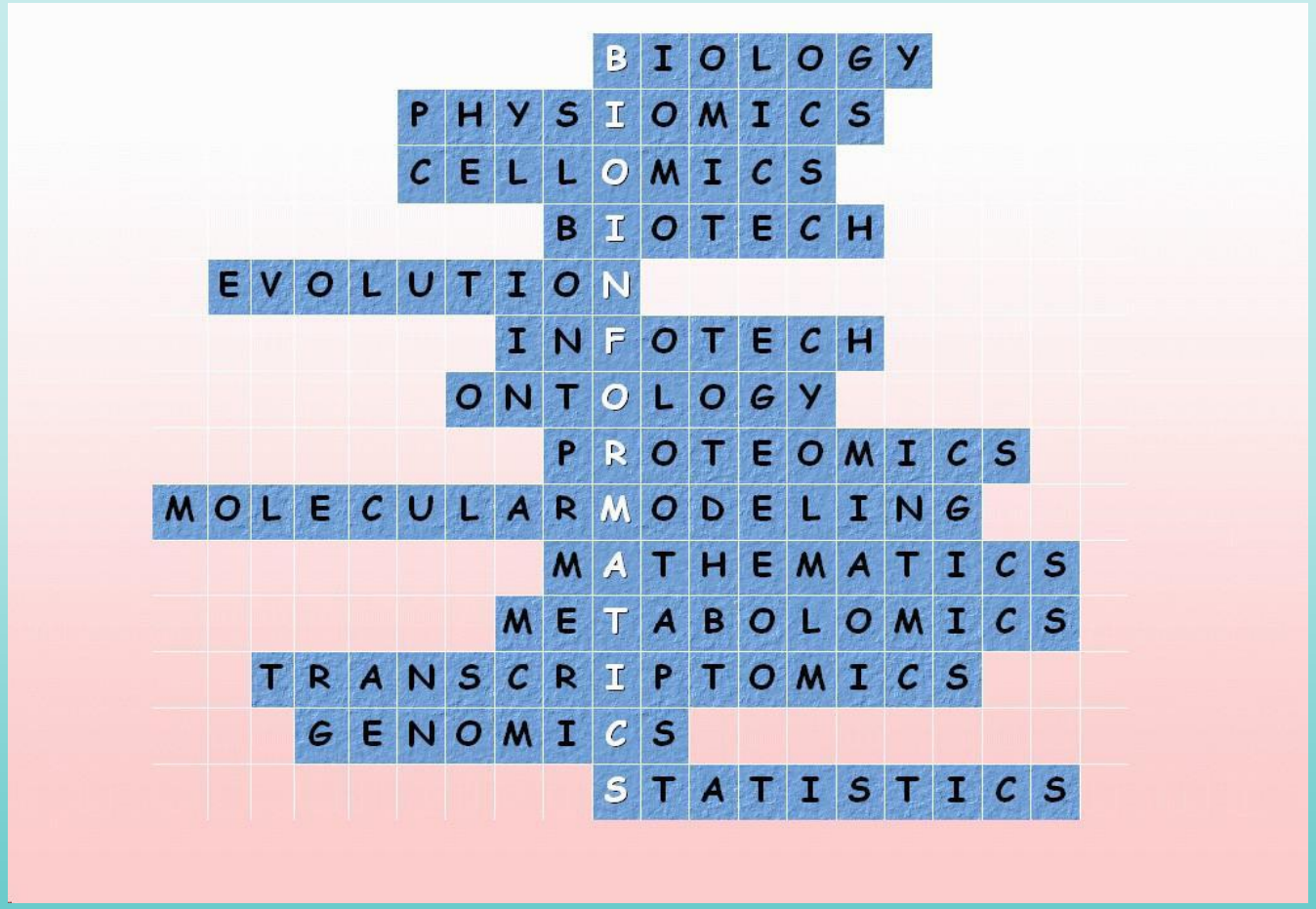
Μηχανισμός επιδιόρθωσης εκτομής βάσης: Base Excision Repair (BER)



AP ενδονουκλεάσες 'κόβουν' 5΄ ενός AP σημείου, δημιουργώντας μία μονόκλωνη θραύση (SSB):

-----3΄-OH.....5΄-dRP-----

ΕΦΑΡΜΟΓΕΣ ΜΕ ΤΗ ΧΡΗΣΗ ΒΙΟΠΛΗΡΟΦΟΡΙΚΗΣ.....


