Φλεγμονή και καρκίνος

Ιωάννης Πατέρας, Επ. Καθηγητής

Εργαστήριο Ιστολογίας και Εμβρυολογίας

Ιατρική Σχολή

Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

Αθήνα, 24 Οκτωβρίου 2018

Φλεγμονή

Κλινικά Σημεία Φλεγμονής

25 B.C. - 50 A.D.
AC. Celsius

1821-1902
R. Virchow

Redness, heat, swelling, pain
(AC. Celsus)

Loss of function
(R. Virchow)

https://en.wikipedia.org/wiki/Aulus_Cornelius_Celsus
https://en.wikipedia.org/wiki/Rudolf_Virchow

late 19th – early 20th century **Αγγειακές/κυτταρικές αλλαγές**

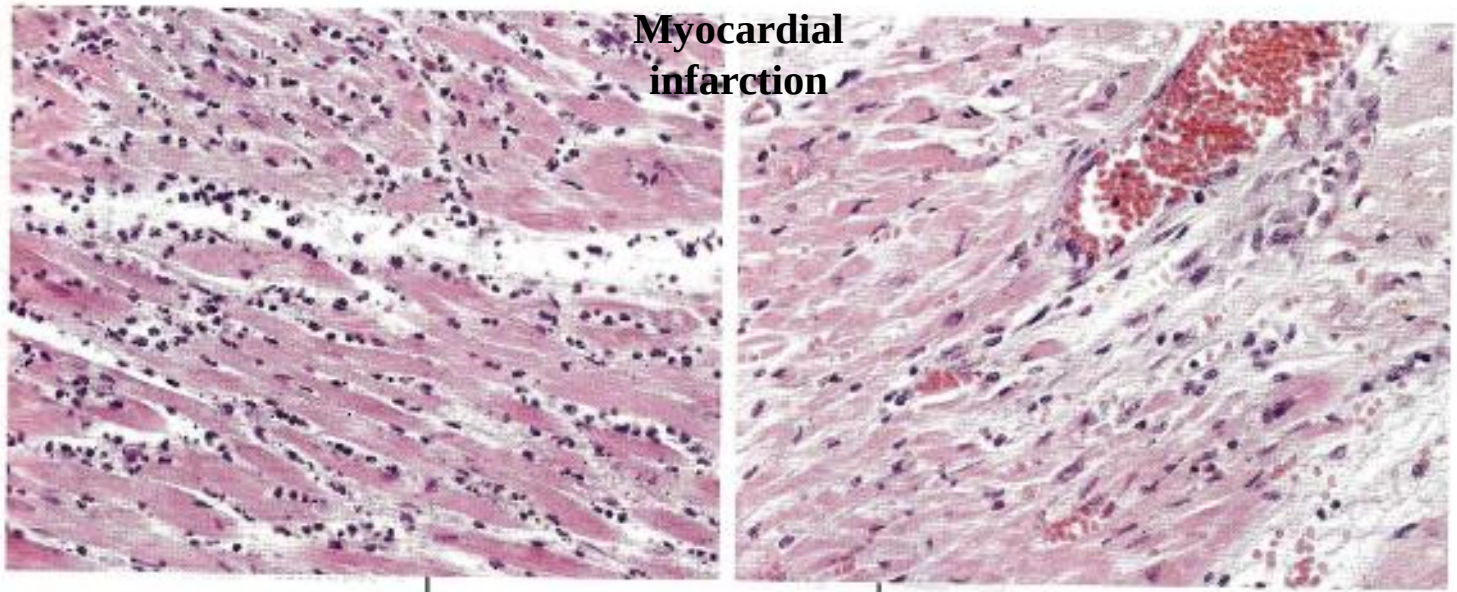
leukocyte migration phagocytosis triple response

1- red reaction, 2- wheal, 3- flare

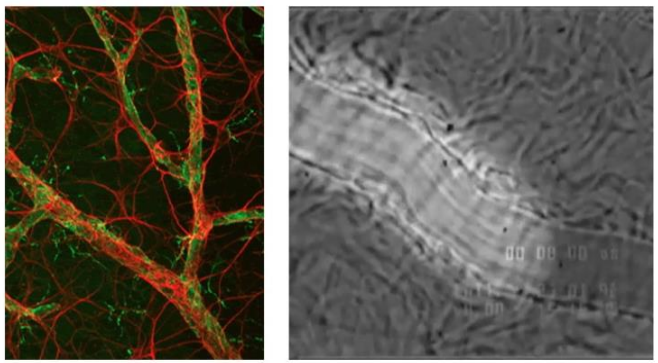
https://www.slideshare.net/anushareddy999/inflammation-84417407

Φλεγμονή

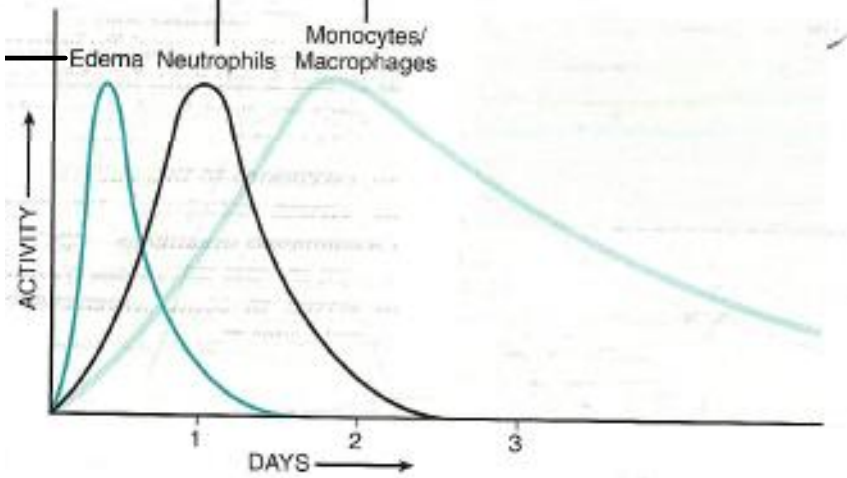
Με την ευρύτερη έννοια θα λέγαμε ότι συνιστά απάντηση του οργανισμού απέναντι σε ερεθίσματα που διαταράσσουν την ομοιοστασία



Vascular and cellular changes.



vascular: vasodilation, increased permeability, exudate,
cellular: recruitment, extravasation, phagocytosis



Robbins and Cotran Review of Pathology, Klatt and Kumar, 2nd edition

Η διαδικασία της επούλωσης αποτελεί μέρος της φλεγμονώδους διεργασίας, προάγοντας της ομοιόσταση του οργανισμού

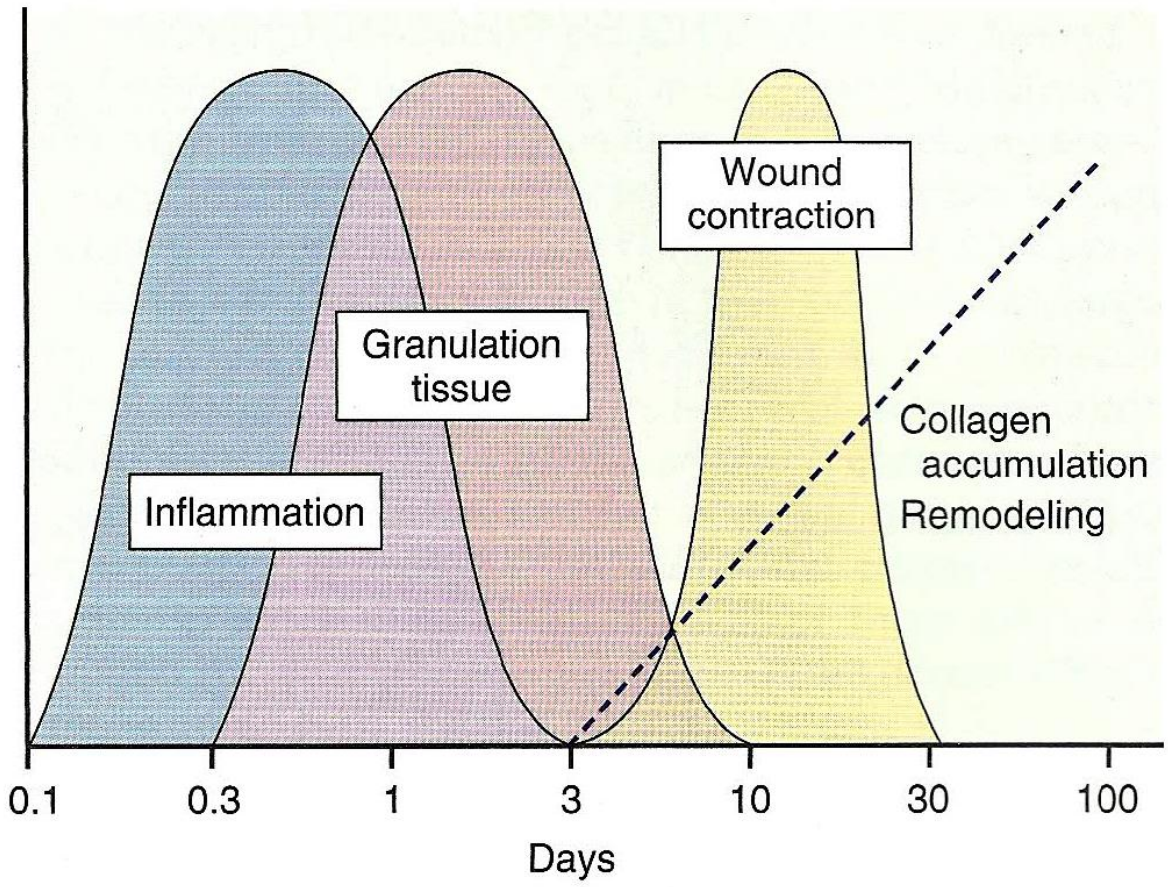


FIGURE 3–20 Phases of wound healing. (Modified from Clark RAF: Wound repair. In Clark RAF (ed): The molecular and cellular biology of wound repair, 2nd ed, New York, Plenum Press, 1996, p. 3.)

Robbins and Cotran Review of Pathology, Klatt and Kumar, 2nd edition

Το μονοπάτι της φλεγμονής

Inducers → Sensors → Mediators → Effectors

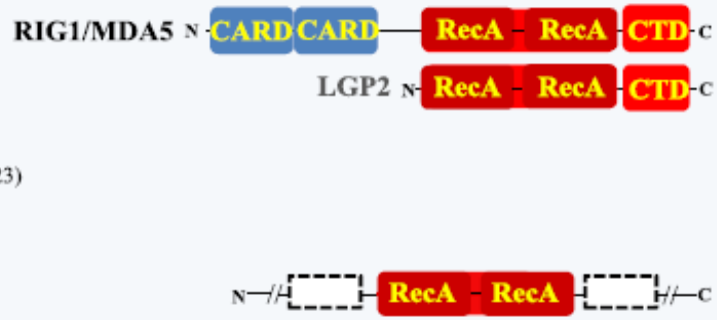
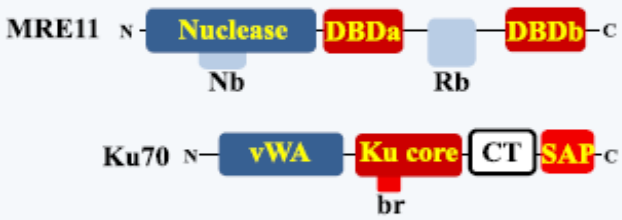
Table 1| Examples of inflammatory pathways

Inducer	Sensor	Mediator	Effectors
Lipopolysaccharide	TLR4	TNF-α, IL-6 and PGE_2	Endothelial cells, hepatocytes, leukocytes, the hypothalamus, and others
Allergens	IgE	Vasoactive amines	Endothelial cells and smooth muscle cells
Monosodium urate crystals and calcium pyrophosphate dihydrate crystals	NALP3	IL-1β	Endothelial cells, hepatocytes, leukocytes, the hypothalamus, and others
Collagen	Hageman factor	Bradykinin	Endothelial cells and smooth muscle cells

Medzhitov Nature 2008

Table 1

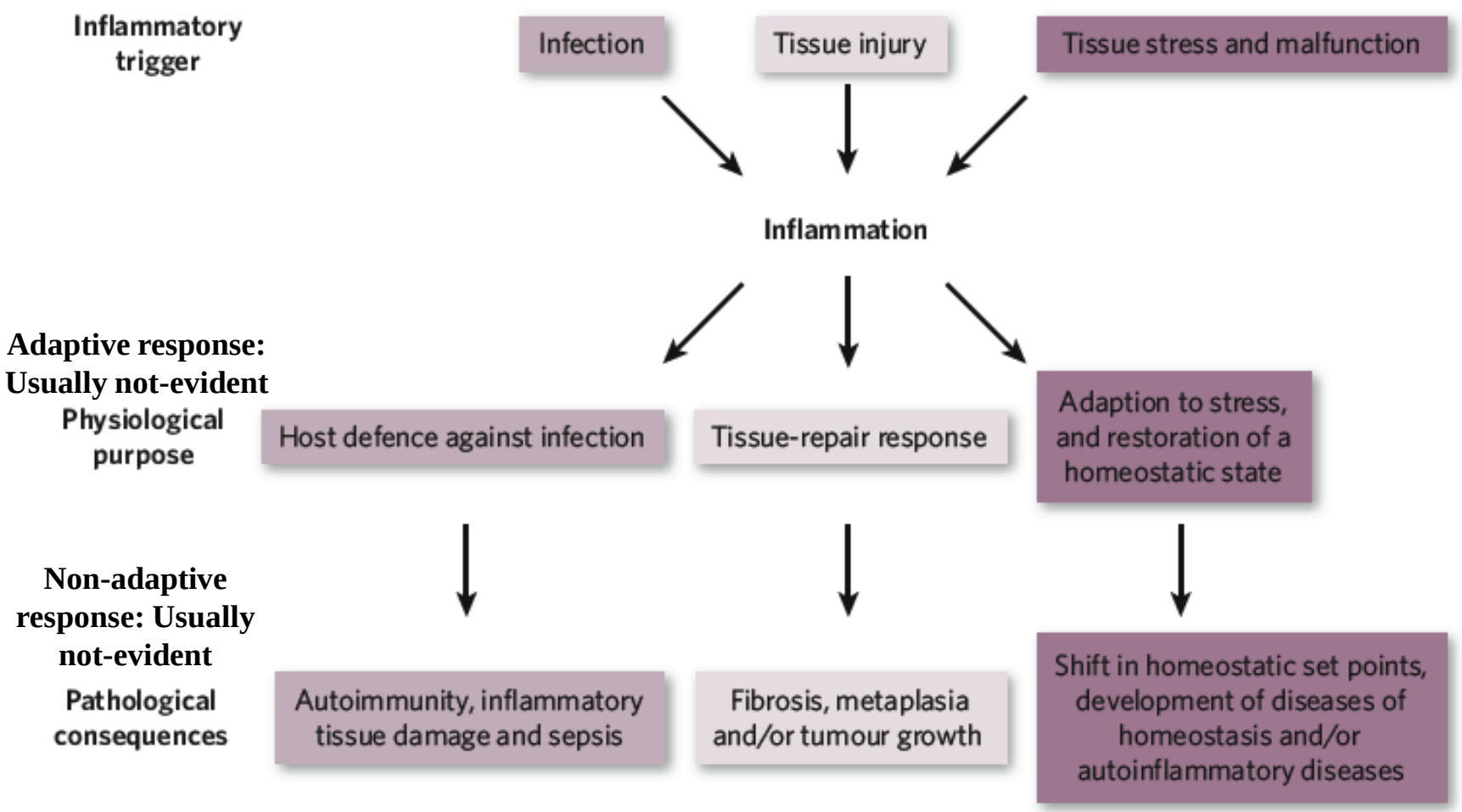
Well-characterized types of PRRs along with the corresponding members functioning as intracellular DNA/RNA sensors. A few still-undassified PRRs are presented as "other." The size of the protein domains is not depicted to scale; blue-colored domains are implicated in protein–protein interactions, whereas red-colored domains interact with nucleic acids. Detailed description of each PRR member is provided in the corresponding Supplemental Data.

Type	Members	Protein domains
TLR	TLR3 (4q35) TLR7 (Xp22.3) TLR8 (Xp22.2) TLR9 (3p21.3)	
NLR	NOD2/CARD15 (16q21)	
PYHIN	AIM2 (1q21-23) IFI16 (1q21-23)	
DExD/H-box helicases	RLR helicases RIGI/DDX58 (9p12) MDA5/IFIH1 (2q24.2) LGP2/DHX58 (17q21.2) Other helicases DDX1 (2p24) DDX3/DDX3X (Xp11.3-p11.23) DDX21 (10q21) DHX36/DDX36 (3q25.2) DDX41 (5q35.3) DDX60 (4q32.3) DHX9/DDX9/RHA/NDHII (1q25) DHX15/DDX15 (4p15.3) DHX33/DDX33 (17p13) DHX36/DDX36 (3q25.2)	
DDR/R	MRE11 (11q21) Ku70 (22q13.2)	
Other	PKR (2q31.2) DAI/ZBP1/DLM-1 (20q13.31) RNA pol III HMGB1(13q12),2(4q31),3(Xq28) LSm14A (19q13.2) LRRFIP1 (2q37.3) cGAS/MB21D1 (6q13)	

