Inflammation and Cancer

Inflammation and Cancer: *An Ancient Link with Modern Evidence*

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Inflammation and Cancer

INFLAMMATION AND CANCER

PubMed Search Oct 11, 2016
Inflammation & cancer= 37,201 articles
published in the last 10 years

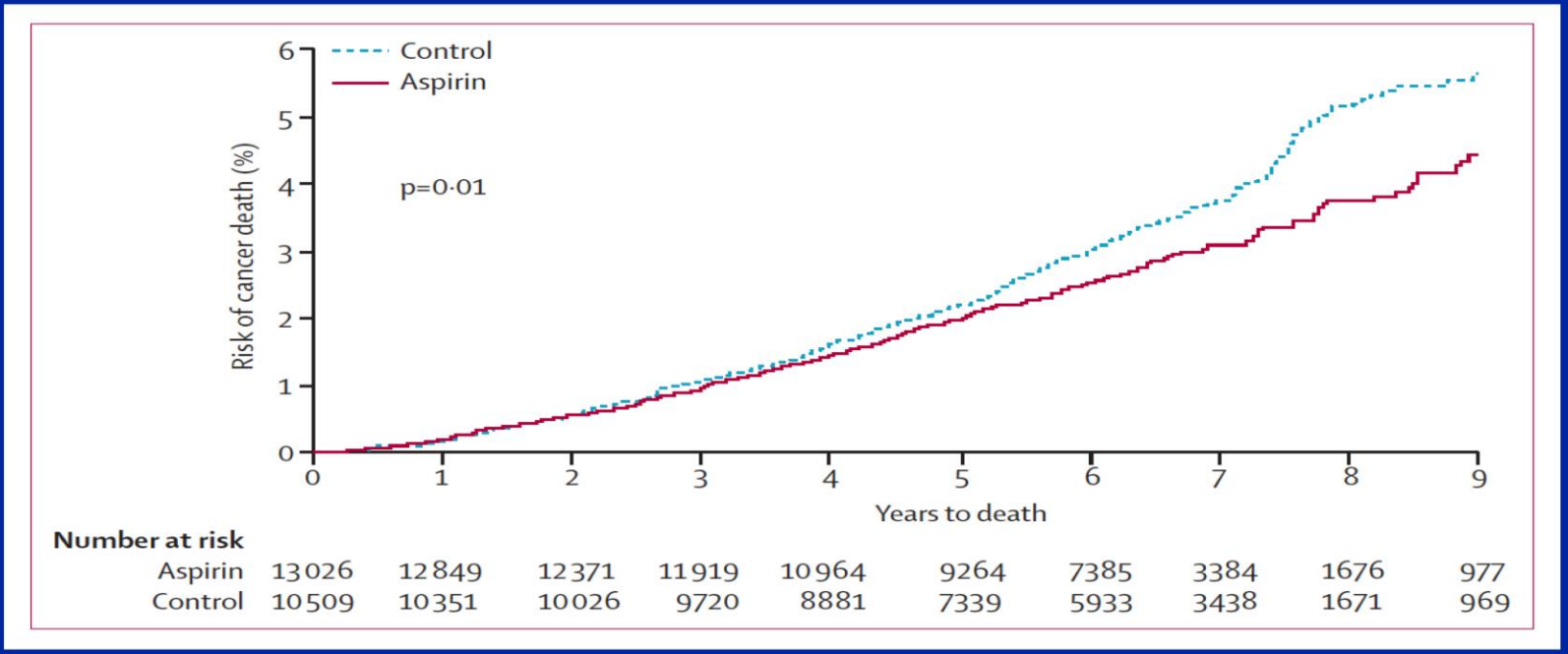
In 1863 Rudolf Virchow noted leucocytes in neoplastic tissues and made a connection between inflammation and cancer.

Recent Evidence have supported Virchow's hypothesis, and the links between inflammation and cancer may have potential implications in prevention and treatment.