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

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/

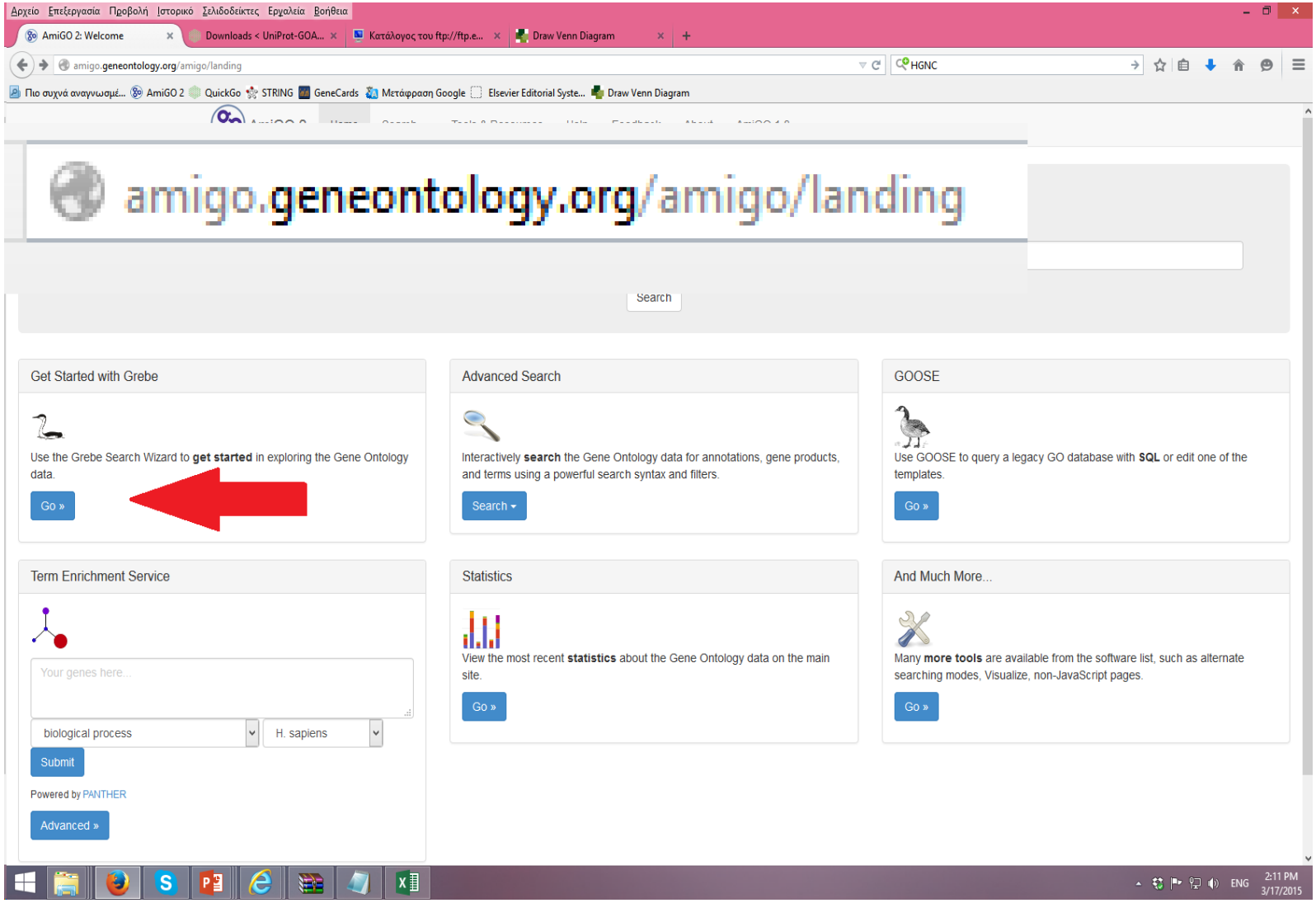
STRINGdb http://string-db.org/

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 – GLAD4U

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

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

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

Example for GLAD4U: Ionizing radiation response

- Ticket number: t2efceb88p3ro6fhd768ddqvg0
- Generated on: March 20, 2019
- Query: ionizing radiation response (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: 31,654
- Number of publications containing gene information (among the 31,654): 2,282
- Number of genes in these 2,282 publications: 1,797
- Number of genes after the score threshold: 238 Show all excluded genes

The results for your query (**ionizing radiation response**) were displayed and processed by GLAD4U in **24.72s.**

Please, visit our website to retrieve the results, using the ticket number: **t2efceb88p3ro6fhd768ddqvg0**.
The results will be kept for 48hrs on our server.
Thank you for using GLAD4U (http://bioinfo.vanderbilt.edu/glad4u).
-- *GLAD4U development team.*

http://webgestalt.org/

WEB-based GEne SeT AnaLysis Toolkit

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

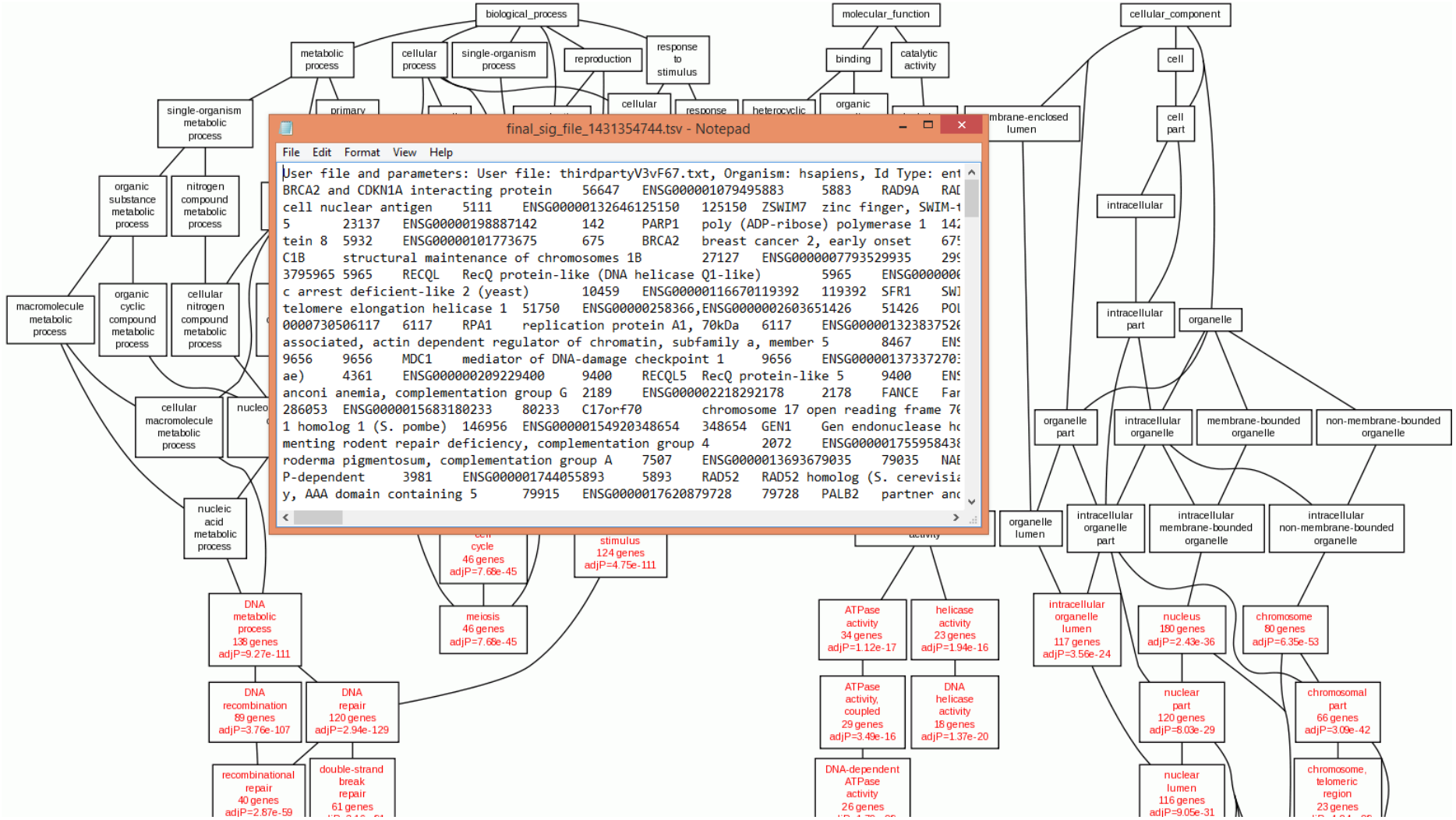
Click on this button to download or view a tab separated list of significant GO categories with corresponding User Uploaded IDs, Entrez IDs, Ensembl Gene Stable IDs, Gene Symbols, and descriptic