Αισθητήρες [Pattern Recognition Receptors, (PRRs)] που αναγνωρίζουν DNA/RNA

Pateras IS, Havaki S *et al.* Pharmacol Therap 2015

Φλεγμονώδης απάντηση (Inflammatory response): Ελεγχόμενη – Μη ελεγχόμενη



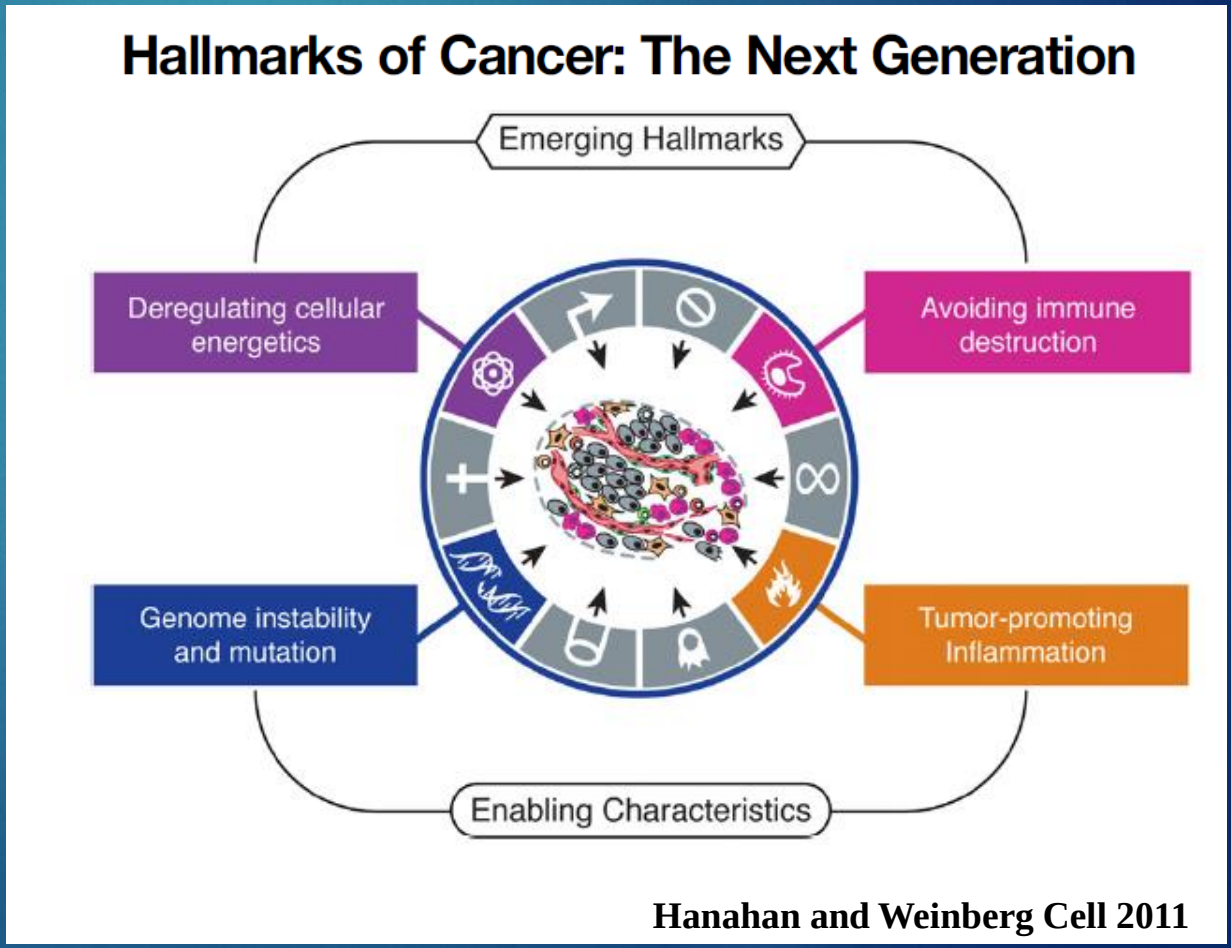
Medzhitov Nature 2008

«μηδέν άγαν» Σόλωνα (639-559 π.Χ.)

nothing in excess

Rudolph Virchow (1821-1902)

Linking inflammation with cancer
"lymphoreticular infiltration of tumors"



Hanahan and Weinberg Cell 2011

Χρόνια Φλεγμονή → **Καρκίνο**

- **Γενωμική αστάθεια (Genomic instability)**
- **Αγγειογένεση (Angiogenesis)**
- **Διήθηση και Μετάσταση (Invasion and Metastasis)**
- **Ανοσοδιαφυγή (Immune invasion, i.e. T cell exhaustion)**

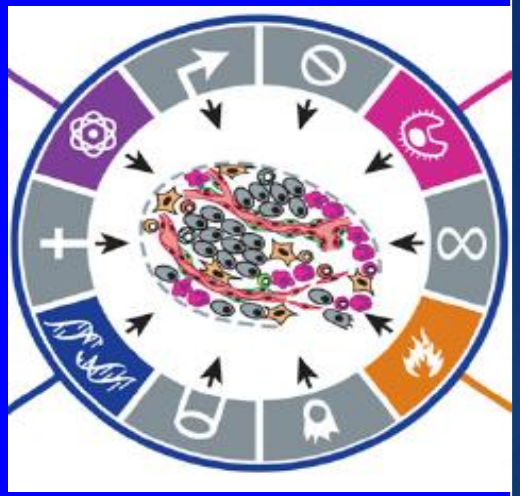


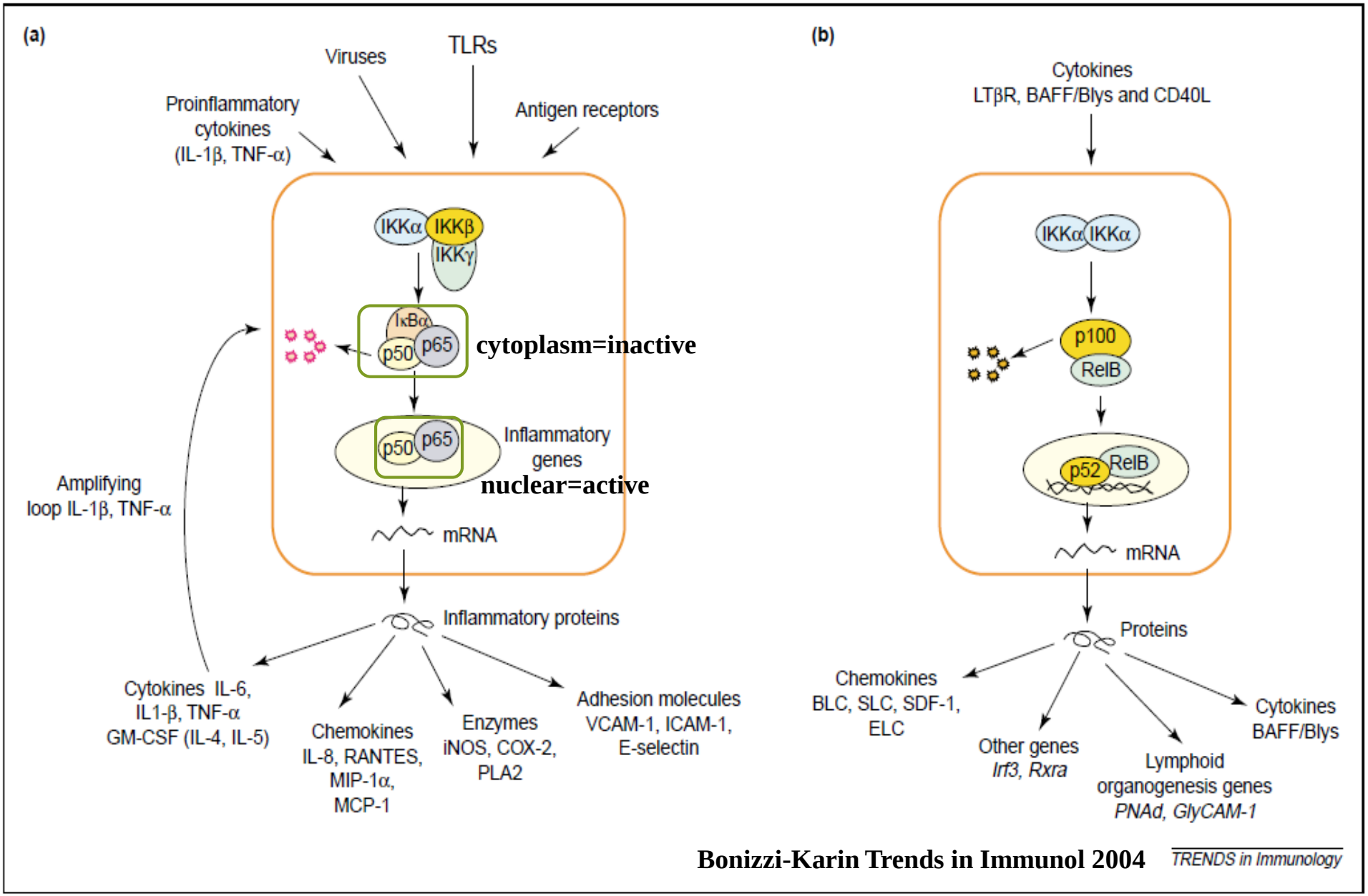
Table 1 **Chronic inflammatory conditions associated with neoplasms**

Pathologic condition	Associated neoplasm(s)	Aetiologic agent
Asbestosis, silicosis	Mesothelioma, lung carcinoma	Asbestos fibres, silica particles
Bronchitis	Lung carcinoma	Silica, asbestos, smoking (nitrosamines, peroxides)
Cystitis, bladder inflammation	Bladder carcinoma	Chronic indwelling, urinary catheters
Gingivitis, lichen planus	Oral squamous cell carcinoma	
Inflammatory bowel disease, Crohn's disease, chronic ulcerative colitis	Colorectal carcinoma	
Lichen sclerosus	Vulvar squamous cell carcinoma	
Chronic pancreatitis, hereditary pancreatitis	Pancreatic carcinoma	Alcholism, mutation in trypsinogen gene on Ch. 7
Reflux oesophagitis, Barrett's oesophagus	Oesophageal carcinoma	Gastric acids
Sialadenitis	Salivary gland carcinoma	
Sjögren syndrome, Hashimoto's thyroiditis	MALT lymphoma	
Skin inflammation	Melanoma	Ultraviolet light
Cancers associated with infectious agents		
Opisthorchis, Cholangitis	Cholangiosarcoma, colon carcnoma	Liver flukes (*Opisthorchis viverrini*), bile acids
Chronic cholecystitis	Gall bladder cancer	Bacteria, gall bladder stones
Gastritis/ulcers	Gastric adenocarcinoma, MALT	*Helicobacter pylori*
Hepatitis	Hepatocellular carcinoma	Hepatitis B and/or C virus
Mononucleosis	B-cell non-Hodgkin's lymphoma, Burkitts lymphoma,	Epstein-Barr Virus
AIDS	Non-Hodgkin's lymphoma, squamous cell carcinomas, Kaposi's sarcoma	Human immunodeficiency virus, human herpesvirus type 8
Osteomyelitis	Skin carcinoma in draining sinuses	Bacterial infection
Pelvic inflammatory disease, chronic cervicitis	Ovarian carcinoma, cervical/anal carcinoma	Gonnorrhoea, chlamydia, human papillomavirus
Chronic cystitis	Bladder, liver, rectal carcinoma, follicular lymphoma of the spleen	Schistosomiasis

Modified from refs 29, 67. MALT, mucosa-associated lymphoid tissue.

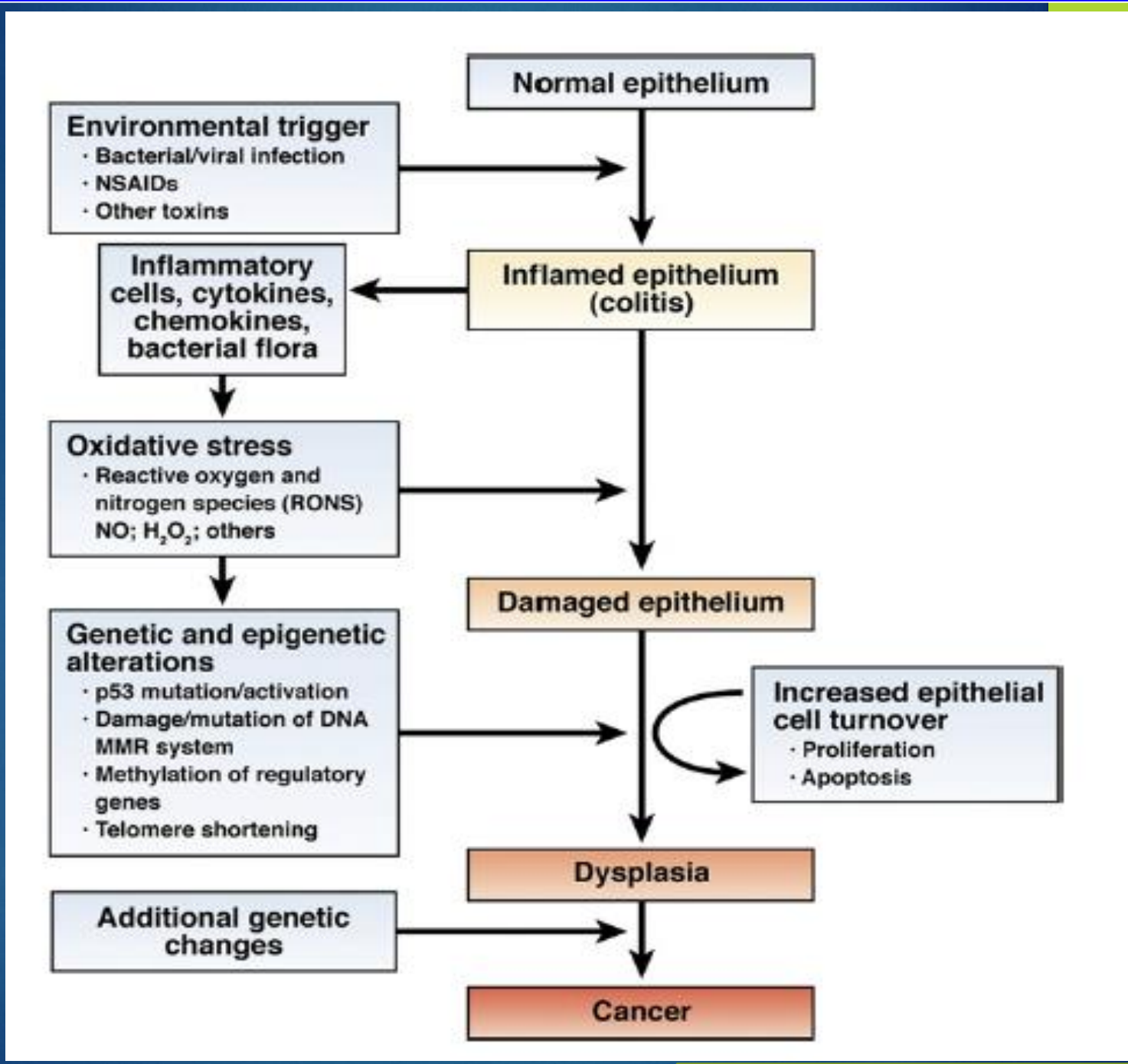
Coussens and Werb Nature 2002

NFκB: ο κύριος ρυθμιστής τη φλεγμονής και ως εκ τούτου σημαντικός ρυθμιστής στην ανάπτυξη καρκίνου που σχετίζεται με χρόνια φλεγμονή - "Είναι το πρώτο βιολί"



Bonizzi-Karin Trends in Immunol 2004 TRENDS in Immunology

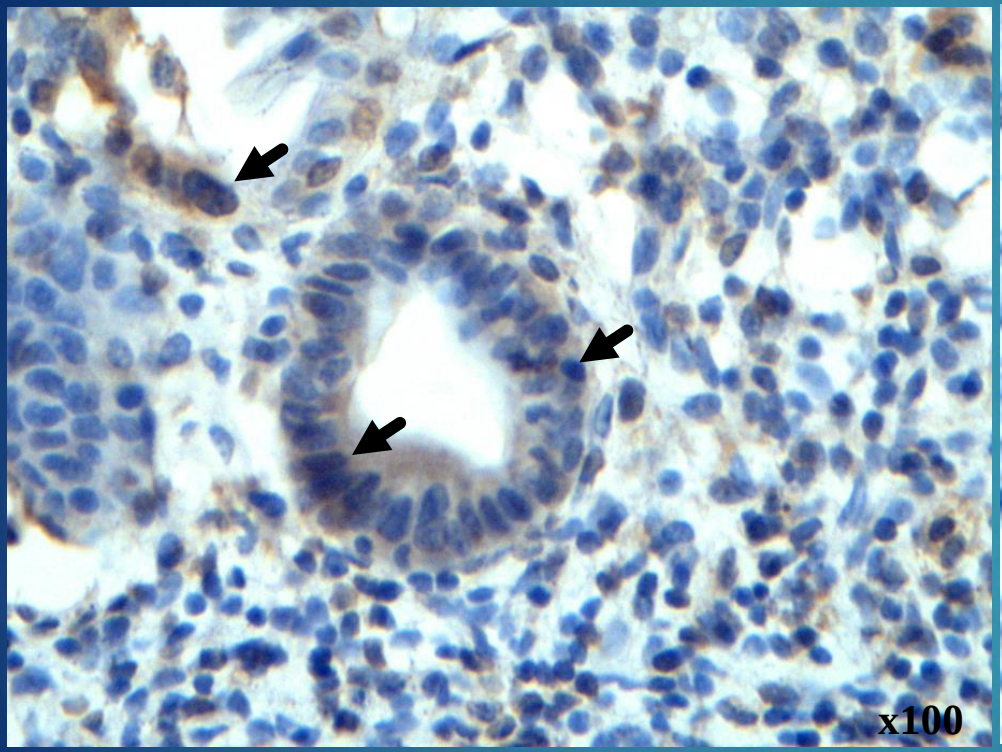
Καρκίνος που αναπτύσσεται σε ΙΦΝΕ

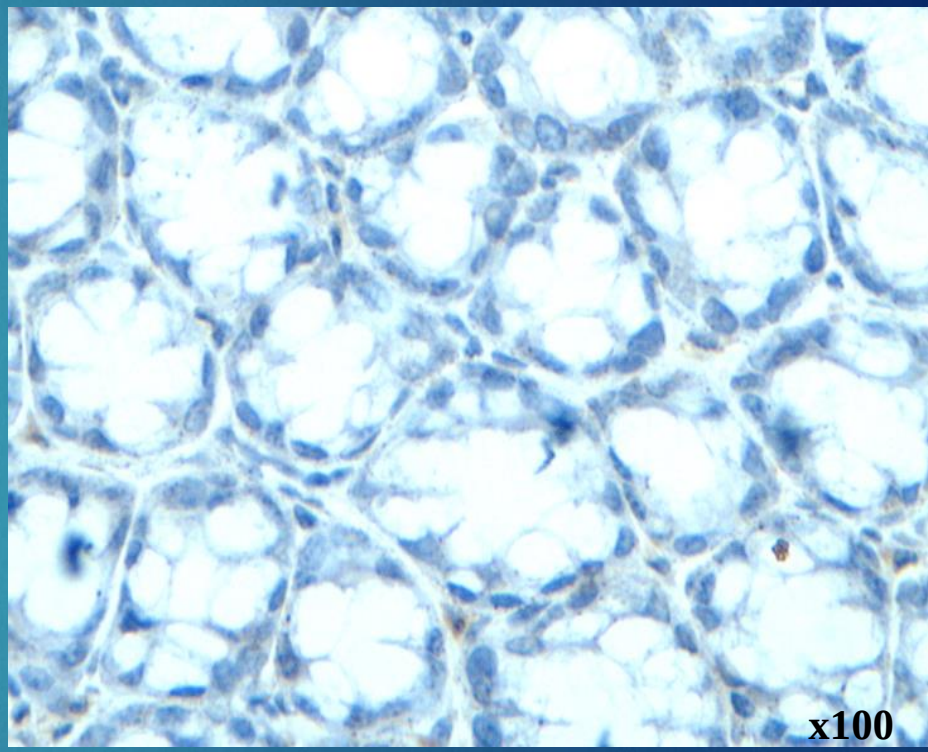


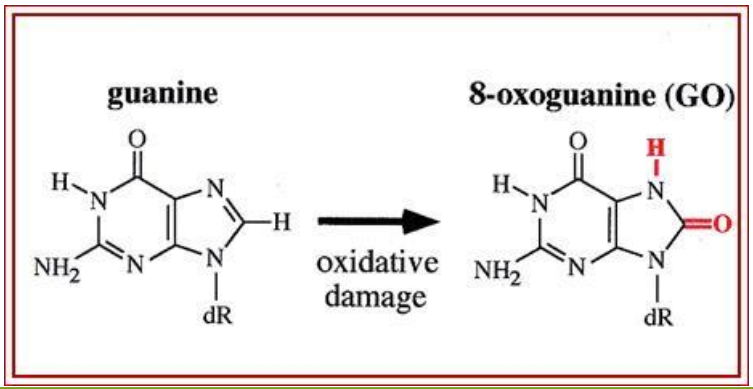
ΙΦΝΕ: Ιδιοπαθή Φλεγμονώδη Νόσο του Εντέρου (νόσο του Crohn και ελκώδη κολίτιδα)