Balkwill & Montovani; Lancet, 357; 2001

Aspirin Use

Aspirin Use Reduced Risk of Cancer Deaths



Rothwell PM et al., Lancet, 377, 2011

Chronic Inflammation and Infection

CHRONIC INFLAMMATION AND INFECTION CAN INCREASE CANCER RISK

Inherited

Disease	Tumor Site	Risk
Hemochromatosis	Liver	219
Hereditary Pancreatitis	Pancreas	53
Ulcerative Colitis	Colon	6
Crohn's Disease	Colon	3

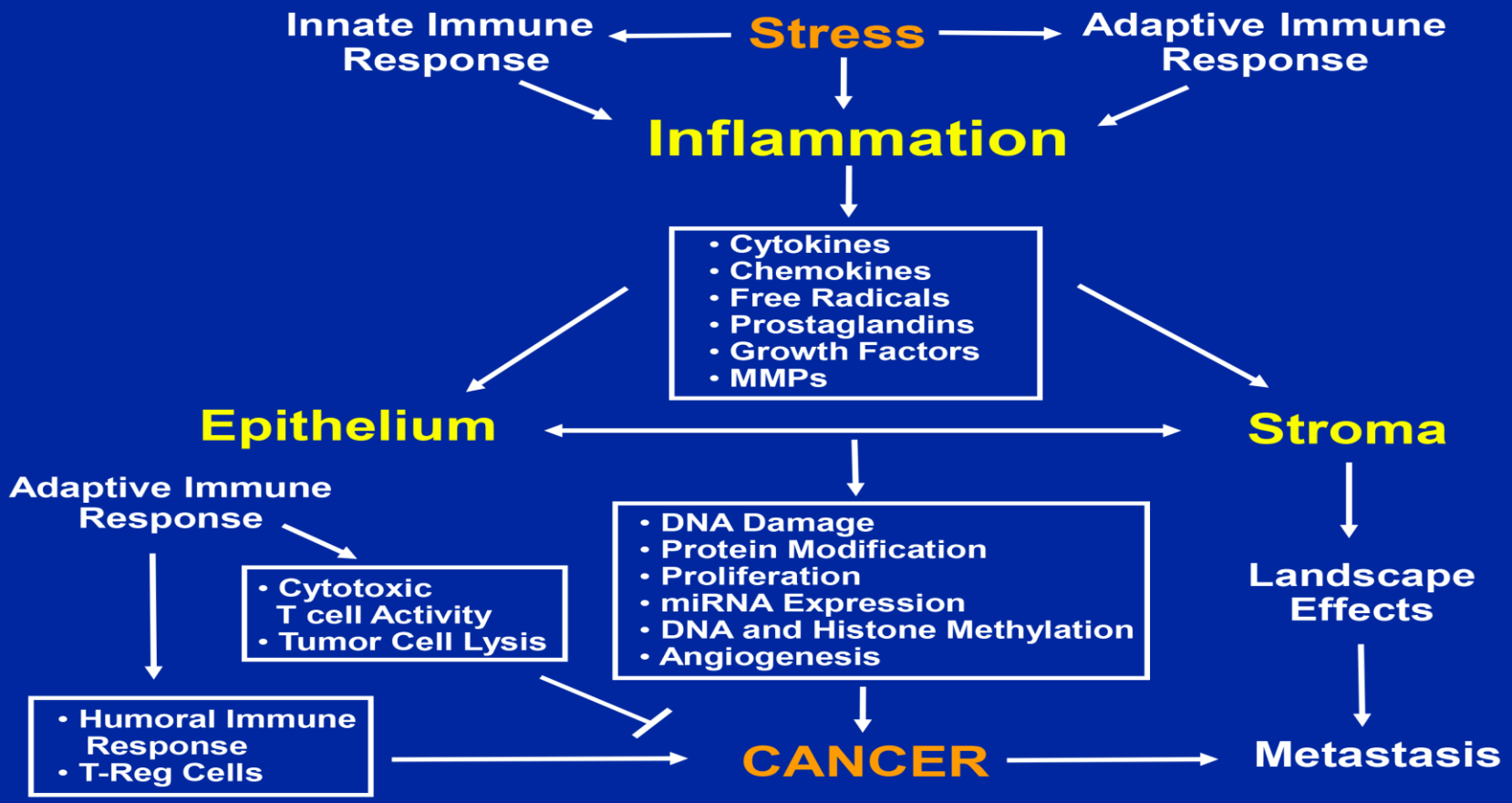
"18% of human cancers, i.e., 1.6 million per year, are related to infection."