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).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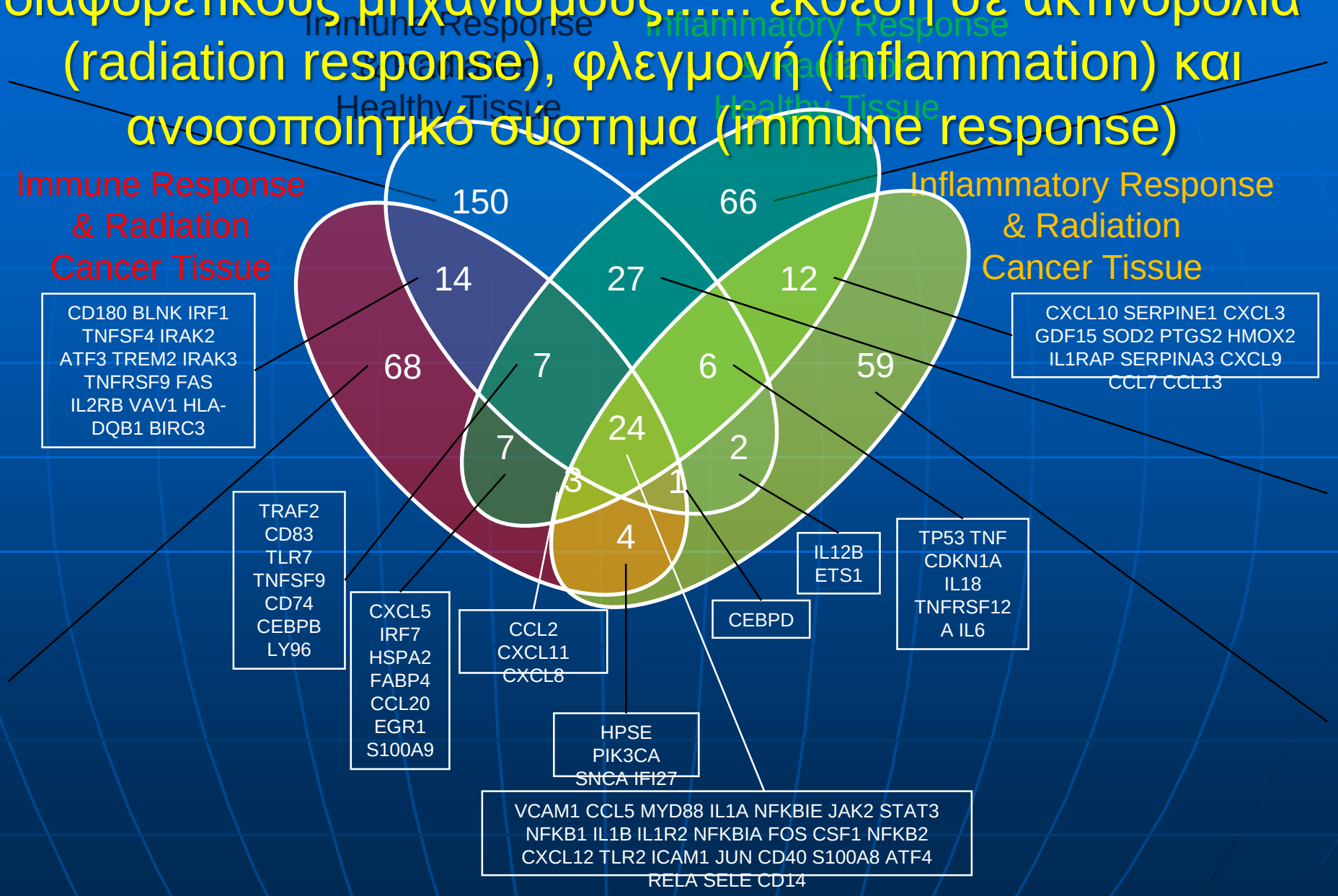
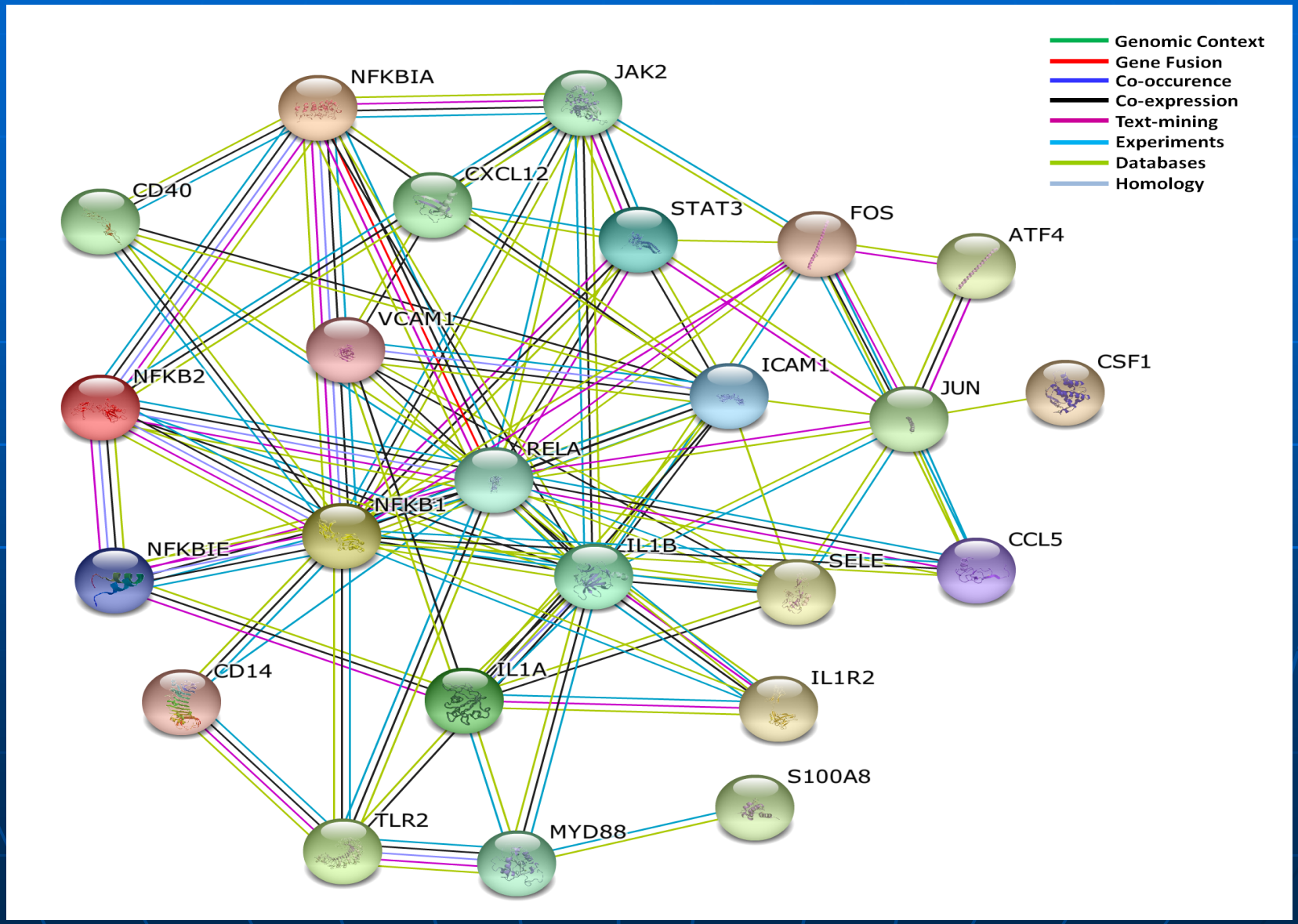
molecular_function
cellular_component
metabolic process
cellular process
single-organism process
reproduction
response to stimulus
binding
catalytic activity
cell
single-organism metabolic process
cellular
response
heterocyclic
organic
membrane-enclosed lumen
cell part
organic substance metabolic process
nitrogen compound metabolic process
intracellular
macromolecule metabolic process
organic cyclic compound metabolic process
cellular nitrogen compound metabolic process
intracellular part
organelle
cellular macromolecule metabolic process
organelle part
intracellular organelle
membrane-bounded organelle
non-membrane-bounded organelle
nucleic acid metabolic process
organelle lumen
intracellular organelle part
intracellular membrane-bounded organelle
intracellular non-membrane-bounded organelle
cell cycle 46 genes adjP=7.68e-45
stimulus 124 genes adjP=4.75e-111
DNA metabolic process 136 genes adjP=9.27e-111
meiosis 46 genes adjP=7.68e-45
ATPase activity 34 genes adjP=1.12e-17
helicase activity 23 genes adjP=1.94e-16
intracellular organelle lumen 117 genes adjP=3.56e-24
nucleus 180 genes adjP=2.43e-36
chromosome 80 genes adjP=6.35e-53
DNA recombination 89 genes adjP=3.76e-107
DNA repair 120 genes adjP=2.94e-129
ATPase activity, coupled 29 genes adjP=3.49e-16
DNA helicase activity 18 genes adjP=1.37e-20
nuclear part 120 genes adjP=8.03e-29
chromosomal part 66 genes adjP=3.09e-42
recombinational repair 40 genes adjP=2.87e-59
double-strand break repair 61 genes
DNA-dependent ATPase activity 26 genes
nuclear lumen 116 genes adjP=9.05e-31
chromosome, telomeric region 23 genes
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 ENSG000000
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