Ullman-Itzkowitz Gastroenterology 2011

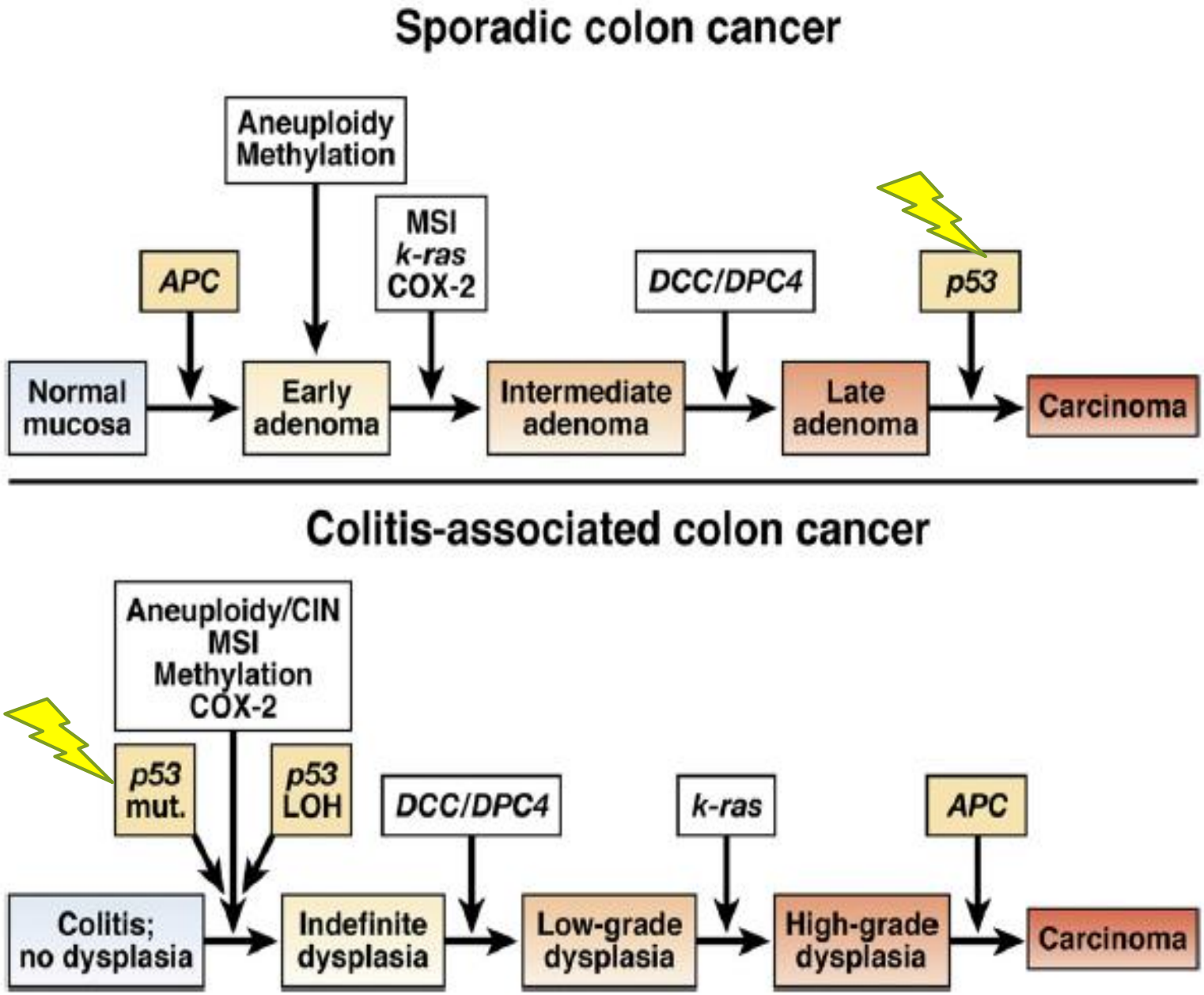
Αυξημένα επίπεδα 8-οχο-G σε περιστατικά με μετρίου/σοβαρού βαθμού κολίτιδα (αριστερά) σε σύγκριση με περιστατικά με ήπια χρόνια φλεγμονή (δεξιά)







http://mol-biol4masters.masters.grkraj.org/html/DNA_Damage_And_Repair2-Types_of_Damages_and_Effects.htm



Ullman-Itzkowitz Gastroenterology 2011

Η σημασία της παρουσίας μεταλλαγμένων μορφών της πρωτεΐνης P53 πρώιμα στην εμφάνιση καρκίνου του παχέος εντέρου σε έδαφος ΙΦΝΕ

Ομάδα Καθηγητή Βασίλη Γοργούλη (ΕΚΠΑ) σε συνεργασία με Ομάδα Καθηγητή Moshe Oren (Weizmann Institute)

letters to nature

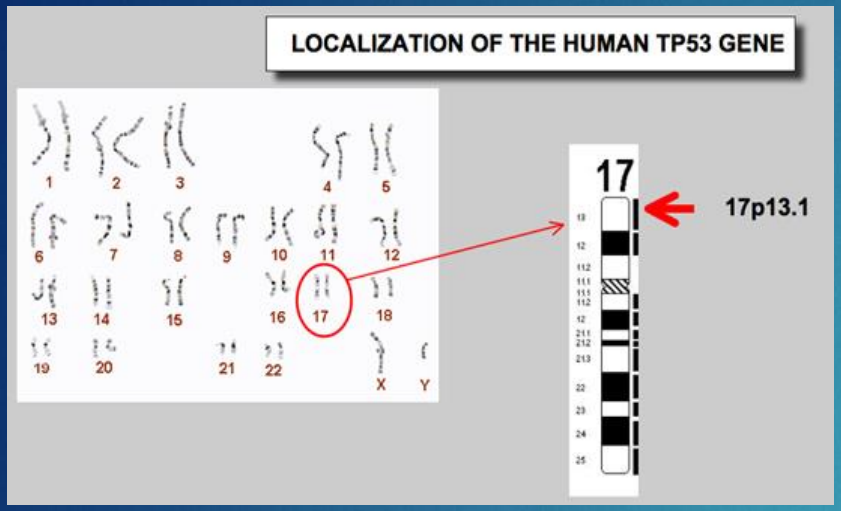
316, 158 - 160 (11 July 1985)

Overproduction of p53 antigen makes established cells highly tumorigenic

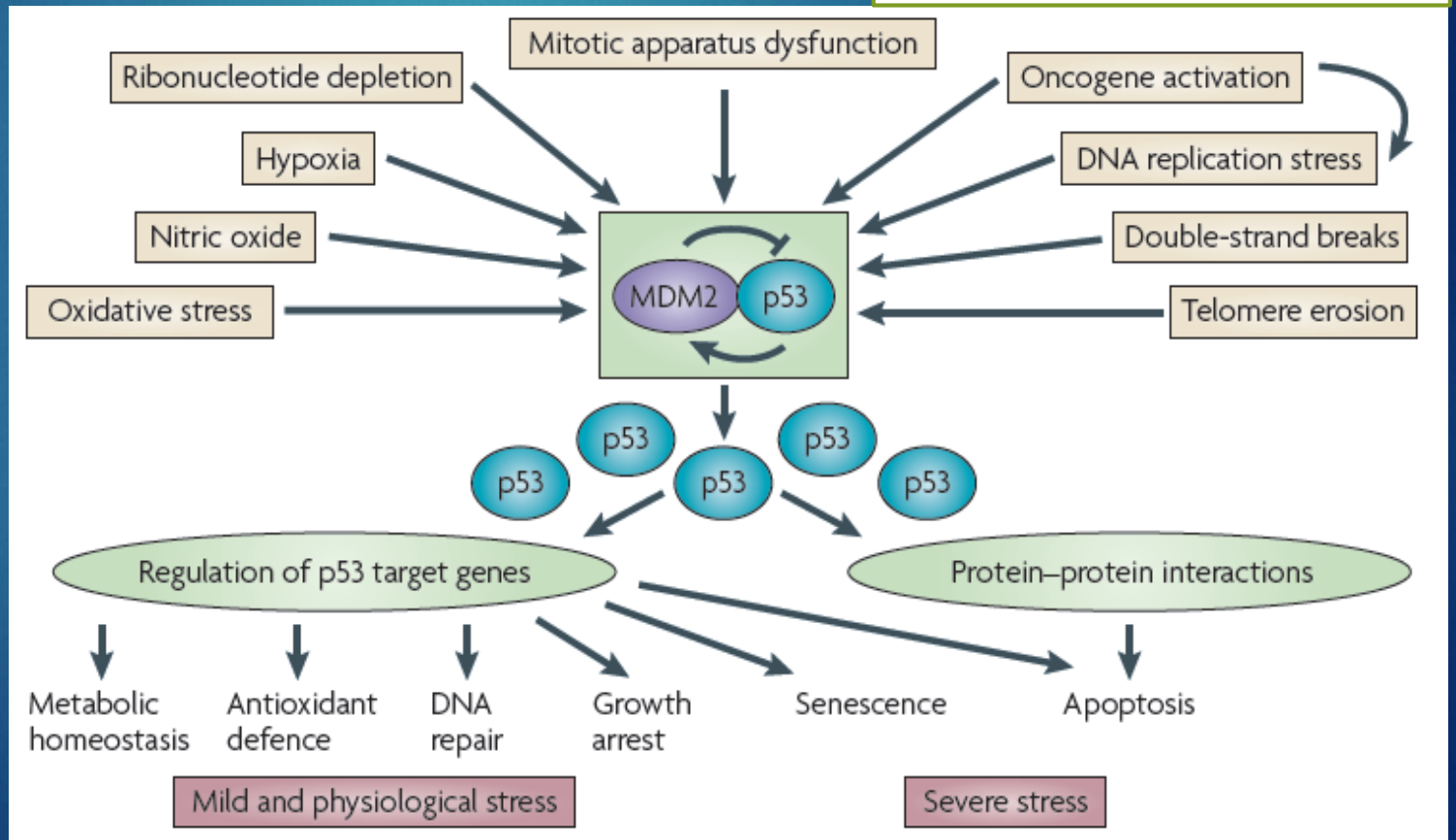
D. ELIYAHU, D. MICHALOVITZ & M. OREN

Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel

“Cancer. P53, guardian of the genome” Lane DP, Nature 1992, Jul 2;358(6381):15-6



Levine-Oren Nat Rev Cancer 2009



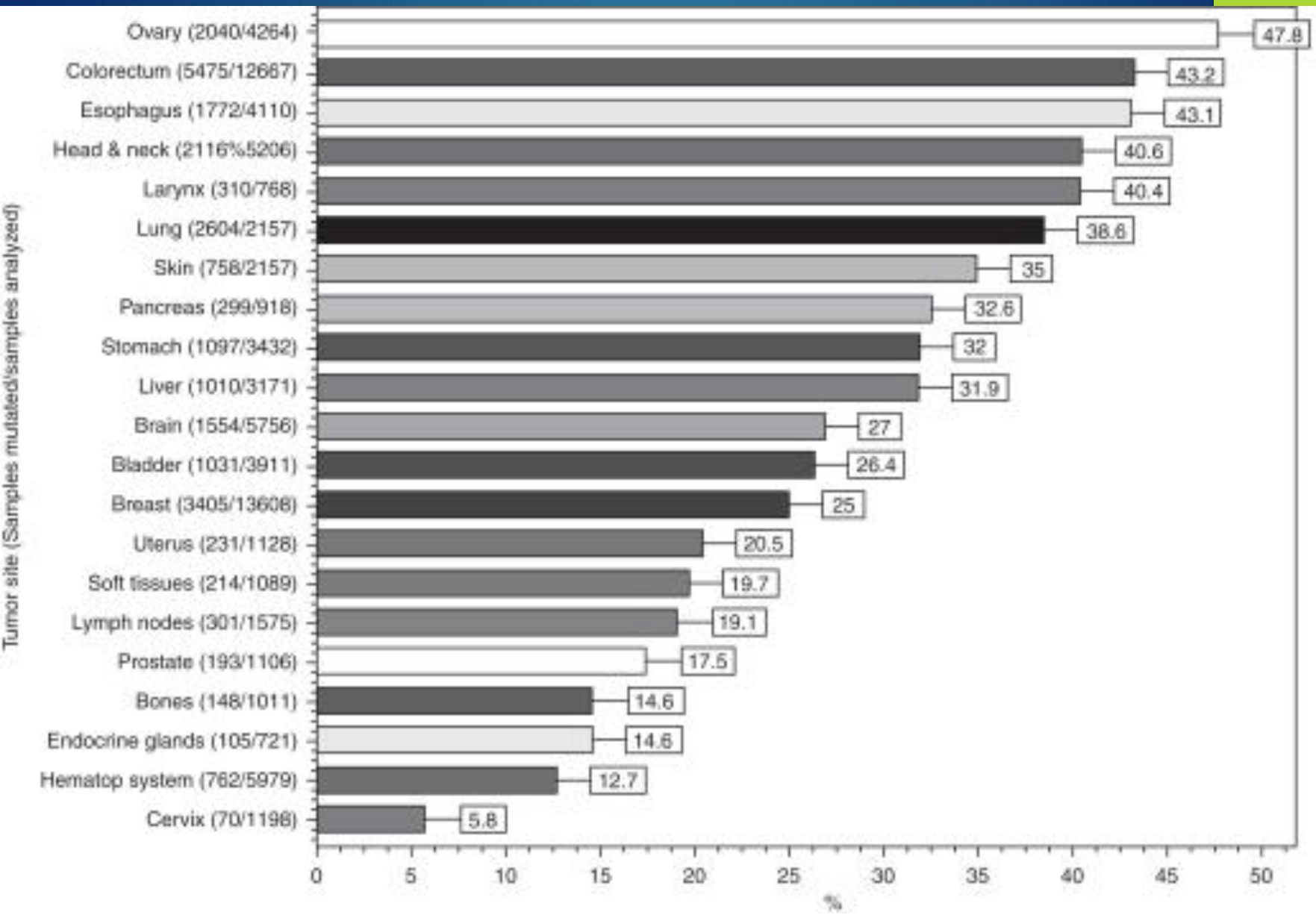
Ακέραιο (Wild type) p53

Μεταλλαγμένο (Mutant) p53

Dominant negative function (DNF)

Gain of function (GOF)

Το γονίδιο *P53* μεταλλάσσεται πολύ συχνά σε συνήθεις σποραδικούς καρκίνους



Data from IARC*TP53* Database (R13, November 2008) (Petitjean et al. Hum Mutation 2007)

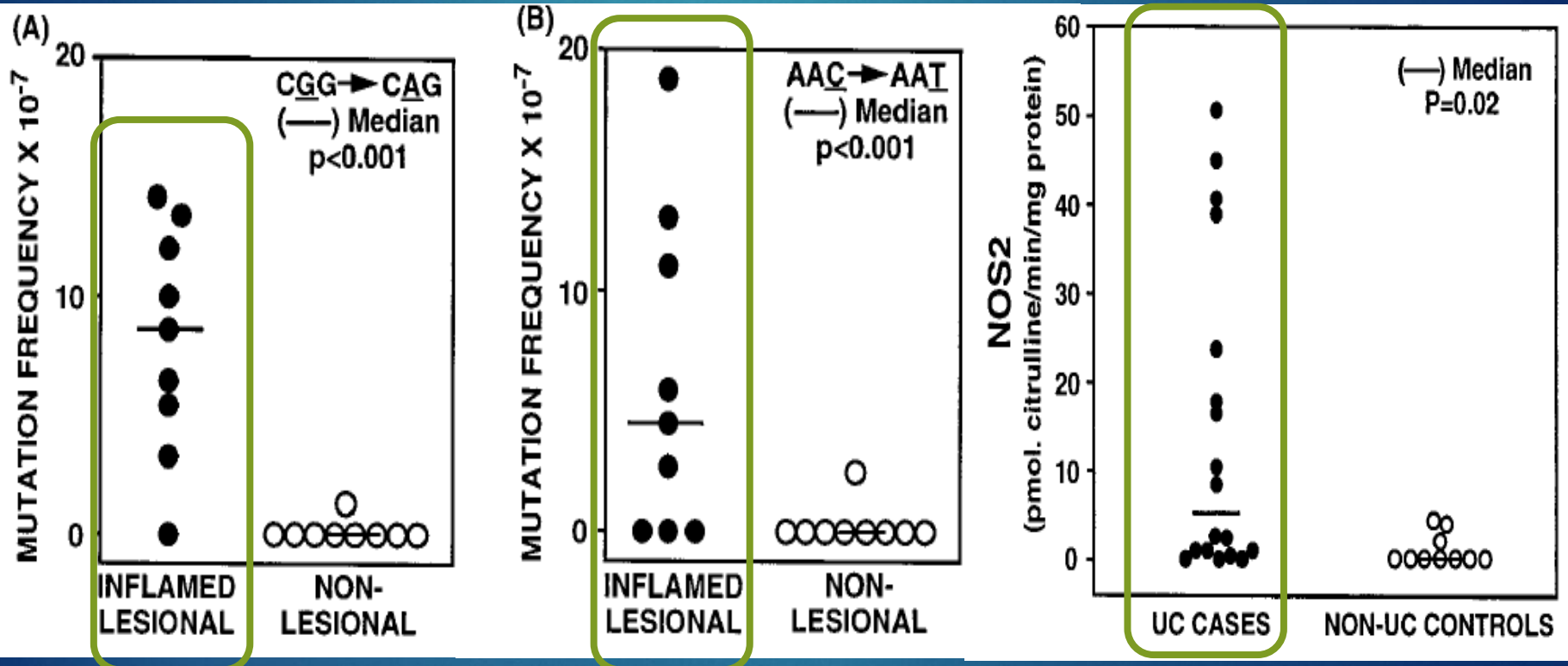
[CANCER RESEARCH 60, 3333–3337, July 1, 2000]

Advances in Brief

Increased *p53* Mutation Load in Noncancerous Colon Tissue from Ulcerative Colitis: A Cancer-prone Chronic Inflammatory Disease