Acquired

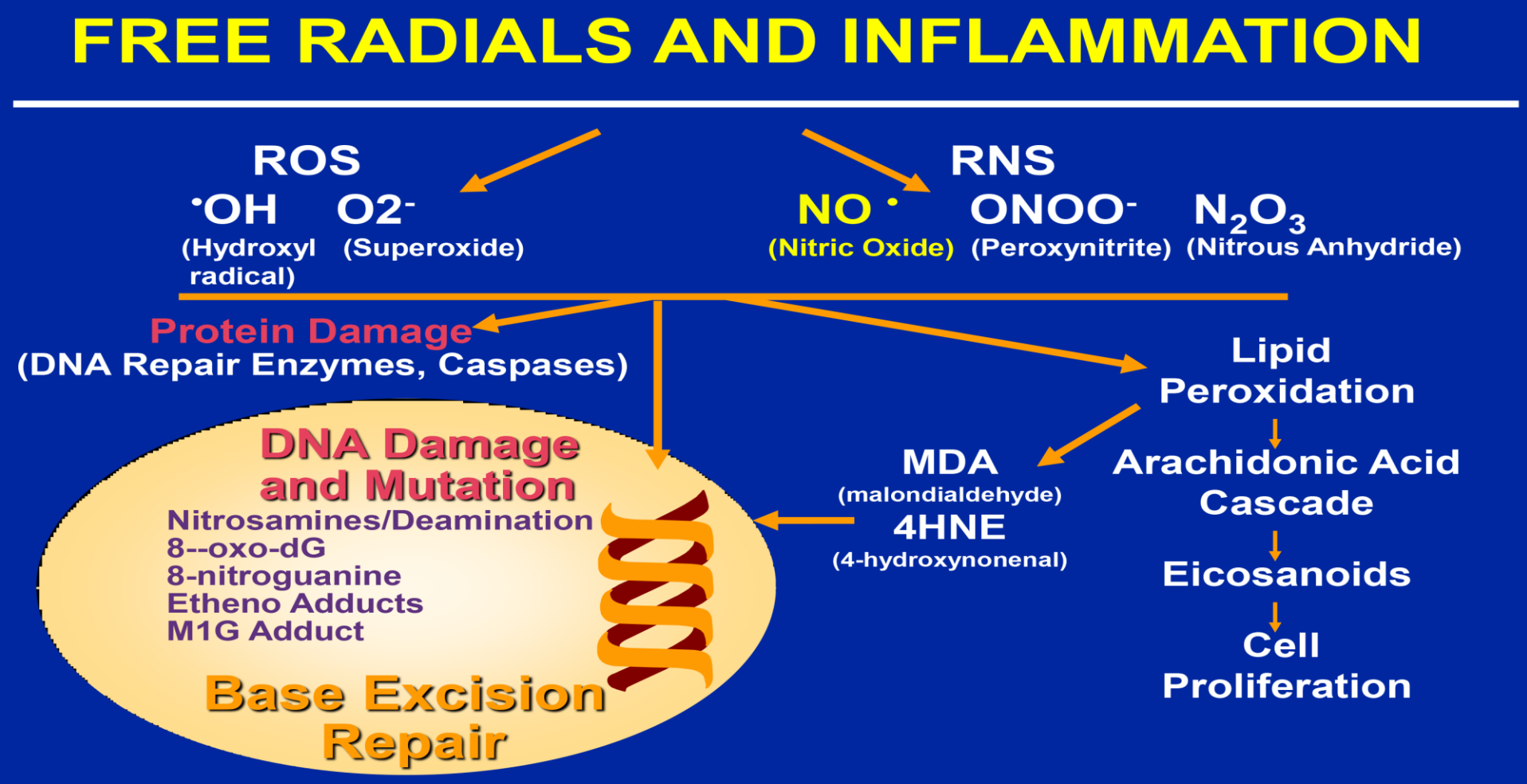
Disease	Tumor Site	Risk
Viral		
Hepatitis B	Liver	88
Hepatitis C	Liver	30
Bacterial		
Helicobacter Pylori	Gastric	11
PID	Ovary	3
Parasitic		
S. hematobium	Urinary Bladder	2-14
S. japonicum	Colon	2-6
Liver Fluke	Liver	14
Chemical/ Physical/Metabolic		
Acid reflux	Esophagus	50-100
Pancreatitis	Pancreas	17
Asbestos	Lung pleural	>10
Obesity	Multiple sites	1.3-6.5