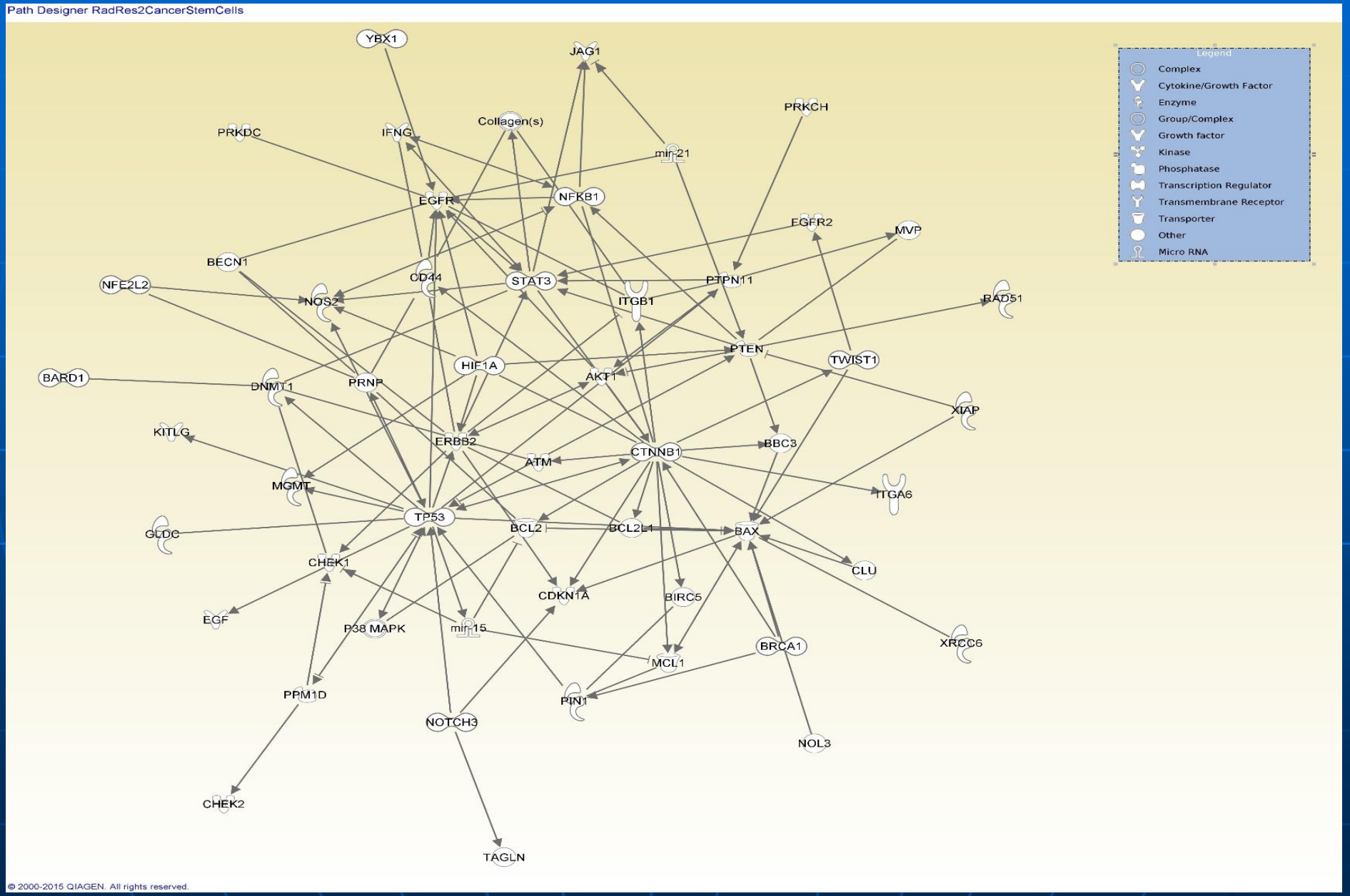
Ανιχνεύοντας γονίδια που εμπλέκονται σε τρείς διαφορετικούς μηχανισμούς.....: έκθεση σε ακτινοβολία (radiation response), φλεγμονή (inflammation) και ανοσοποιητικό σύστημα (immune response)