S. Perwez Hussain, Paul Amstad,[1] Kamran Raja, Stefan Ambs,[2] Makoto Nagashima, William P. Bennett,[3] Peter G. Shields, Amy-Joan Ham,[4] James A. Swenberg,[4] Aizen J. Marrogi, and Curtis C. Harris[5]

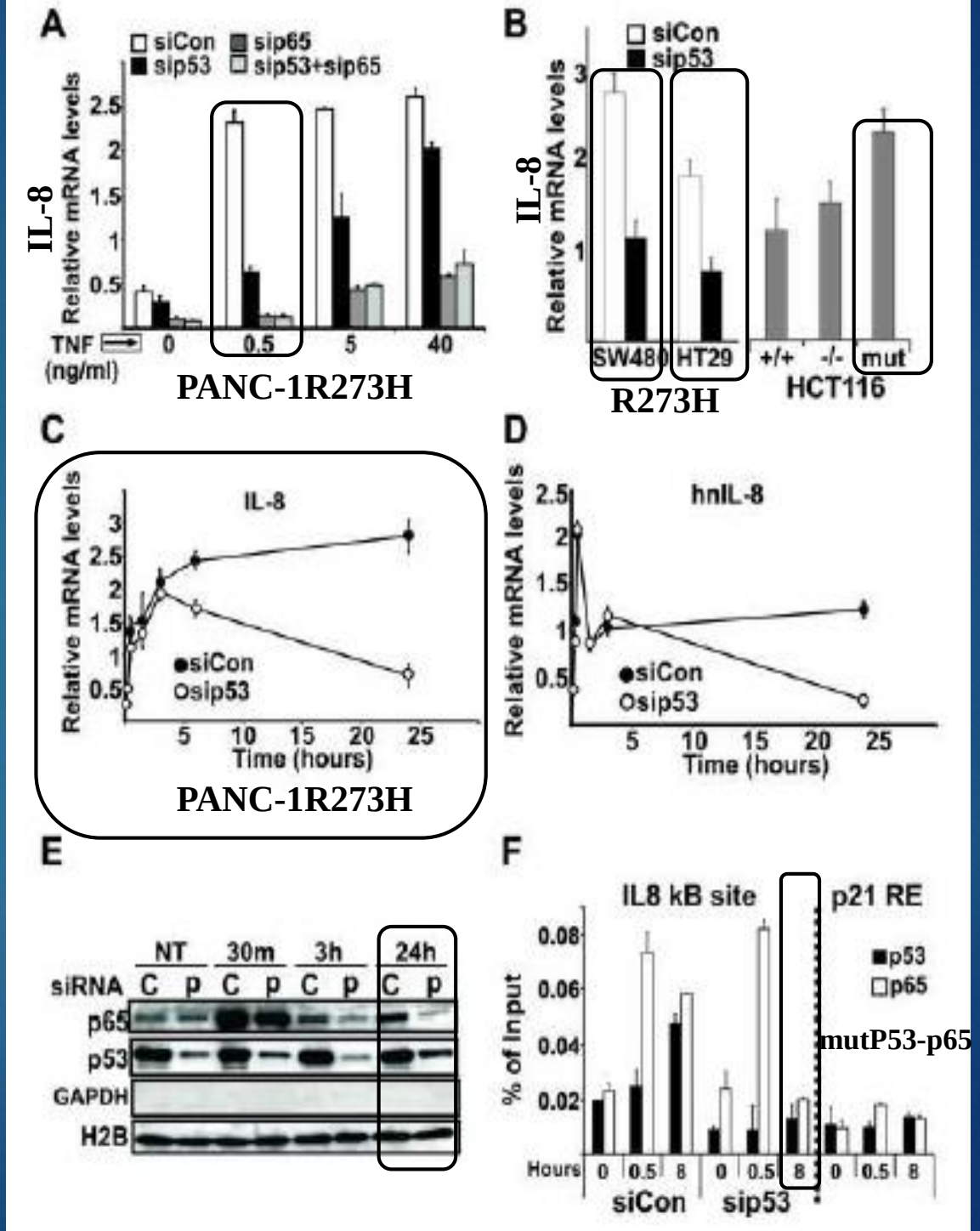
Laboratory of Human Carcinogenesis, National Cancer Institute, NIH, Bethesda, Maryland 20892



without UC by using a highly sensitive genotypic mutation assay. Higher *p53* mutation frequencies of both G:C to A:T transitions at the CpG site of codon 248 and C:G to T:A transitions at codon 247 were observed in

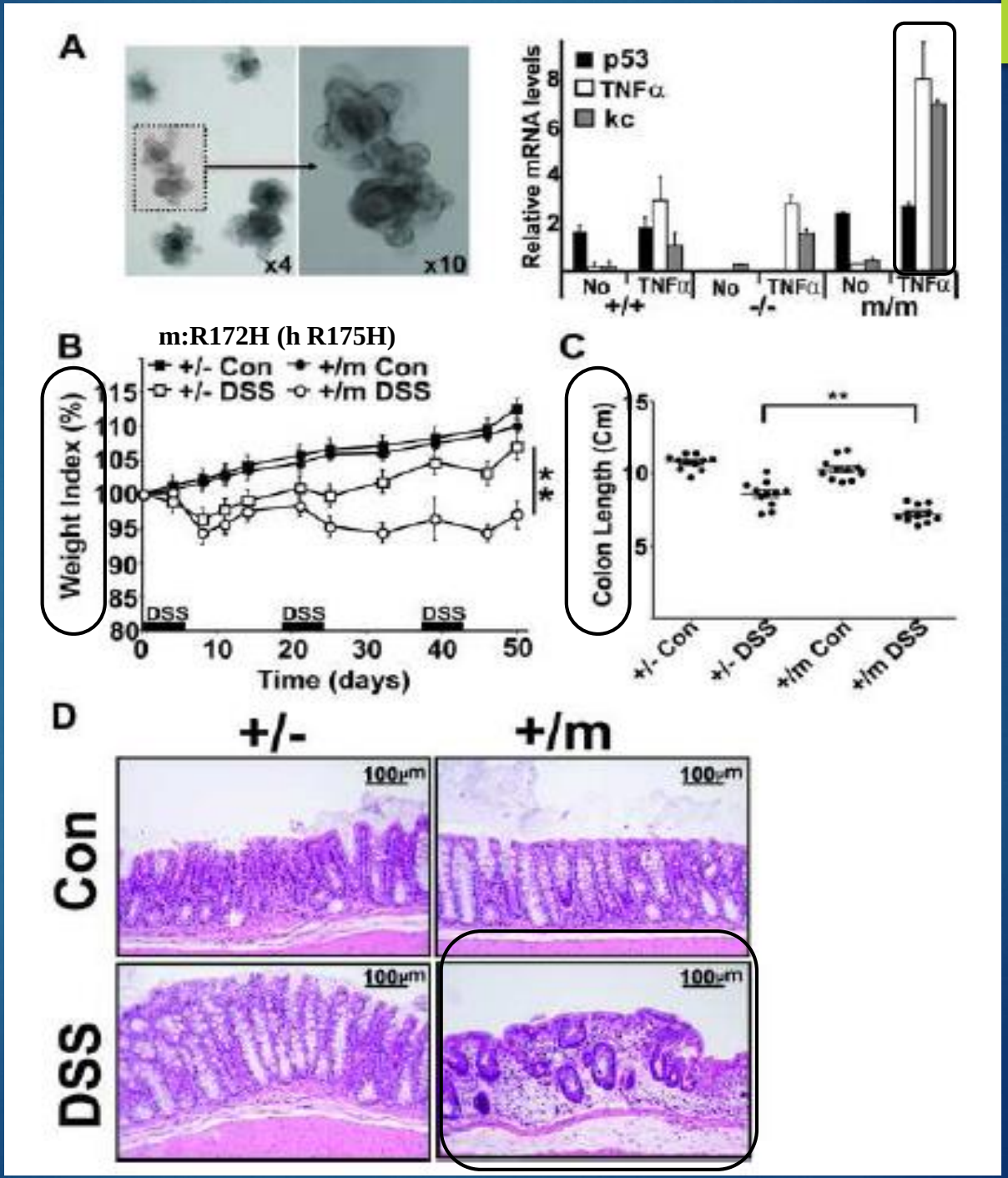
Μπορούν μεταλλαγμένες μορφές της πρωτεΐνης p53 να προάγουν μέσω ενεργοποίησης του NFκB την χρόνια φλεγμονή και κατά συνέπεια το καρκίνο που αναπτύσσεται στο έδαφος της χρόνιας φλεγμονής;

Mutp53 prolongs NF-κB activation by TNF-α

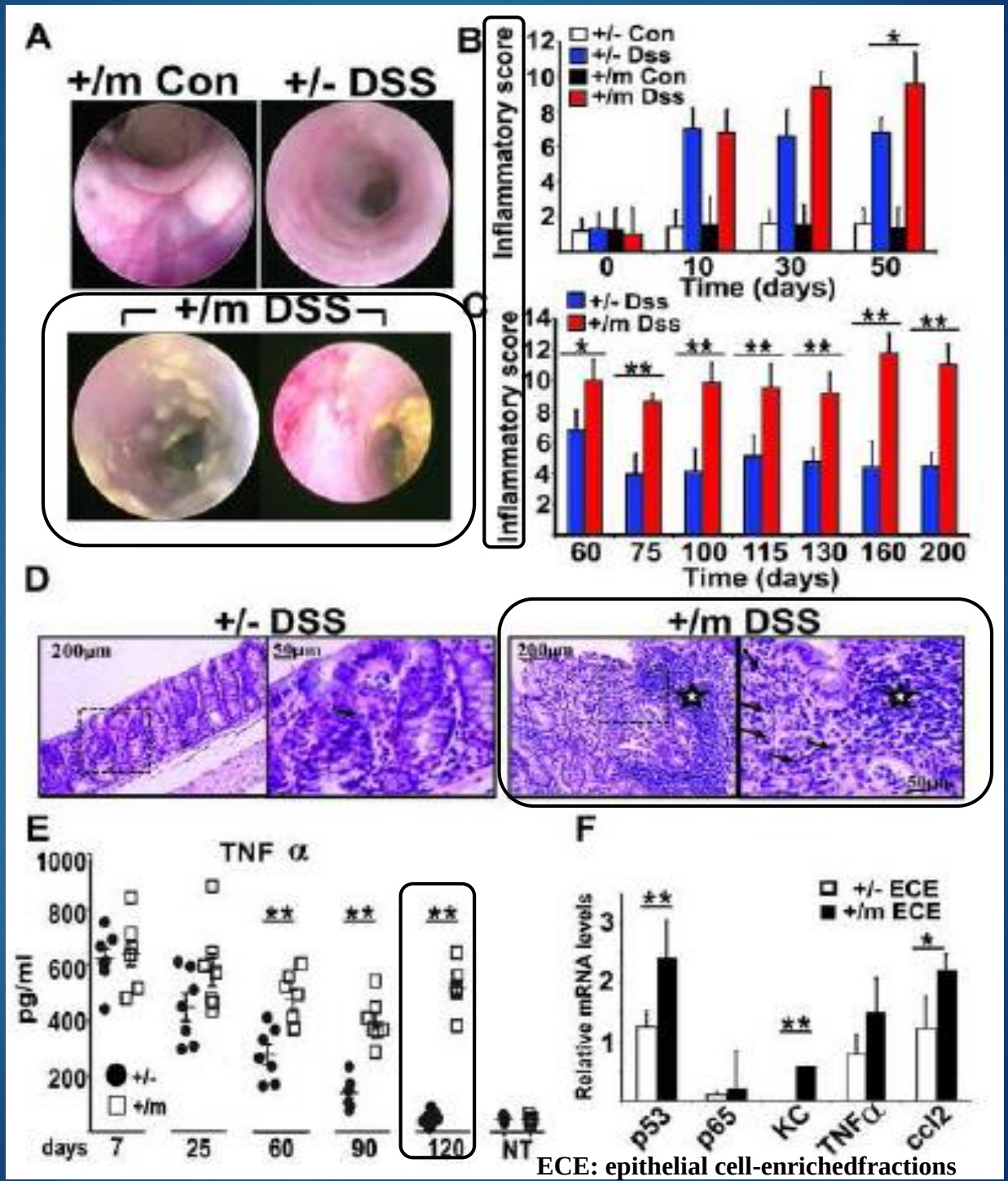


Τα ανωτέρω ευρήματα αναπαράγονται σε μη-μετασχηματισμένα επιθηλιακά συστήματα;

Mice expressing mutp53 (R172H, human homolog R175H) are excessively susceptible to DSS

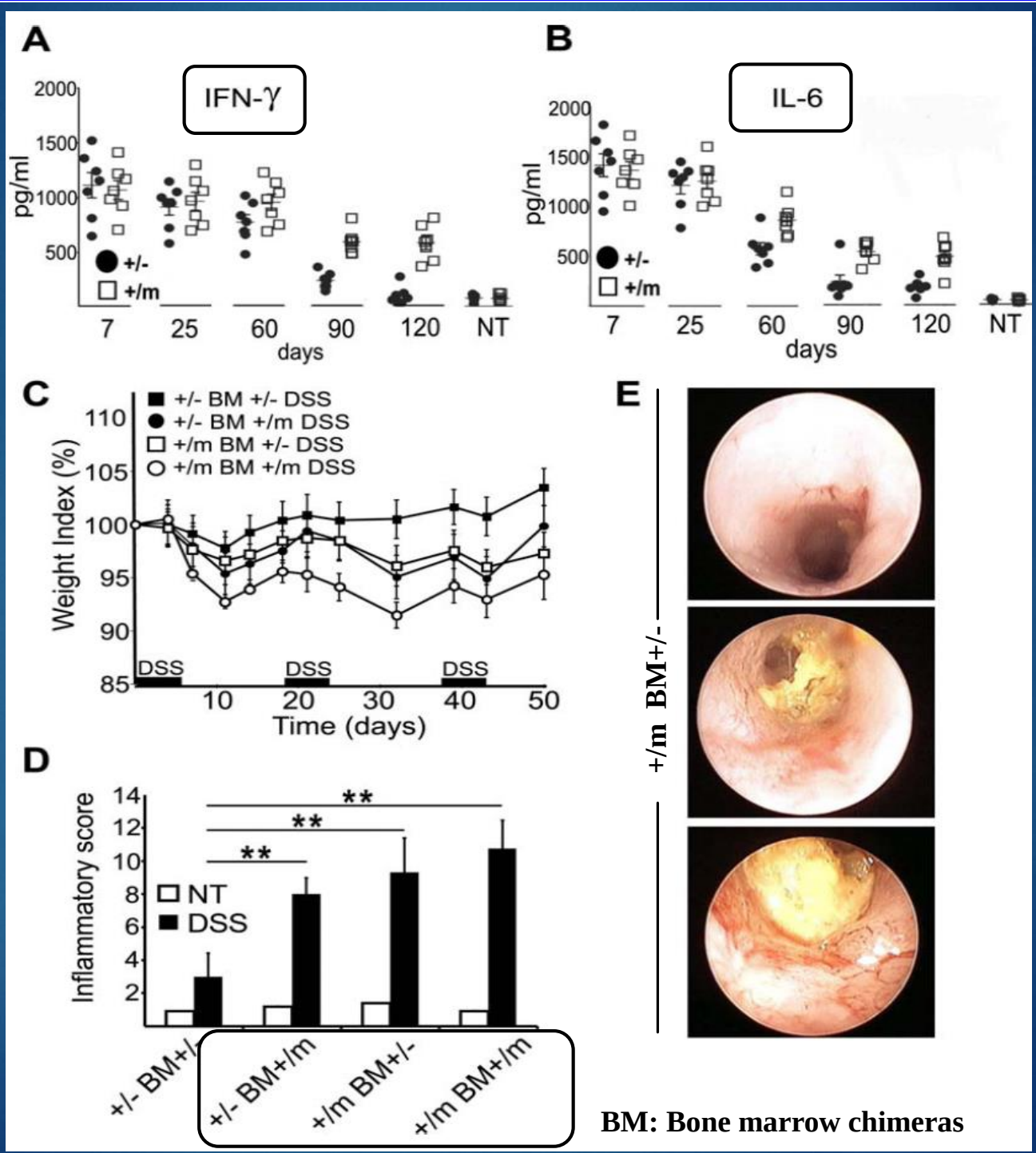


Mice expressing mutp53 are prone to chronic inflammation



ECE: epithelial cell-enrichedfractions

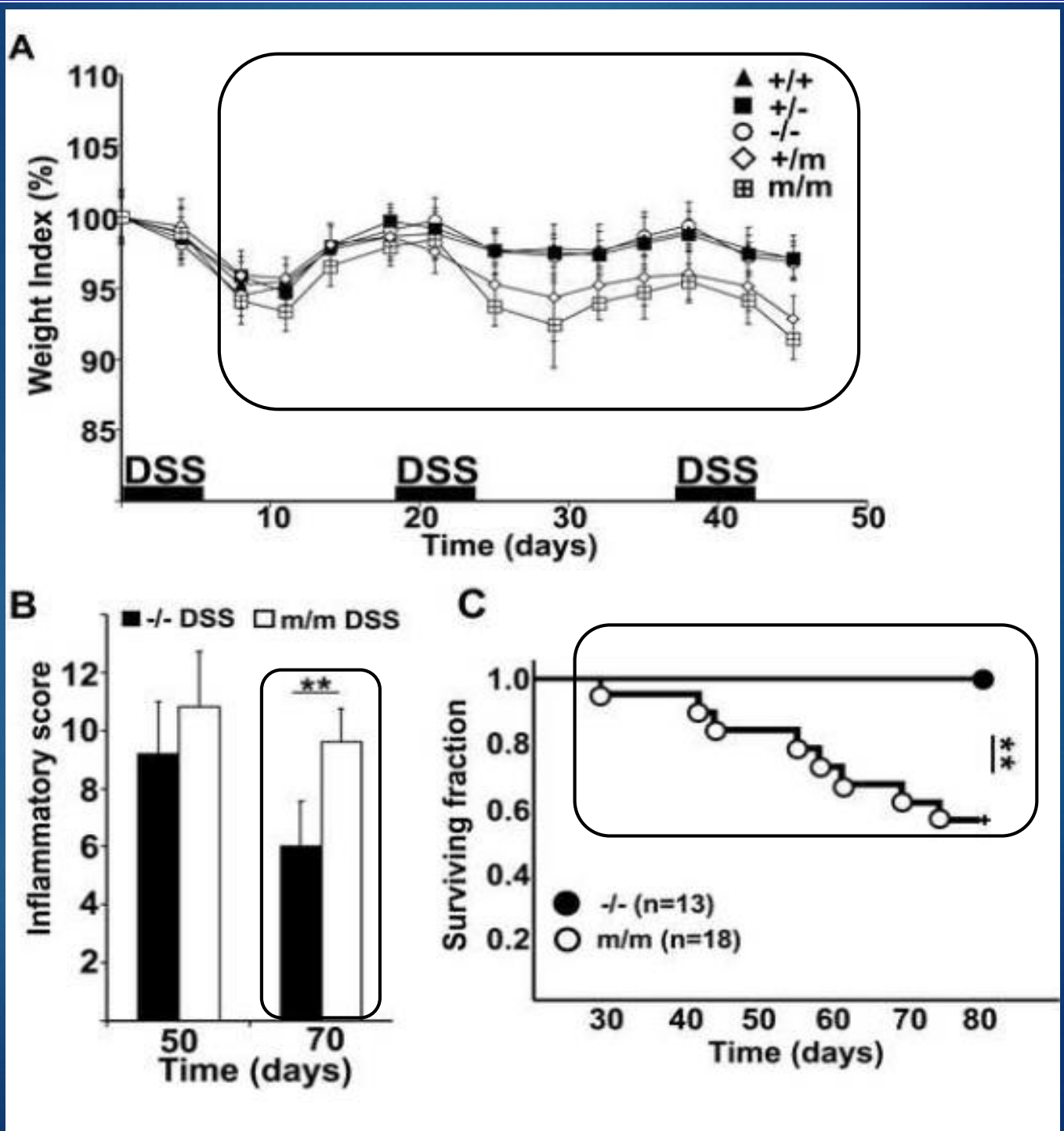
Mice expressing mutp53 in the epithelial or myeloid compartment are more susceptible to chronic inflammation



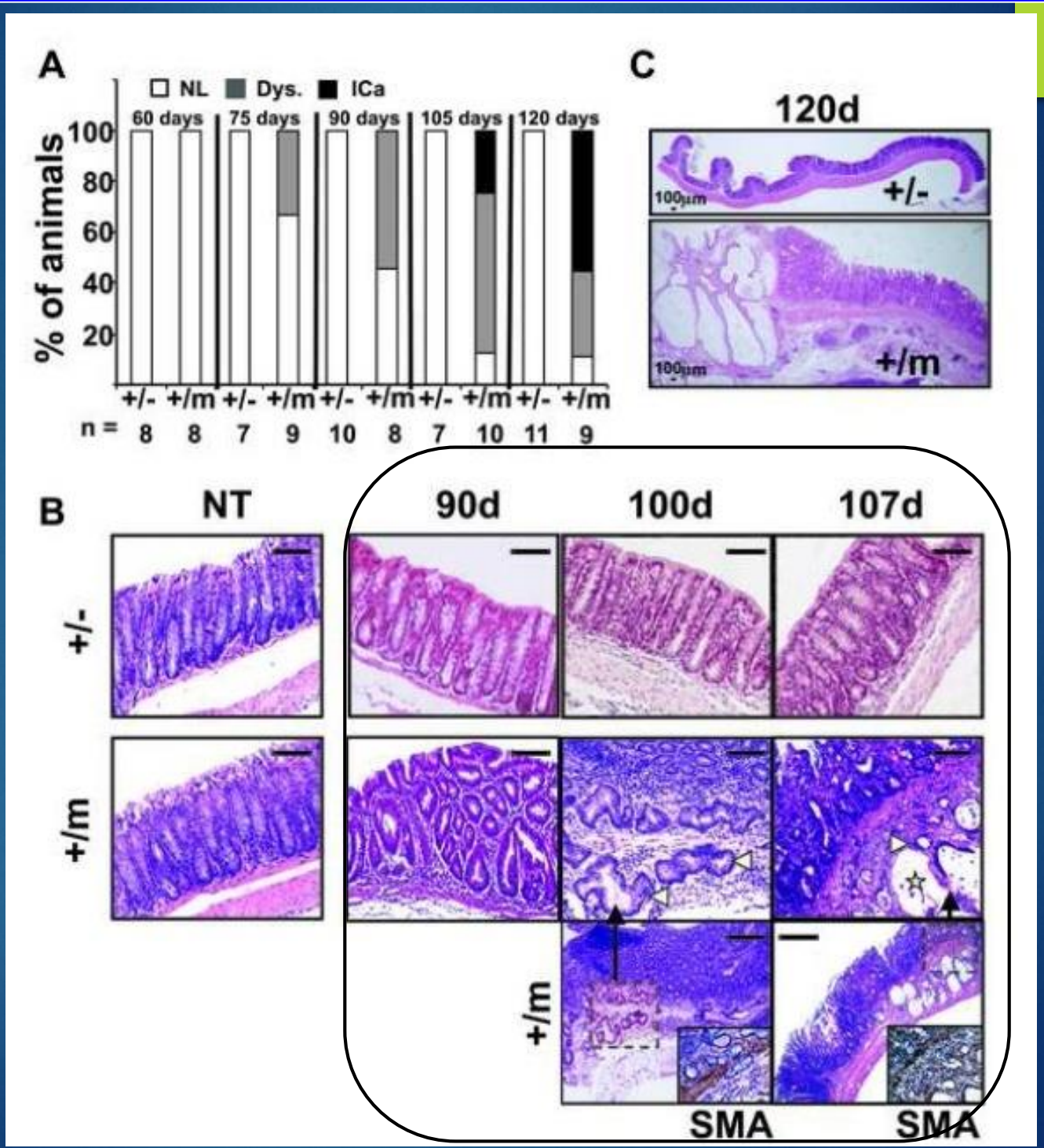
BM: Bone marrow chimeras

Συμπερασματικά μεταλλαγμένες μορφές της πρωτεΐνης P53 τόσο στο επιθηλιακό στοιχείο όσο και στο στρωματικό στοιχείο μπορούν να επάγουν την έκφραση μεσολαβητών της φλεγμονής (όπως κυτταροκινών).

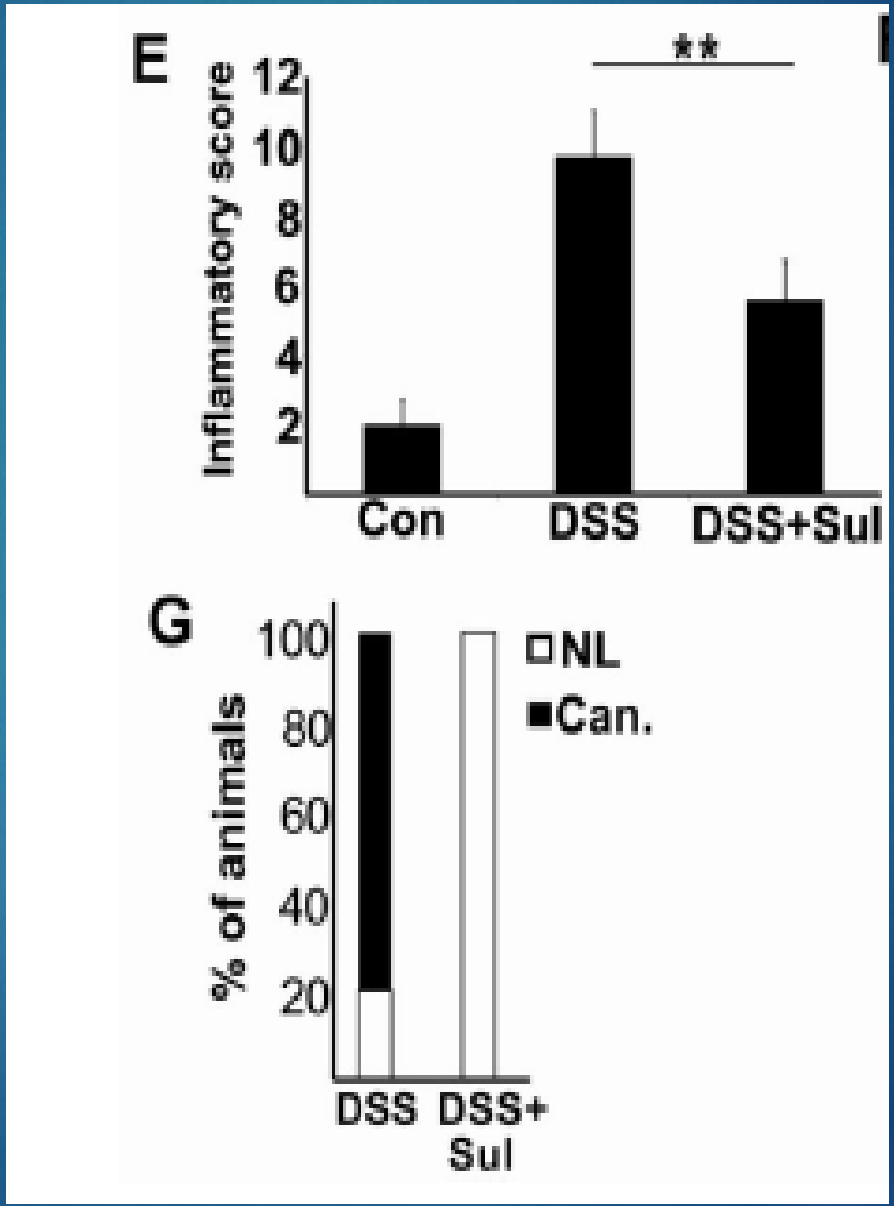
Gain-of-function (GOF) effect of mutp53: not attributed to a dominant negative mechanism



Mutp53 mice are highly prone to DSS-induced colon carcinoma



Treatment with NSAID sulindac (given after the 3 cycles of DSS) inhibited the DSS-induced carcinogenesis