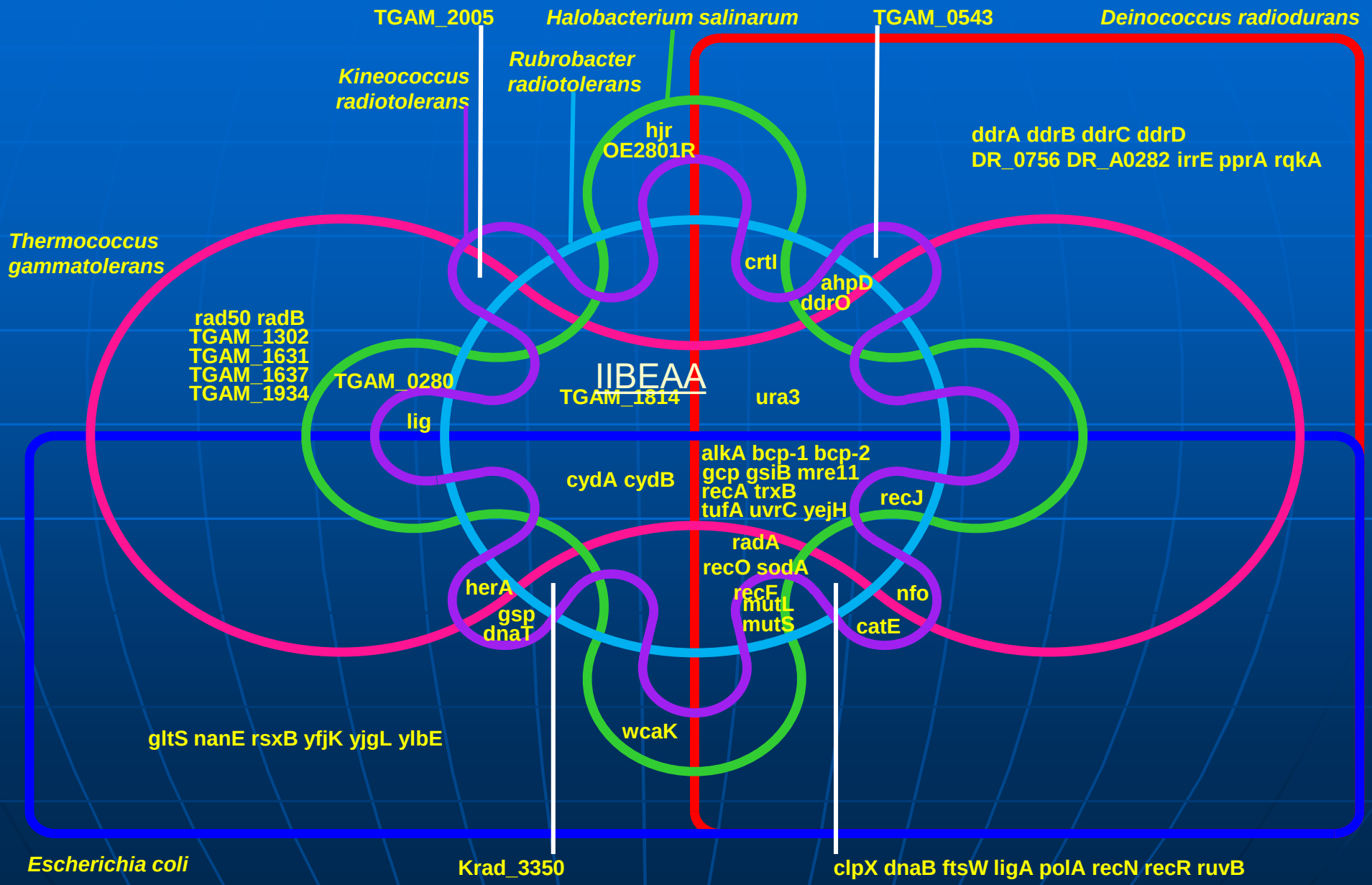
Αυτά τα 24 γονίδια-πρωτείνες βρέθηκαν να αλληλεπιδρούν έντονα μεταξύ τους:



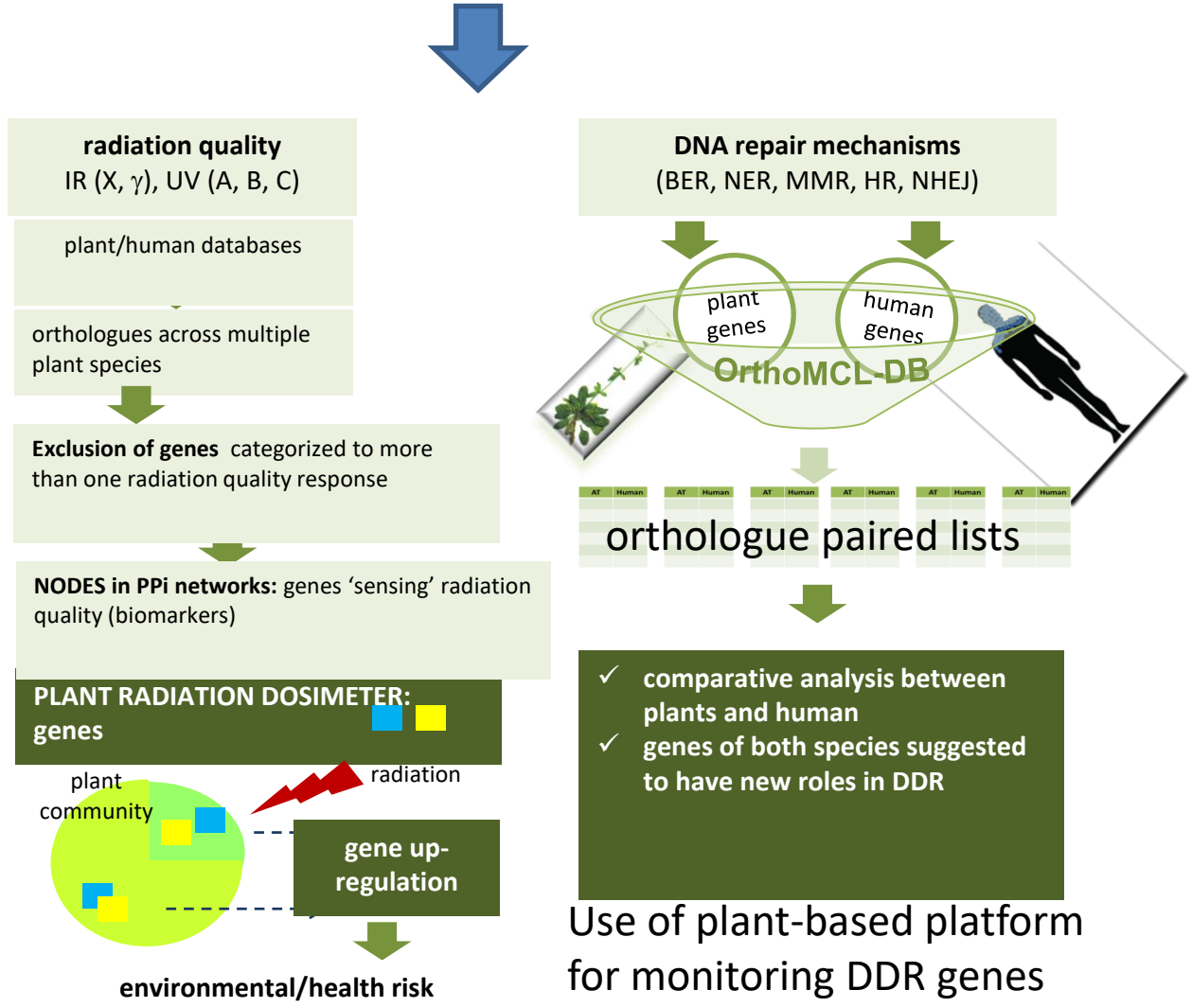
Αντοχή στην ακτινοβολία καρκινικών κυττάρων χρησιμοποιώντας βιβλιογραφικά δεδομένα και ειδικό λογισμικό όπως το ingenuity pathway analysis



Ακτινο-αντοχή (radiation resistance) σε βακτήρια



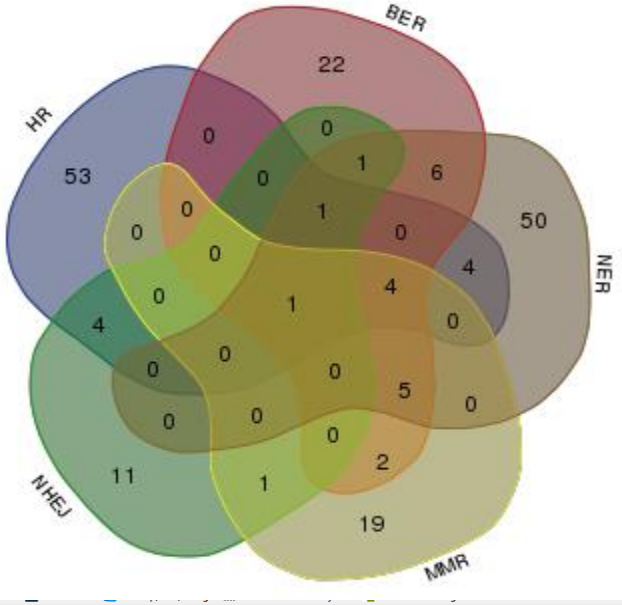
Bridging plant and animal responses

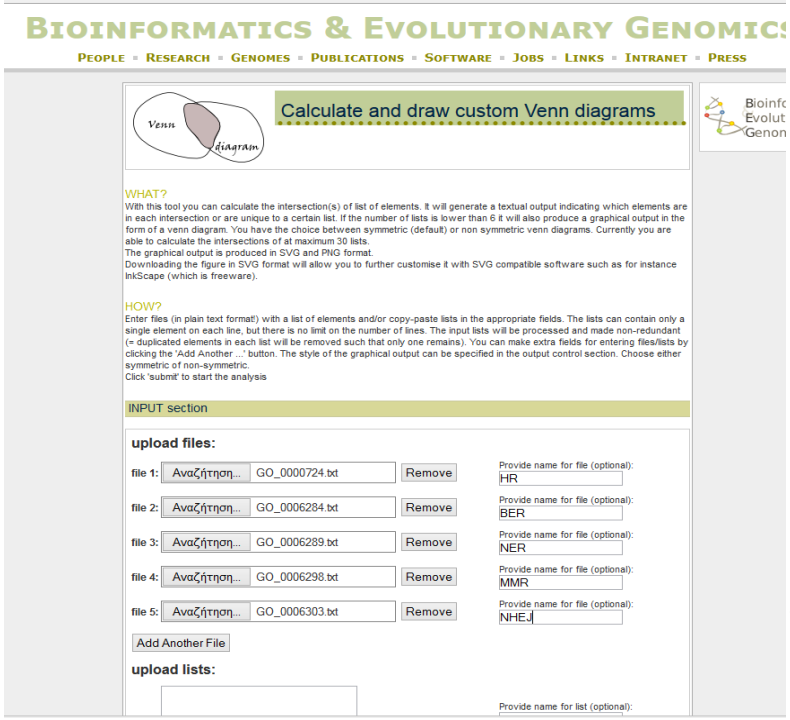


Use of plant-based platform for monitoring DDR genes and genotoxic stress

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.*

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

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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.