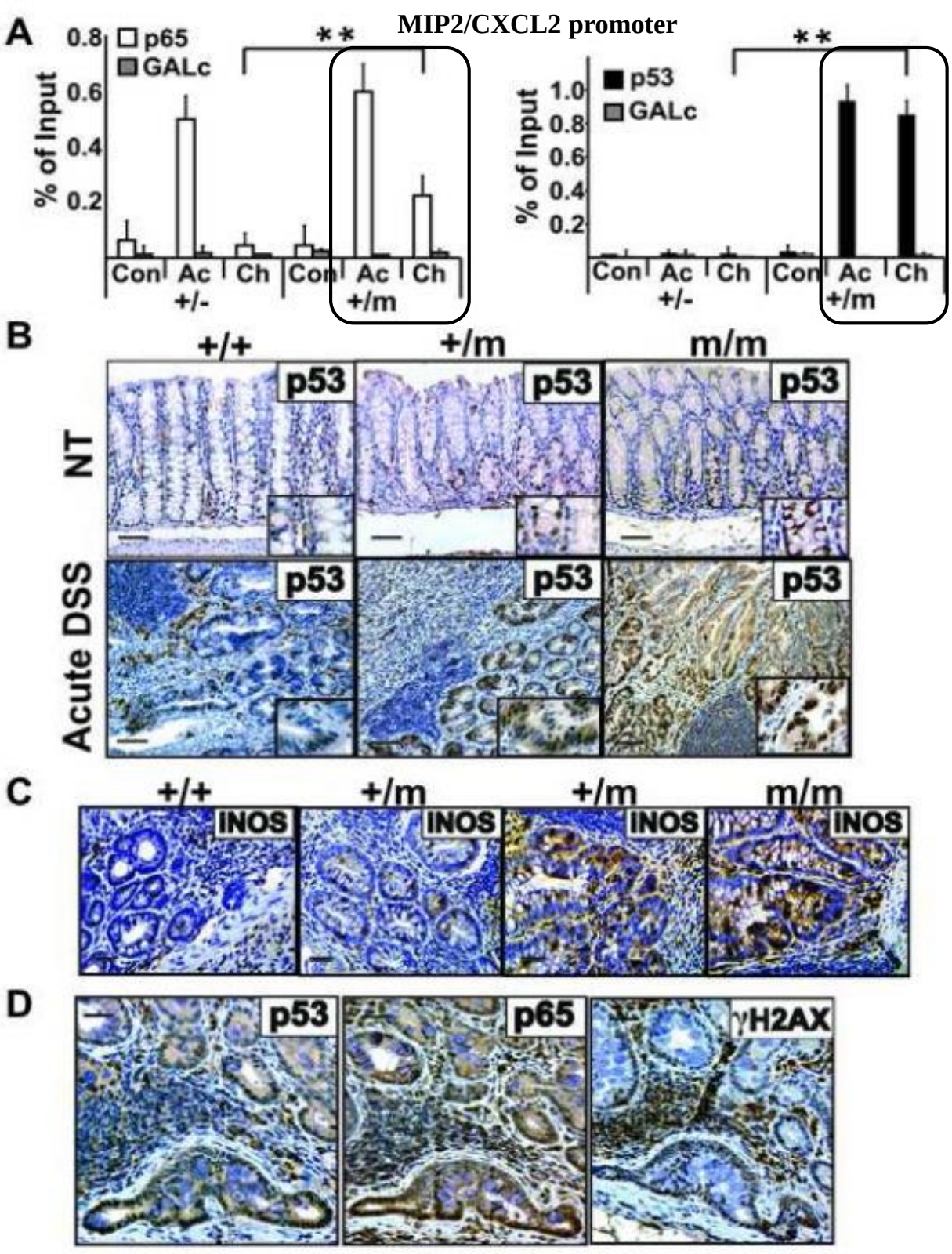


Mutp53 accumulates in

the inflamed colon and in cancerous glands

concomitantly with NF-κB activation and

sustained DNA damage



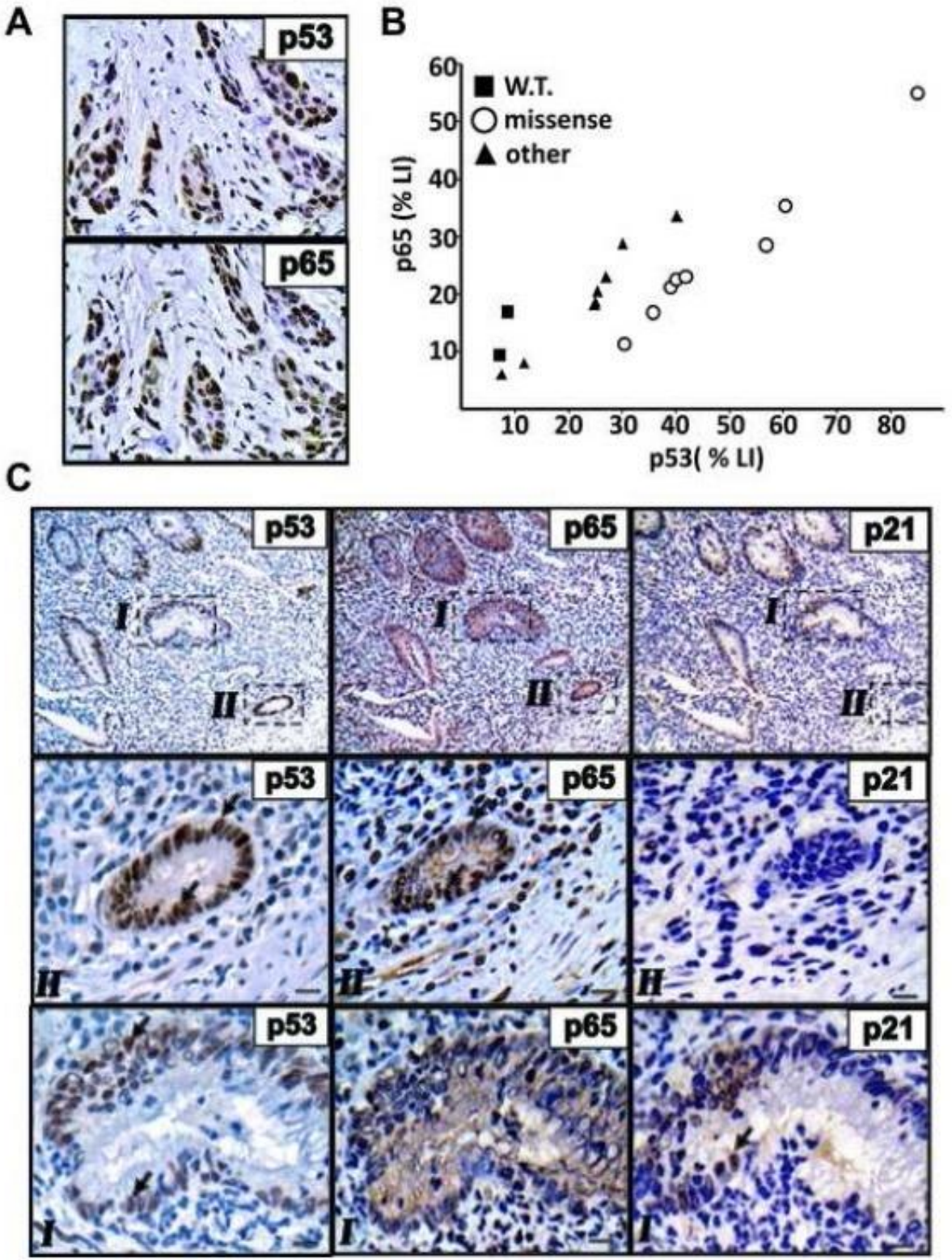
Mutp53 accumulation

correlates with

NF-κB activation

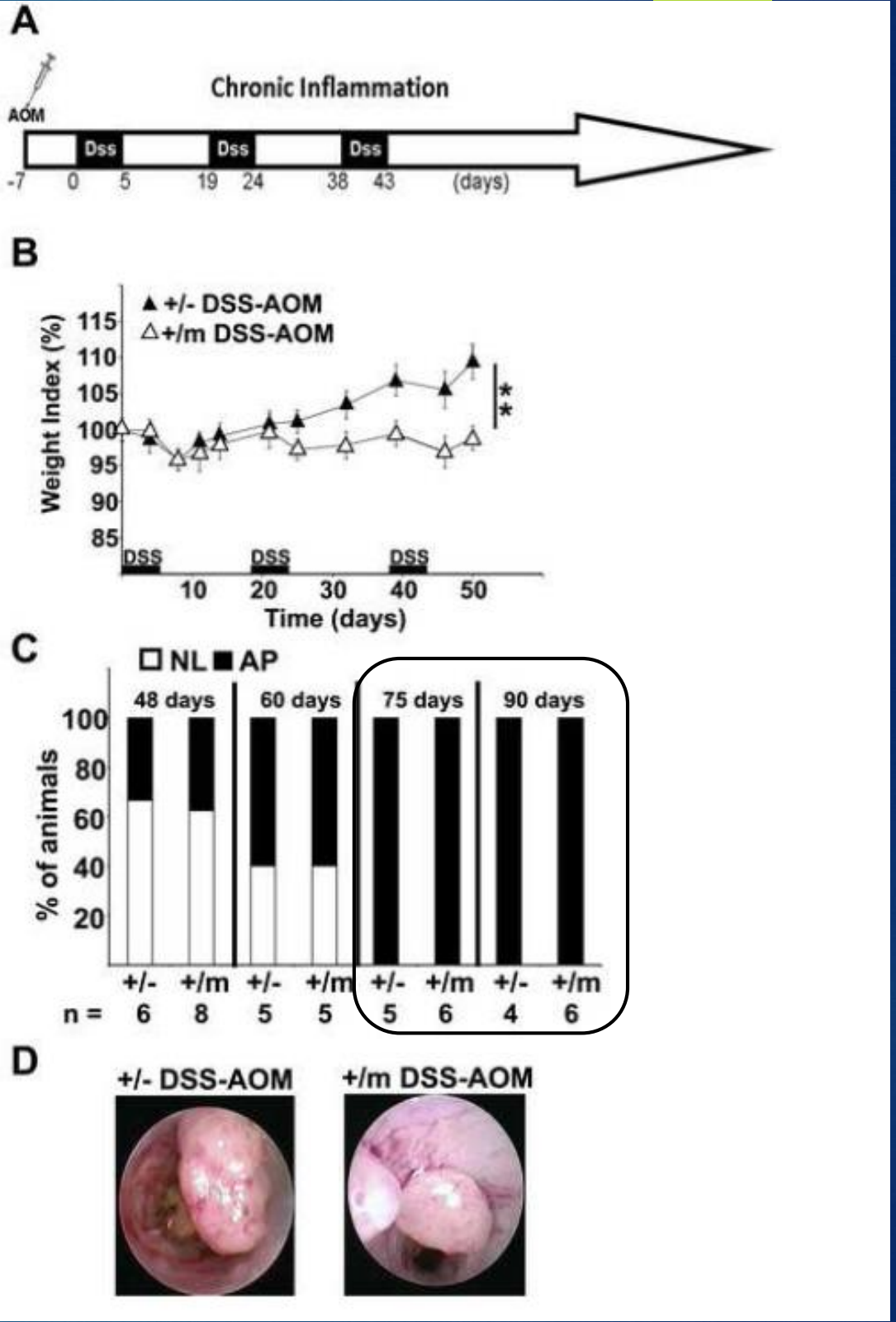
in human colitis-associated cancer and

non-neoplastic glands



AOM bypasses the dependence on

mutp53 GOF for accelerated tumorigenesis



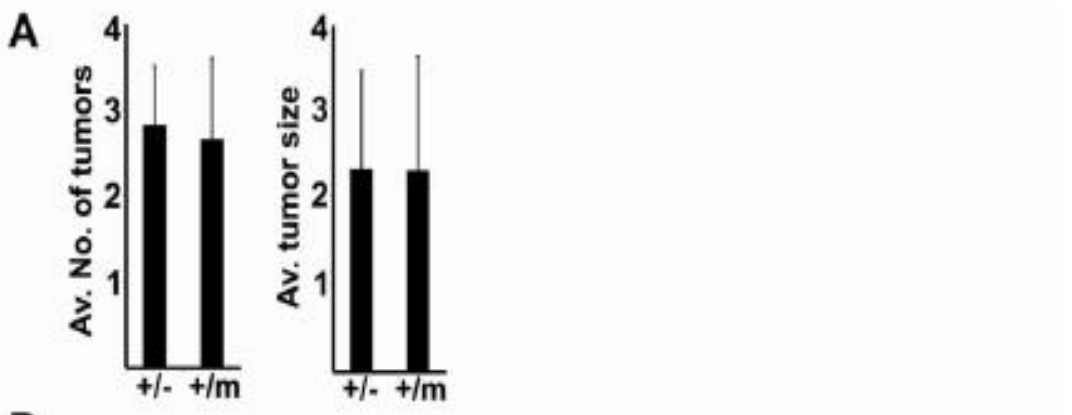
AOM switches the response

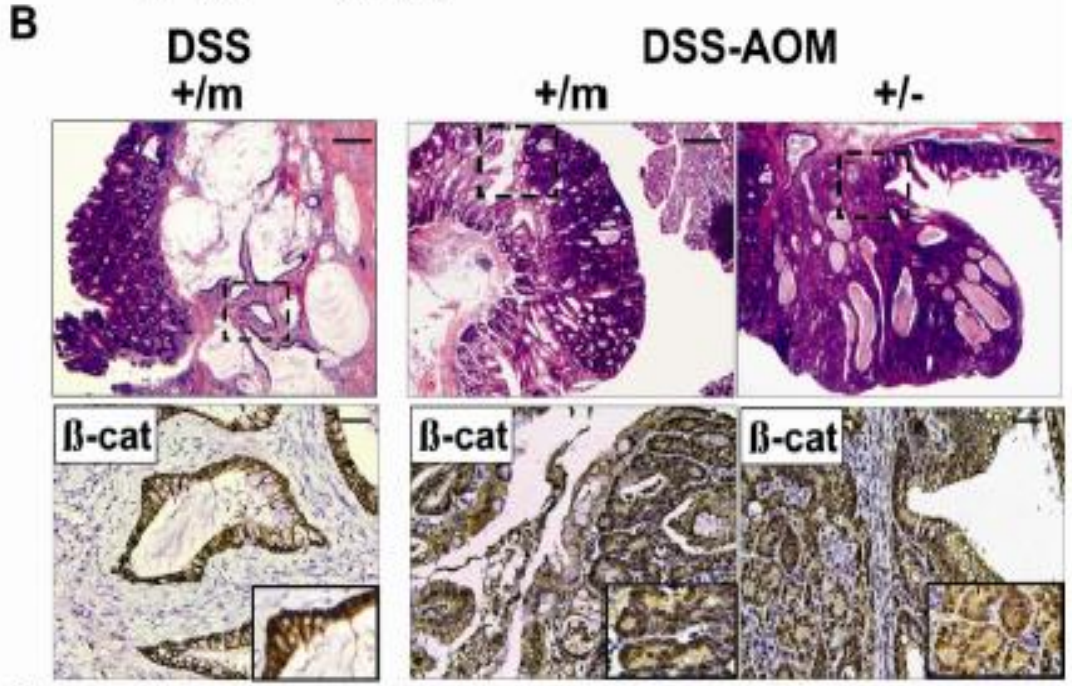
towards a different course

with pathological and molecular features

reminiscent of

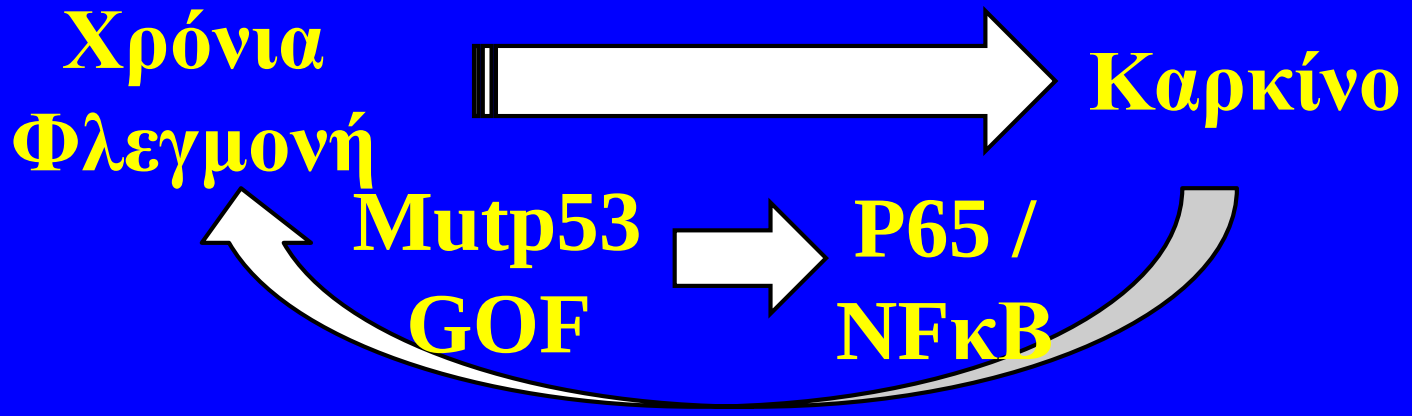
sporadic colorectal carcinoma



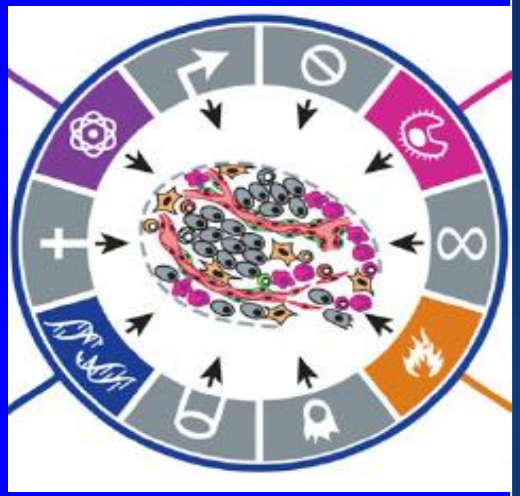


C

p53	Treat.	Pathology	me	me/cy	cy/nu
+/m	DSS	high grade flat dys.	2	1	
+/m	DSS	mucin. adenocarcinoma	5		
+/m	DSS	well differen. adenocarcinoma	1	1	
+/-	DSS-AOM	adenoma (high grade dys.)		1	6
+/-	DSS-AOM	*in situ* carcinoma		1	2
+/m	DSS-AOM	adenoma (high grade dys.)			4
+/m	DSS-AOM	*in situ* carcinoma			3



- Γενωμική αστάθεια (Genomic instability)
- Αγγειογένεση (Angiogenesis)
- Διήθηση και Μετάσταση (Invasion and Metastasis)
- Ανοσοδιαφυγή (Immune invasion, i.e. T cell exhaustion)



Mutant p53 Prolongs NF-κB Activation and Promotes Chronic Inflammation and Inflammation-Associated Colorectal Cancer

Tomer Cooks,[1] Ioannis S. Pateras,[2] Ohad Tarcic,[1] Hilla Solomon,[1] Aaron J. Schetter,[3] Sylvia Wilder,[1] Guillermina Lozano,[4] Eli Pikarsky,[5,6] Tim Forshew,[7] Nitzan Rozenfeld,[7] Noam Harpaz,[8] Steven Itzkowitz,[9] Curtis C. Harris,[3] Varda Rotter,[1] Vassilis G. Gorgoulis,[2,10] and Moshe Oren[1,*]

[1]Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot 76100, Israel
[2]Molecular Carcinogenesis Group, Department of Histology-Embryology, School of Medicine, University of Athens, 15771 Athens, Greece
[3]Laboratory of Human Carcinogenesis, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA
[4]Department of Genetics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[5]Department of Immunology and Cancer Research
[6]Department of Pathology
Hebrew University Hadassah Medical School, Jerusalem 91120, Israel
[7]Cancer Research UK Cambridge Institute, University of Cambridge, Li Ka Shing Centre, Cambridge CB2 0RE, UK
[8]Department of Pathology
[9]Division of Gastroenterology, Department of Medicine
Mount Sinai School of Medicine, New York, NY 10029, USA
[10]Biomedical Research Foundation, Academy of Athens, 11527 Athens, Greece
*Correspondence: moshe.oren@weizmann.ac.il
http://dx.doi.org/10.1016/j.ccr.2013.03.022

SUMMARY

The tumor suppressor p53 is frequently mutated in human cancer. Common mutant p53 (mutp53) isoforms can actively promote cancer through gain-of-function (GOF) mechanisms. We report that mutp53 prolongs TNF-α-induced NF-κB activation in cultured cells and intestinal organoid cultures. Remarkably, when exposed to dextran sulfate sodium, mice harboring a germline p53 mutation develop severe chronic inflammation and persistent tissue damage, and are highly prone to inflammation-associated colon cancer. This mutp53 GOF is manifested by rapid onset of flat dysplastic lesions that progress to invasive carcinoma with mutp53 accumulation and augmented NF-κB activation, faithfully recapitulating features frequently observed in human colitis-associated colorectal cancer (CAC). These findings might explain the early appearance of p53 mutations in human CAC.

INTRODUCTION

The connection between inflammation and cancer has drawn intensive research (Ben-Neriah and Karin, 2011; Demaria et al., 2010; Hanahan and Weinberg, 2011; Schetter et al., 2010), and has highlighted the context-dependent modulation of inflammation-associated cancer by the transcription factor NF-κB (Ben-Neriah and Karin, 2011; He and Karin, 2011). One well-documented link between chronic inflammation and human cancer involves colorectal cancer (CRC) in patients suffering from inflammatory bowel disease (IBD) (Asquith and Powrie, 2010; Ullman and Itzkowitz, 2011). Continuous tissue destruction and renewal, together with persistent oxidative damage inflicted by the inflamed microenvironment, can trigger mutagenic processes that serve as cancer-initiating events. Further tumor progression is augmented by the continuous presence

Significance

The links between chronic inflammation and cancer are the subject of extensive research. Identification of the underlying molecular mechanisms may be of high relevance for cancer prevention and treatment. Here, we demonstrate that a cancer-associated mutant isoform of the p53 tumor suppressor promotes chronic inflammation and inflammation-driven cancer. Specifically, we report that mutant p53 acquires a significant proinflammatory activity mediated by NF-κB, which may promote both tumor initiation and tumor progression. Furthermore, we describe a mouse model that faithfully mimics features frequently seen in human colitis-associated colorectal cancer. As p53 mutations occur very early in the course of inflammation-associated human colorectal cancer, targeting those mutations in premalignant lesions may be clinically beneficial.

Με βάση τα ακόλουθα ευρήματα:

- Τα αυξημένα επίπεδα χρόνιας φλεγμονής λόγω μετάλλαξεων της P53 τόσο στο επιθηλιακό όσο και στο στρωματικό στοιχείο

- Τα αυξημένα επίπεδα των μεσολαβητών της φλεγμονής CCL2 και IL6 σε περιστατικά όπου η P53 είναι μεταλλαγμένη. Σημειώνεται ότι και οι δύο κυτταροκίνες προάγουν την M2 πολικότητα των μακροφάγων.

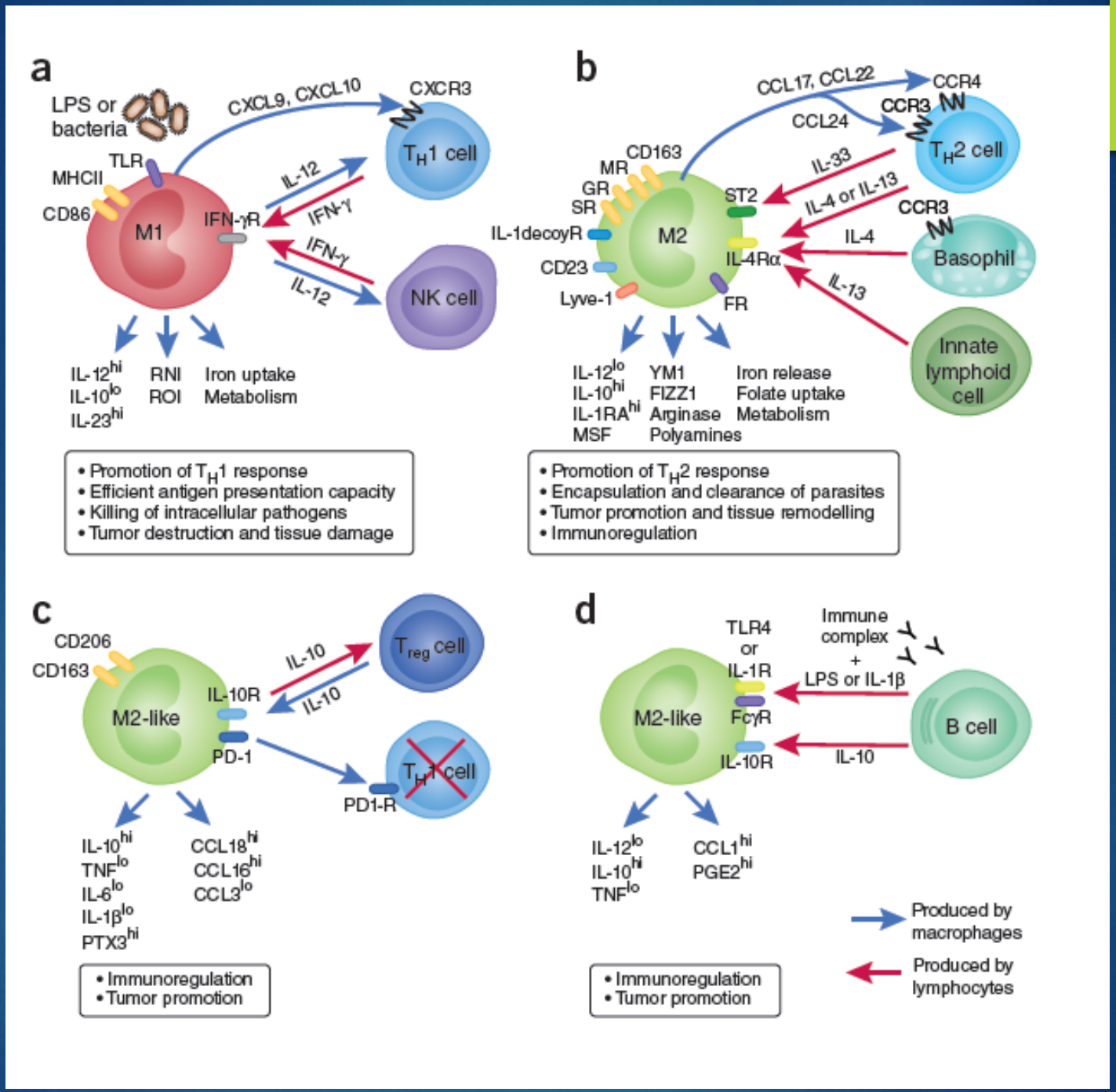
-

-Το γεγονός ότι ινοβλάστες που φέρουν μεταλλαγμένες μορφές της P53 προάγουν την ανάπτυξη όγκου μέσω του μεσολαβητή της φλεγμονής SDF1/CXL12 (Moskovit's et al., Cancer Res, 2006, by Moshe's group) . Αυτός ο παράγοντας προάγει την πολικότητα προς Τ ρυθμιστικά λεμφοκύτταρα (reviewed by Karin N J of Leuk Biol 2010)

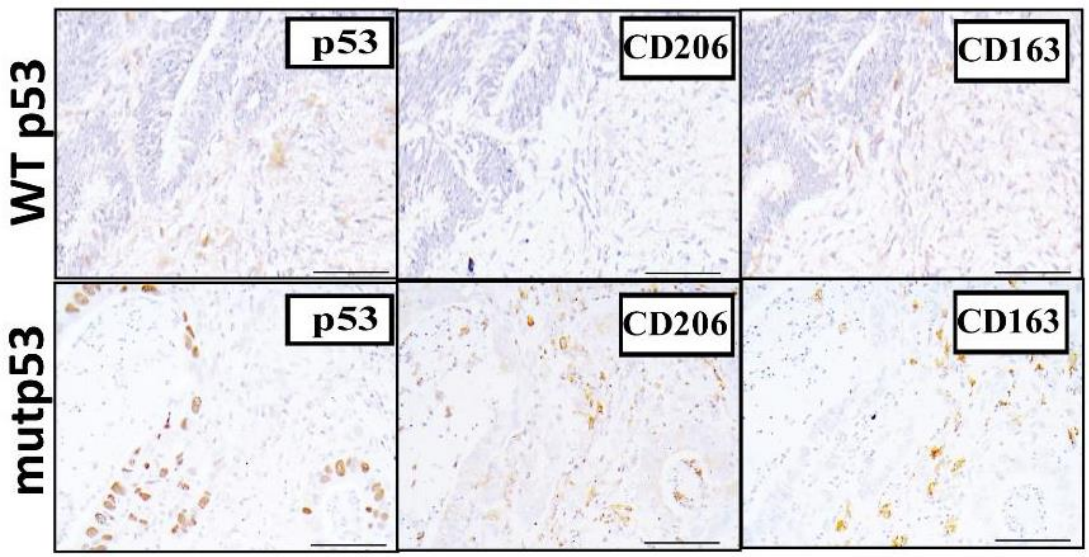
-Τ ρυθμιστικά λεμφοκύτταρα με φαινότυπο "CD4+CD25+Foxp3+ επάγουν την πολικότητα προς M2 μακροφάγα (Tiemessen *et al.* PNAS 2007)

Ερώτηση

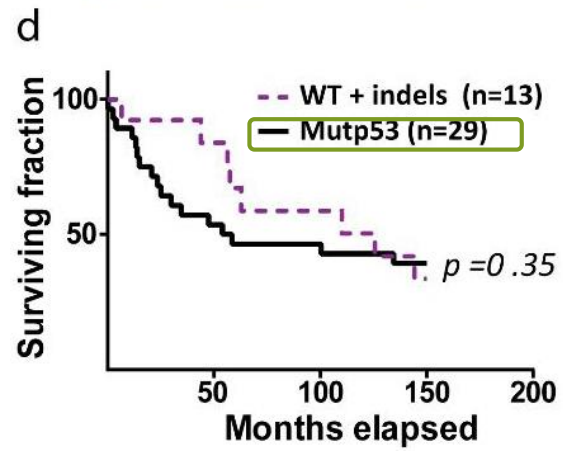
Μπορούν μεταλλαγμένες μορφές της πρωτεΐνης P53 να επαναπρογραμματίζουν τα μακροφάγα που βρίσκονται στο μικροπεριβάλλον του όγκου ώστε να υιοθετήσουν ένα φαινότυπο αντίστοιχο με τον φαινότυπο των Μ2 μακροφάγων?

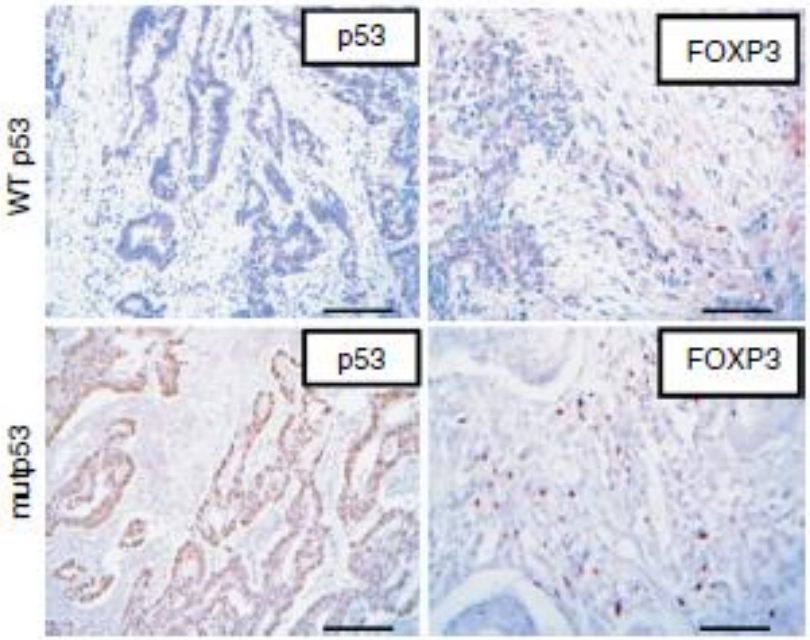


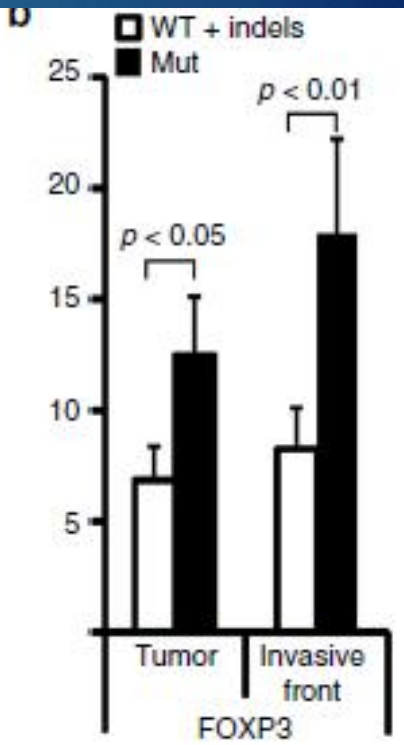
Biswas SK & Mantovani A Nat Immunology 2010



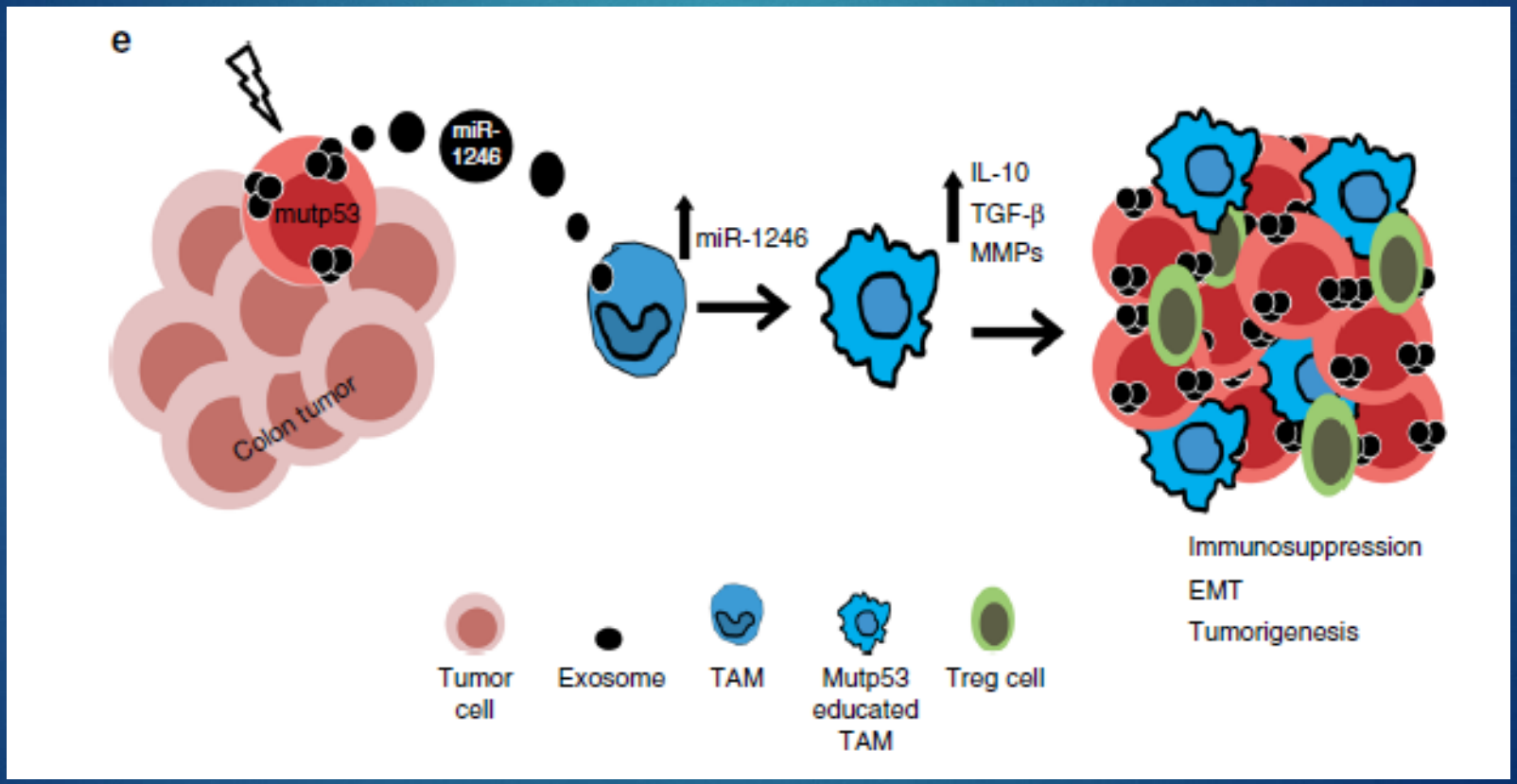
Σε περιστατικά από σποραδικό αδενοκαρκίνωμα του παχέος εντέρου με μεταλλαγμένες μορφές της πρωτεΐνης P53 παρατηρούνται περισσότερα κύτταρα στο στρώμα με CD206+, CD163+ (φαινότυπος M2 μακροφάγων) καθώς και περισσότερα FOXP3+ κύτταρα (δείκτης Τ ρυθμιστικών λεμφοκυττάρων)







Μεταλλαγμένες μορφές της πρωτεΐνης P53 σε καρκινικά κύτταρα προερχόμενα από σποραδικό αδενοκαρκίνωμα του παχέος εντέρου μπορούν να διαμορφώσουν ένα μικροπεριβάλλον ευνοϊκό προς τον καρκίνο



nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-03224-w OPEN

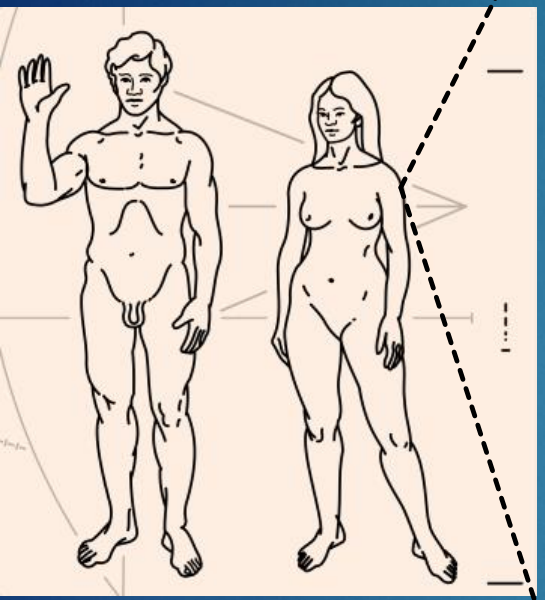
Mutant p53 cancers reprogram macrophages to tumor supporting macrophages via exosomal miR-1246

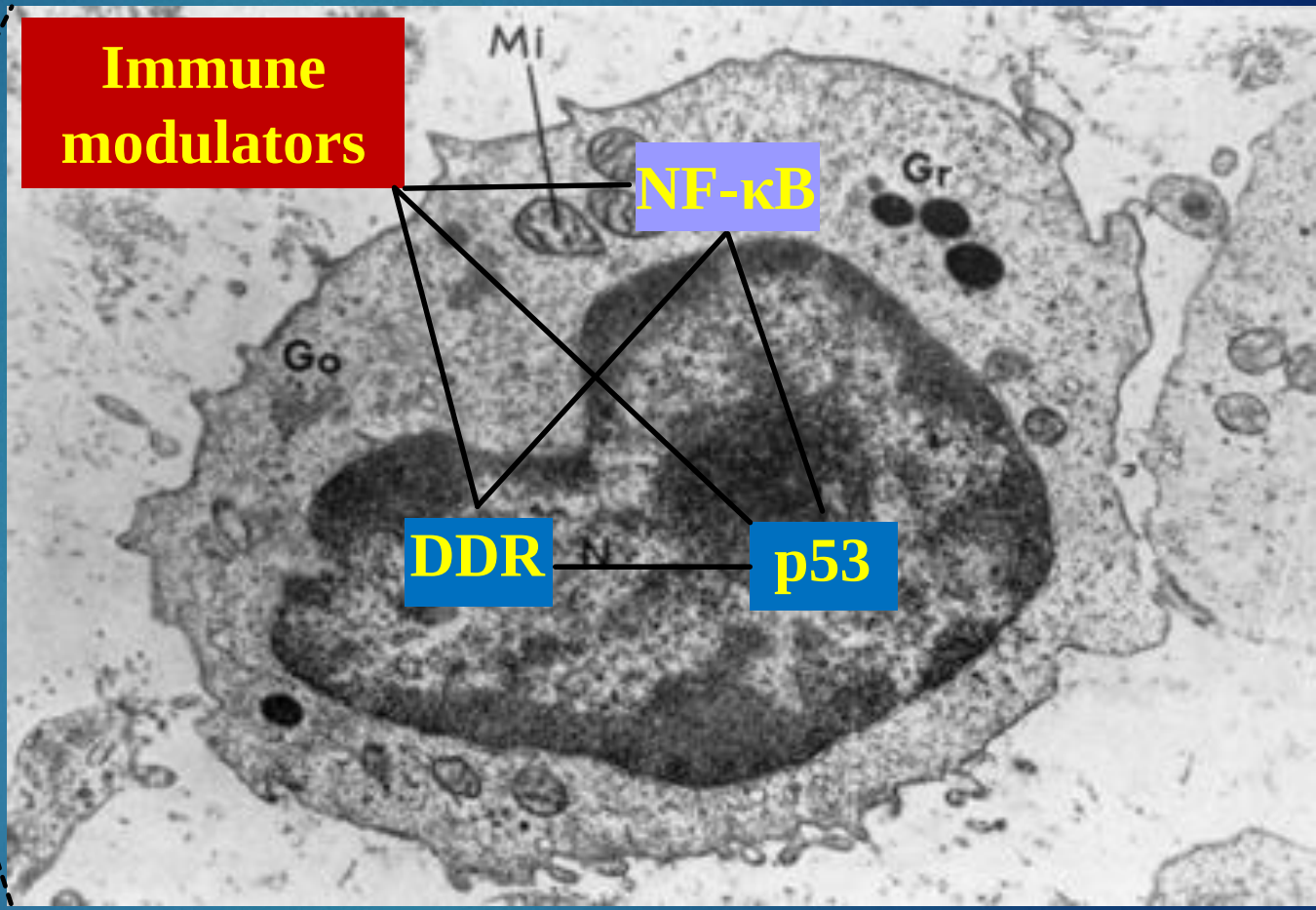
Tomer Cooks[1], Ioannis S. Pateras[2], Lisa M. Jenkins[3], Keval M. Patel[4], Ana I. Robles[1], James Morris[5], Tim Forshew[6], Ettore Appella[3], Vassilis G. Gorgoulis[2,7,8] & Curtis C. Harris[1]

TP53 mutants (mutp53) are involved in the pathogenesis of most human cancers. Specific mutp53 proteins gain oncogenic functions (GOFs) distinct from the tumor suppressor activity of the wild-type protein. Tumor-associated macrophages (TAMs), a hallmark of solid tumors, are typically correlated with poor prognosis. Here, we report a non-cell-autonomous mechanism, whereby human mutp53 cancer cells reprogram macrophages to a tumor supportive and anti-inflammatory state. The colon cancer cells harboring GOF mutp53 selectively shed miR-1246-enriched exosomes. Uptake of these exosomes by neighboring macrophages triggers their miR-1246-dependent reprogramming into a cancer-promoting state. Mutp53-reprogammed TAMs favor anti-inflammatory immunosuppression with increased activity of TGF-β. These findings, associated with poor survival in colon cancer patients, strongly support a microenvironmental GOF role for mutp53 in actively engaging the immune system to promote cancer progression and metastasis.

[1] Laboratory of Human Carcinogenesis, NCI-CCR, National Institutes of Health, Bethesda 20892-4258 MD, USA. [2] Molecular Carcinogenesis Group, Department of Histology and Embryology, School of Medicine, National Kapodistrian University of Athens, 75 Mikras Asias St, Athens GR-11527, Greece. [3] Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda 20892-4258 MD, USA. [4] Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK. [5] Cancer Research UK, Cambridge Research Institute, Robinsons Way, Cambridge CB2 0RE, UK. [6] UCL Cancer Institute, Huntley St, Camden Town, London WC1E 6DD, UK. [7] Biomedical Research Foundation of the Academy of Athens, 4 Soranou Ephessiou St., GR-11527 Athens, Greece. [8] Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health, Science Centre, Wilmslow Road, Manchester M20 4QL, UK. Correspondence and requests for materials should be addressed to C.C.H. (email: curtis_harris@nih.gov)

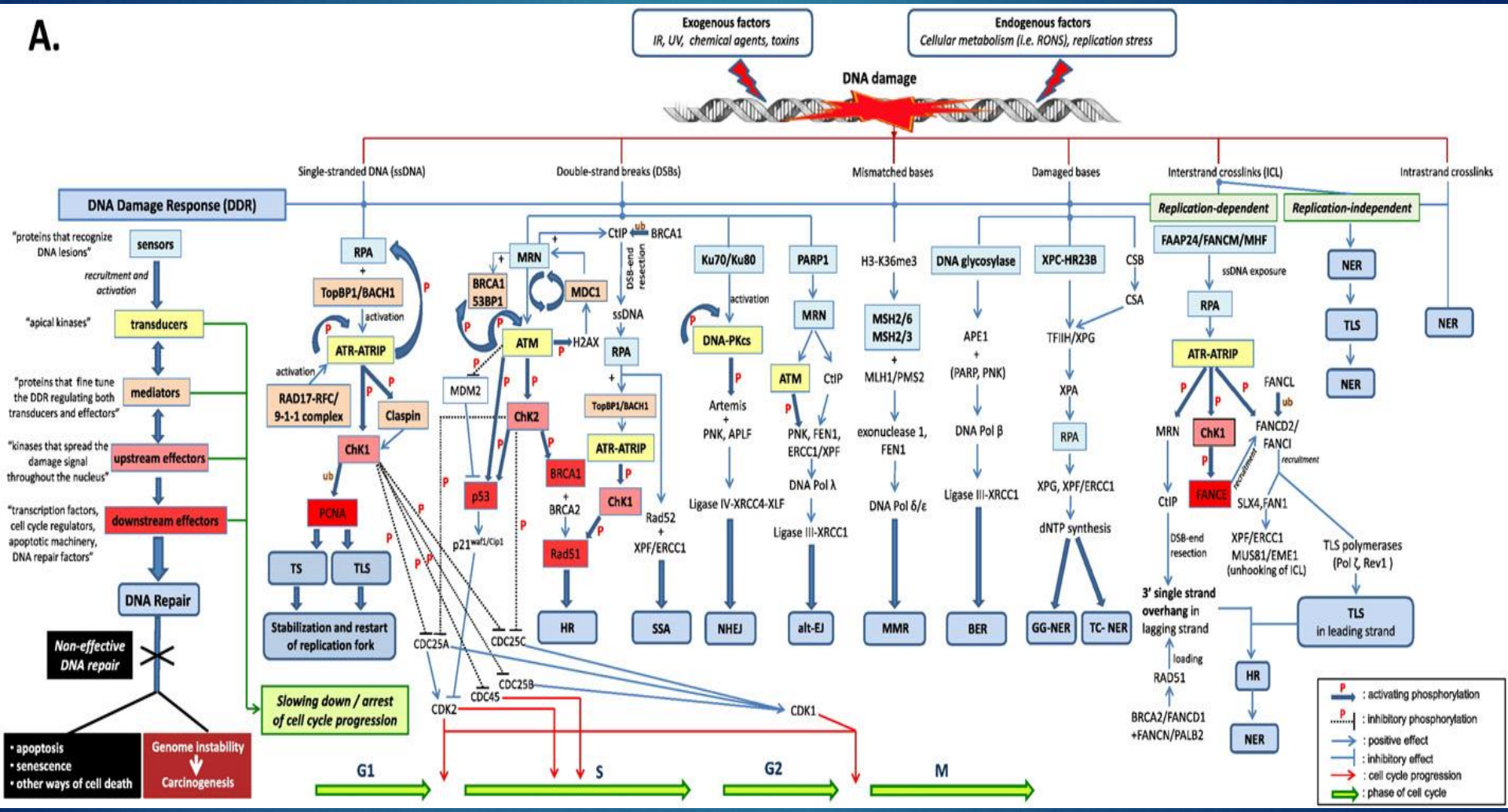
DNA Damage Response/Repair (DDR/R)–Immune Response (ImmR)