Pharmacology & Therapeutics

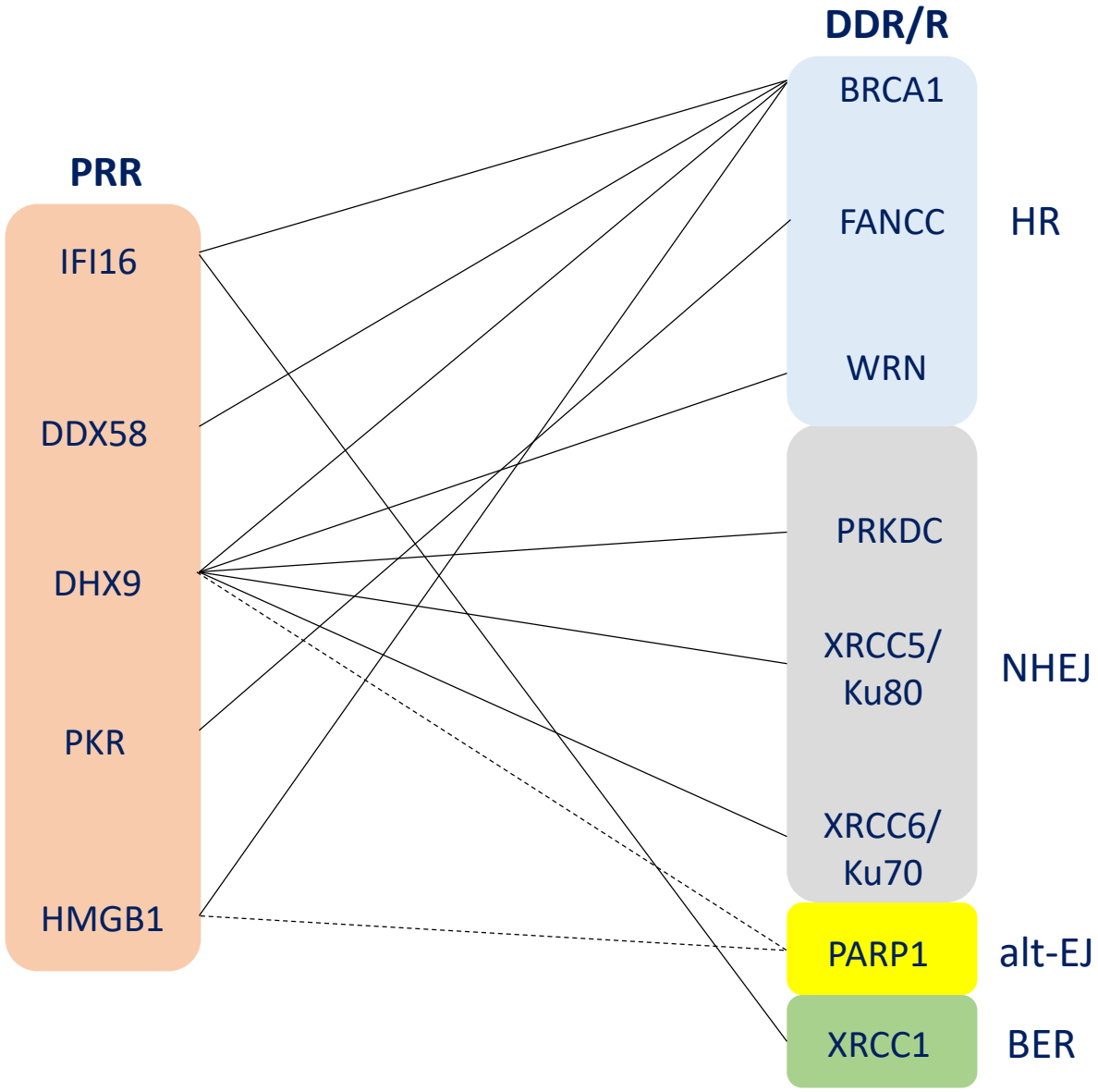
The DNA damage response and immune signaling alliance: Is it good or bad? Nature decides when and where!

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

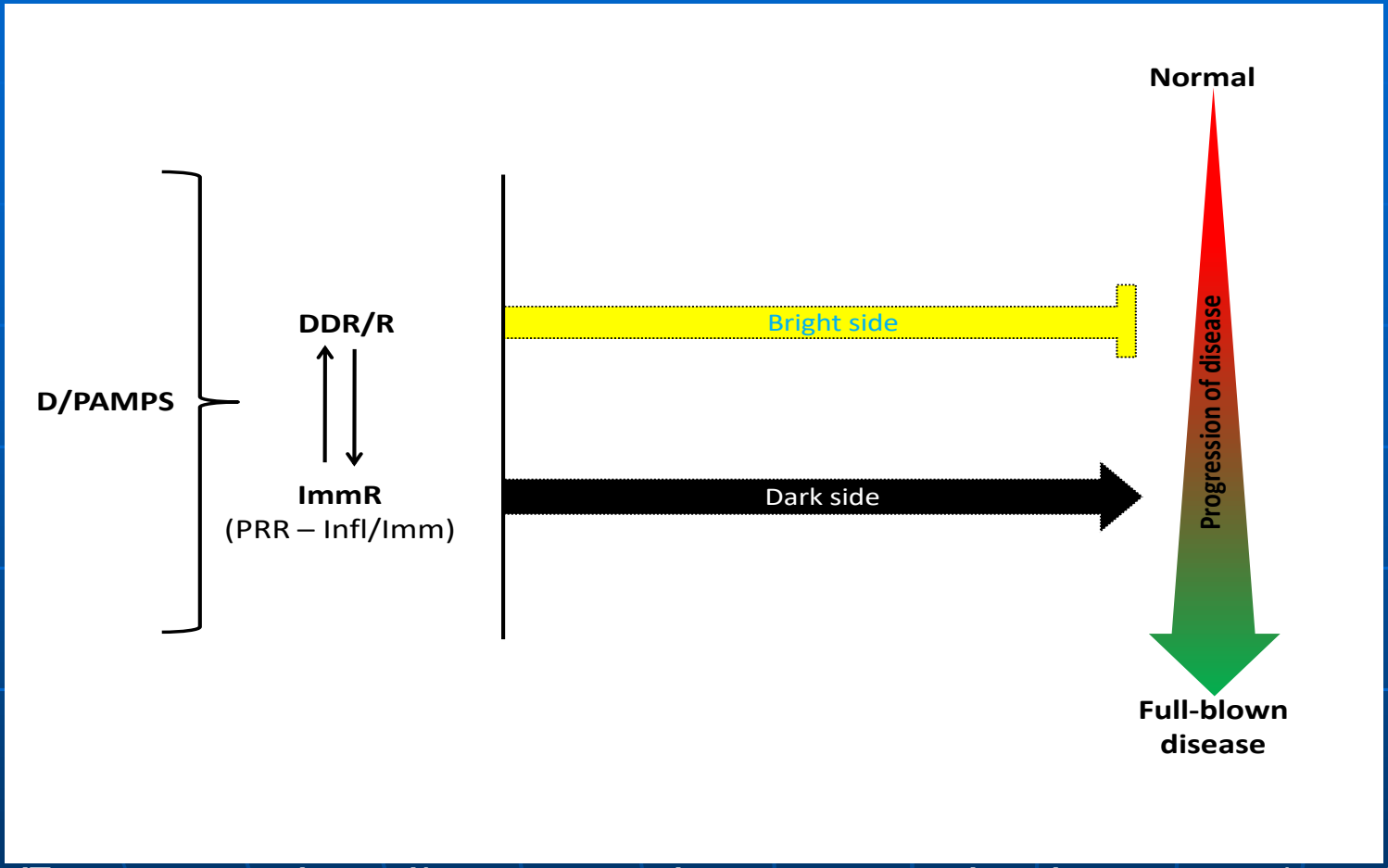
Disruption of DDR/R–ImmR cross talk compromises (multi)cellular integrity, leading to cell-cycle-related and immune defects. The emerging DDR/R–ImmR concept opens up a new avenue of therapeutic options, recalling the Hippocrates quote "everything in excess is opposed by nature."