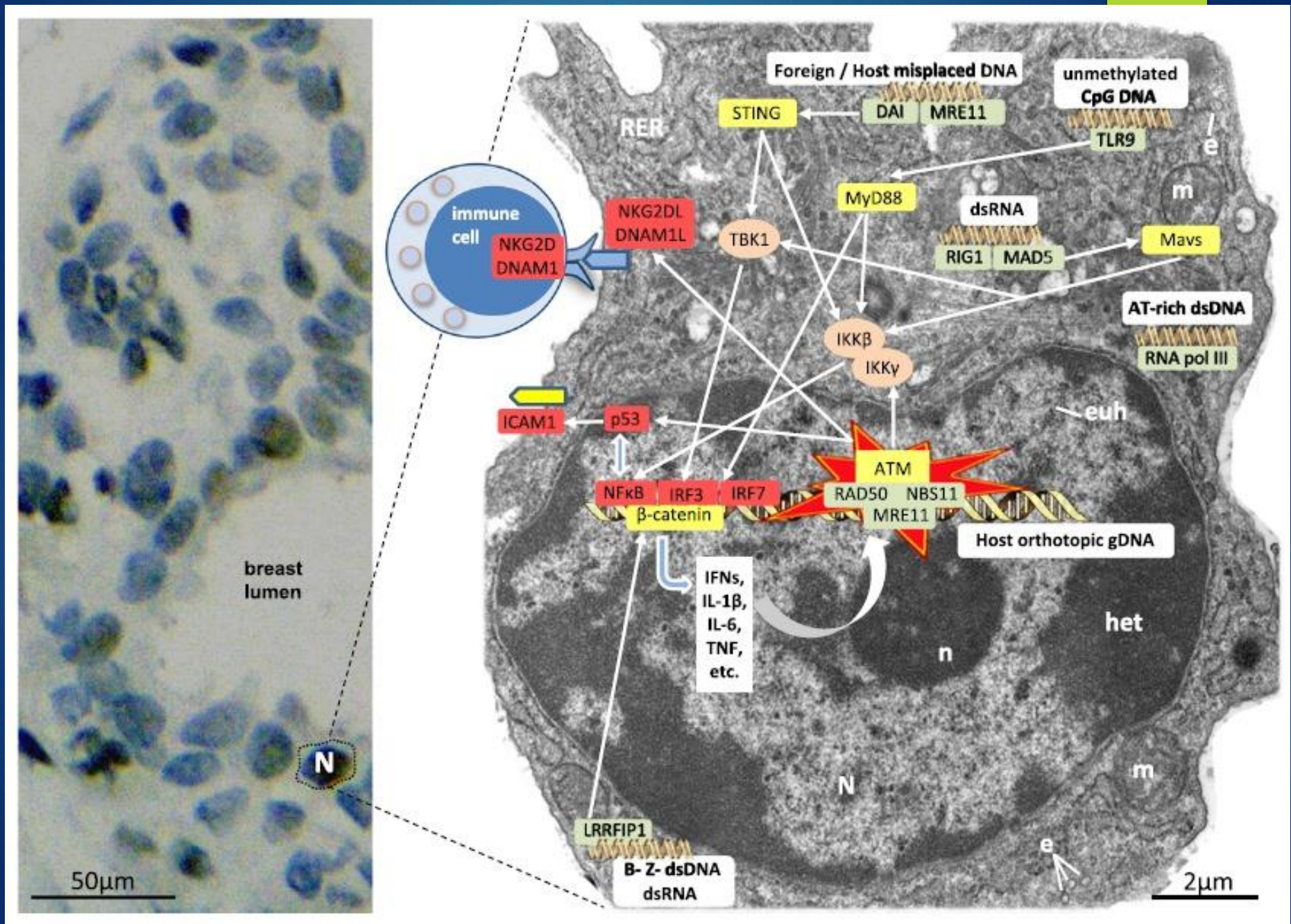


Ο μηχανισμός απόκρισης σε βλάβες στο DNA –

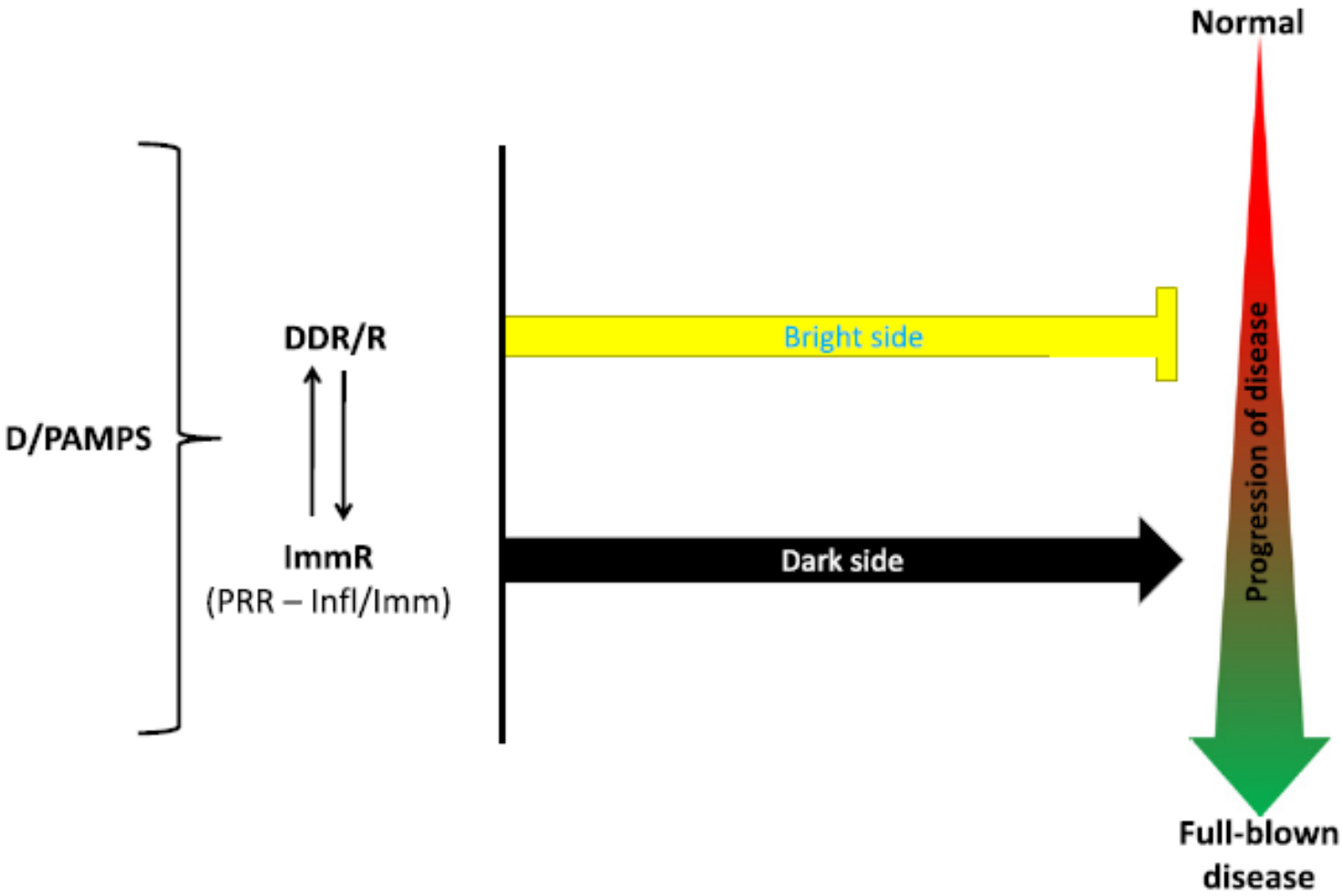
The DNA Damage Response and Repair (DDR/R) machinery activated by endogenous and exogenous insults



Η αλληλεπίδραη DDR/R – ImmR “Unus pro omnibus, omnes pro uno”



A unifying model emerges with DDR/R and ImmR activated in concert as a response to Damage/Pathogen-Associated Molecular Patterns (D/PAMPS)



Pateras IS, Havaki S, *et al.* Pharmac. & Therap. 2015

Pharmacology & Therapeutics 154 (2015) 36–56

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

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

Ioannis S. Pateras [a,1], Sophia Havaki [a,1], Xenia Nikitopoulou [a,1], Konstantinos Vougas [b], Paul A. Townsend [c,d], Michalis I. Panayiotidis [e], Alexandros G. Georgakilas [f], Vassilis G. Gorgoulis [a,b,c,d,*]

[a] Molecular Carcinogenesis Group, Department of Histology and Embryology, School of Medicine, University of Athens, Athens, Greece
[b] Biomedical Research Foundation, Academy of Athens, Athens, Greece
[c] Institute for Cancer Sciences, University of Manchester, Manchester Academic Health Science Centre, UK
[d] Manchester Centre for Cellular Metabolism, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
[e] School of Life Sciences, Heriot Watt University, Edinburgh, UK
[f] School of Applied Mathematical & Physical Sciences, National Technical University of Athens, Zografou 15780, Greece

Abbreviations: 53BP1 (TP53BP1), P53-binding protein 1; 9–1–1, Rad9–Rad1–Hus1 complex; Ab(s), antibody(s); ACS, Aicardi–Goutières syndrome; AJCC, American Joint Committee on Cancer; alt-EJ, alternative end joining; AMPK, AMP-activated protein kinase; APC, Antigen-presenting cell; APE1, Apyrimidinic/apurinic endonuclease 1; APLF, Aprataxin and PNK-like factor; ARF, Alternative reading frame; ASC, Apoptosis-associated speck-like protein containing a CARD; ATM, Ataxia telangiectasia mutated; ATR, Ataxia telangiectasia and Rad3 related; BCR, B cell receptor; BER, Base excision repair; BRCA(1), Breast cancer susceptibility gene (1); BRCA(2), Breast cancer susceptibility gene (2); CARD, Caspase activation and recruitment domain; CD, Cluster of differentiation; CDC25A, Cell division cycle 25A; CDC25B, Cell division cycle 25B; CDC25C, Cell division cycle 25C; CDC45, Cell division cycle 45; CDK1, Cyclin-dependent kinase 1; CDK2, Cyclin-dependent kinase 2; CFS, Common fragile sites; cGAS/MB21D1, cyclic GMP-AMP synthase/Mab-21 domain containing 1; Chk1, Checkpoint kinase 1; Chk2, Checkpoint kinase 2; CKD, Catalytic kinase domain; COX, Cyclooxygenase; CSA, Cockayne syndrome group A; CSB, Cockayne syndrome group B; CtIP, C-terminal interacting protein; CTLA4, Cytotoxic T-lymphocyte-associated antigen 4; DAI/ZBP1/DLM-1, DNA-dependent activator of interferon (IFN) regulatory factor/Z-DNA- binding protein 1; DAMPs, Damage-associated molecular patterns; DCs, Dendritic cells; DDR/R, DNA damage response/repair; DEXD/H-box helicases, Defined by the Asp–Glu–Ala–Asp (DEAD) pattern and variations thereof (DExD/H); DNAM-1, DNAX accessory molecule-1; DNA-PKcs, DNA protein kinase catalytic subunit; DPAMPs, Damage/pathogen-associated molecular patterns; DSB(s), Double-strand break(s); dsRBM1/2, dsRNA- binding motifs 1 and 2; DSS, Dextran sulfate sodium; e, Endosome; EBNA3C, Epstein–Barr virus nuclear antigen 3C; EME1, Essential meiotic endonuclease 1; EMT, Epithelial and mesenchymal transition; eu/h, Euchromatin; FA, Fanconi anemia; FAAP24, Fanconi anemia-associated protein of 24 kDa; FANCC, Fanconi anemia complementation group C; FANCD2, Fanconi anemia complementation group D2; FANCI, Fanconi anemia complementation group I; FANCM, Fanconi anemia complementation group M; FEN1, Flap endonuclease-1; FRET assay, Fluorescence resonance energy transfer assay; FUO, Fever of unknown origin; G(M)-CSF, Granulocyte (monocyte) colony-stimulating factor; GG-NER, Global genome NER; GOF, Gain of function; H3S10ph, Histone; het, Heterochromatin; HIV, Human immunodeficiency virus; HMGB1,2,3, High-mobility group box 1,2,3; HR, Homologous recombination; HUVEC, Human umbilical endothelial cells; IB, Immunoblotting; ICAM1, Intracellular adhesion molecule 1; ICE, IL-1b-converting enzyme ICE; ICL, Interstrand cross-links; ICOS, Inducible costimulator; ICOS-L, Inducible costimulator ligand; IFN-γ, Interferon -γ; IKK complex, Ikß kinase complex; IL(s), Interleukin(s); ImmR, Immune response; ImmR1, Immune response type 1; ImmR2, Immune response type 2; IR, Ionizing radiation; IRF3,7, INF regulatory factor 3,7; ISG, Interferon stimulatory gene; JAK, Janus kinase; LFA1, Lymphocyte-function-associated antigen 1; LRR/RPI, Leucine-rich repeat (in FLII) interacting protein 1; LT, Lymphotoxin; m, Mitochondrion; M1/M2, Macrophages 1/2; MAPK, Mitogen-activating protein kinase; Mavs, Mitochondrial antiviral signaling protein; MCDS, Monte Carlo damage simulation; MDC1, Mediator of DNA damage checkpoint 1; MDM2, Murine double minute 2; MDSCs, Myeloid-derived suppressor cells; MEFs, Mouse embryo fibroblasts; MHCI, Major histocompatibility complex type I; MICA/B, MHC Class I polypeptide-related sequence A/B; MITA, Mediator of IRF3 activation (also known as STING); MMP, Matrix metalloproteinase; MMR, Mismatch repair; MRN, Mre11–Rad50–Nbs1; mTOR, Mammalian target of rapamycin; MUS81, Methylmethanesulfonate and UV-sensitive clone 81; MyCBB, Myeloid differentiation primary response gene 88; N, Nucleus; n, Nucleolus; NAC, N-Acetyl-cysteine; NBS1, Nijmegen breakage syndrome 1 (Nibrin); NEMO, NF-kappa-B essential modulator (also known as IKKγ (Inhibitor of nuclear factor kappa-B kinase subunit gamma)); NER, Nucleotide excision repair; NF-κB, Nuclear factor kappa light-chain enhancer of activated B cells; NHEJ, Nonhomologous end joining; NK, Natural killer cells; NKG2D, Natural killer group 2, member D; NKG2DL, NKG2D ligand; NLR, Nucleotide-binding oligomerization domain receptors; NLRP3, NOD-like receptor family, pyrin domain containing 3; NSAIDs, Nonsteroidal anti-inflammatory drug(s); OIS, Oncogene-induced senescence; PAMPs, Pathogen-associated molecular patterns; PARP-1, Poly (ADP-ribose) polymerase 1; PCNA, Proliferating cell nuclear antigen; PD1, Programmed death 1; PDL1 (CD274/B7-H1), Programmed death ligand 1; PKR, Protein kinase, interferon-inducible double-stranded RNA-dependent activator; PML, Promyelocytic leukemia protein; PNK, Polynucleotide kinase; pRb, Retinoblastoma protein; PRRDC (DNA-PKcs), Protein kinase, DNA-activated, catalytic polypeptide; PRR, Pattern recognition receptor; PS, Paraneoplastic syndromes; PVR (CD155), Poliovirus receptor; PYHIN, Pyrin/PY and HIN domain-containing protein family; R, Arginine; RAE1, Retinoic acid early transcript 1; RER, Rough endoplasmic reticulum; RIPK1,3, Receptor-interacting protein kinase 1,3; RNA polII, RNA polymerase II; RO(N)S, Reactive oxygen (and nitrogen) species; RPA, Replication protein A; SAR, Systemic acquired resistance; SASP, Senescence-associated secretory phenotype; SCC, Squamous cell carcinoma; Ser, Serine; SIR, Senescence inflammatory response; SLE, Systemic lupus erythematosus; SLX4, Synthetic lethal X (ohunknown function) 4; SSA, Single-strand annealing; SSB, Single-strand break; ssDNA, Single-stranded DNA; STAT, Signal transducer activator of transcription; STING, Stimulator of IFN genes (also known as MITA); TAMs, Tissue-associated macrophages; TBK1, TANK-binding kinase 1; TBK1/IRF, TANK-binding kinase 1/Interferon regulatory factor; TC-NER, Transcription-coupled NER; TCR, T cell receptor; TGFβ1, Transforming growth factor β1; T_h1,2, T helper 1,2; Thr, Threonine; TILs, Tumor-infiltrating lymphocytes; TLR, Toll-like receptors; TLS, Translesion synthesis; TNFα, Tumor necrosis factor alpha; TNM, Tumor, node, metastasis; TopBP1, DNA topoisomerase 2-binding protein 1; T_{reg}, Regulatory T cells; Trex1, Three prime repair exonuclease 1; TS, Template switching; UICC, Union for International Cancer Control; ULBP1-6, UL-binding protein 1-6; UTR, Untranslated region; UV, Ultraviolet; VEGF, Vascular endothelial growth factor; Vpr, Viral protein R; WRN, Werner syndrome helicase; XRCC1, X-ray repair complementing defective repair in Chinese hamster cells 1; XRCC5/Ku80, X-ray repair complementing defective repair in Chinese hamster cells 5; XRCC6/Ku70, X-ray repair complementing defective repair in Chinese hamster cells 6.

* Corresponding author at: Department of Histology–Embryology, School of Medicine, National Kapodistrian University of Athens, 75 Mikras Asias Str., Goudi, GR-11527 Athens, Greece. Tel.: +30 210 7462352; fax: +30 210 7462340.
E-mail addresses: vgorg@med.uoa.gr, vgorgoulis@gmail.com (V.G. Gorgoulis).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.pharmthera.2015.06.011
0163-7258/

Σας Ευχαριστώ