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.

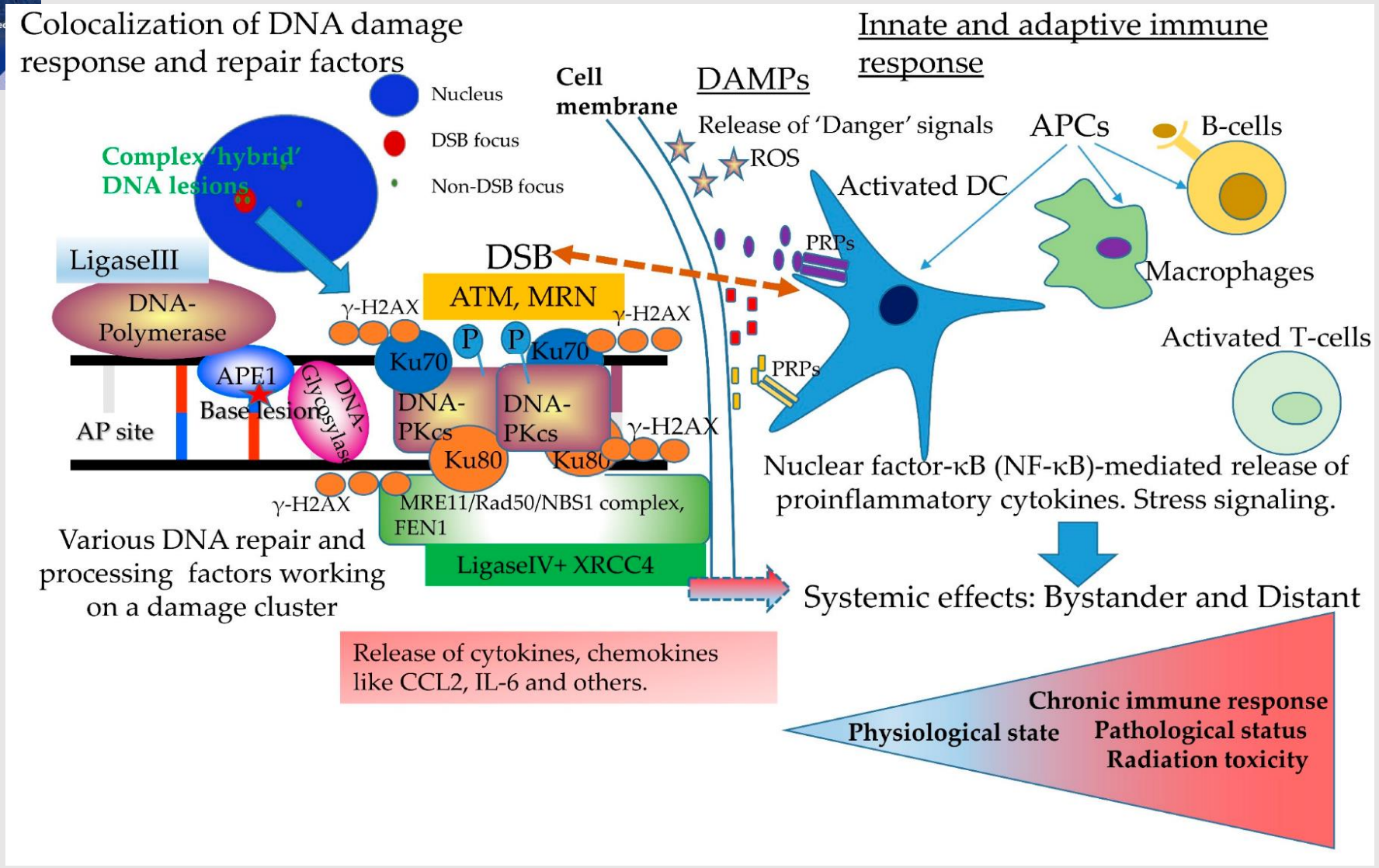
Ένα ενοποιητικό μοντέλο που γεφυρώνει το μηχανισμό απόκρισης DDR/R and ανοσοποιητικό συστημα ImmR (including PRR and Inflammatory/Immune mediators) που ενεργοποιείται όλο μαζί ως μια συμφωνία στην περίπτωση ύπαρξης των λεγόμενων σημάτων κινδύνου DAMPs (Damage Associated Molecular Patterns) ή PAMPs (Pathogen 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,*]



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

Βιβλιογραφία :

[1] Nikitaki Z, Mavragani IV, Laskaratou DA, Gika V, Moskvin VP, Theofilatos K, et al. Systemic mechanisms and effects of ionizing radiation: A new 'old' paradigm of how the bystanders and distant can become the players. Semin Cancer Biol. 2016.

[2] Mavragani IV, Laskaratou DA, Frey B, Candeias SM, Gaipl US, Lumniczky K, et al. Key mechanisms involved in ionizing radiation-induced systemic effects. A current review. Toxicology Research. 2016;5:12-33.

[3] Sprung CN, Ivashkevich A, Forrester HB, Redon CE, Georgakilas A, Martin OA. Oxidative DNA damage caused by inflammation may link to stress-induced non-targeted effects. Cancer Lett. 2015;356:72-81.

[4] Pavlopoulou A, Savva GD, Louka M, Bagos PG, Vorgias CE, Michalopoulos I, et al. Unraveling the mechanisms of extreme radioresistance in prokaryotes: Lessons from nature. Mutation Research/Reviews in Mutation Research. 2015;In press.

[5] Pateras IS, Havaki S, Nikitopoulou X, Vougas K, Townsend PA, Panayiotidis MI, et al. The DNA damage response and immune signaling alliance: Is it good or bad? Nature decides when and where. Pharmacol Ther. 2015;154:36-56.

[6] Nikitaki Z, Hellweg C, Georgakilas AG, Ravanat JL. Stress-induced DNA Damage biomarkers: Applications and limitations Front Chem. 2015;3:35.

[7] Georgakilas AG, Pavlopoulou A, Louka M, Nikitaki Z, Vorgias CE, Bagos PG, et al. Emerging molecular networks common in ionizing radiation, immune and inflammatory responses by employing bioinformatics approaches. Cancer Lett. 2015;368:164-72.

http://scholar.google.gr/citations?user=MAD6KTcAAAAJ&hl=el