Hussain, S.P., et al., *Nature Rev. Cancer*, 3, 276-285, 2003

Stress and Inflammation

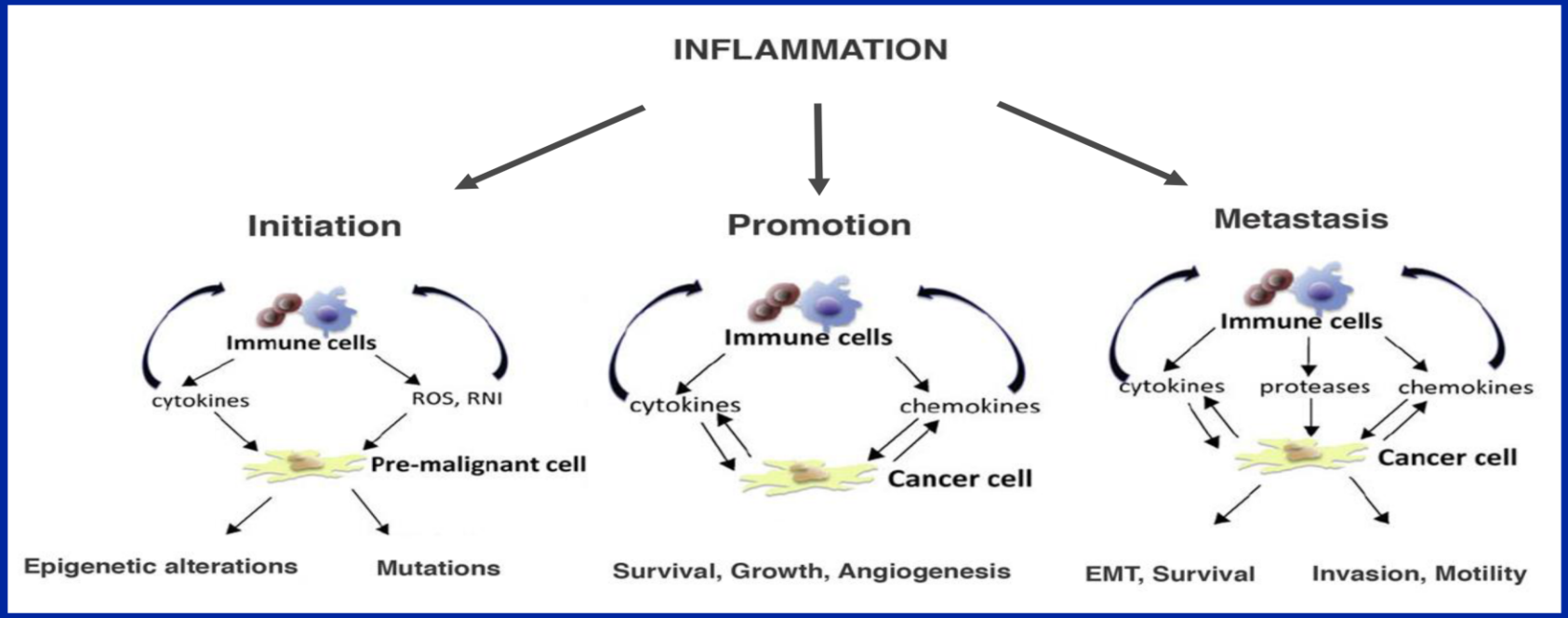


Free Radials and Inflammation



Tumorigenesis

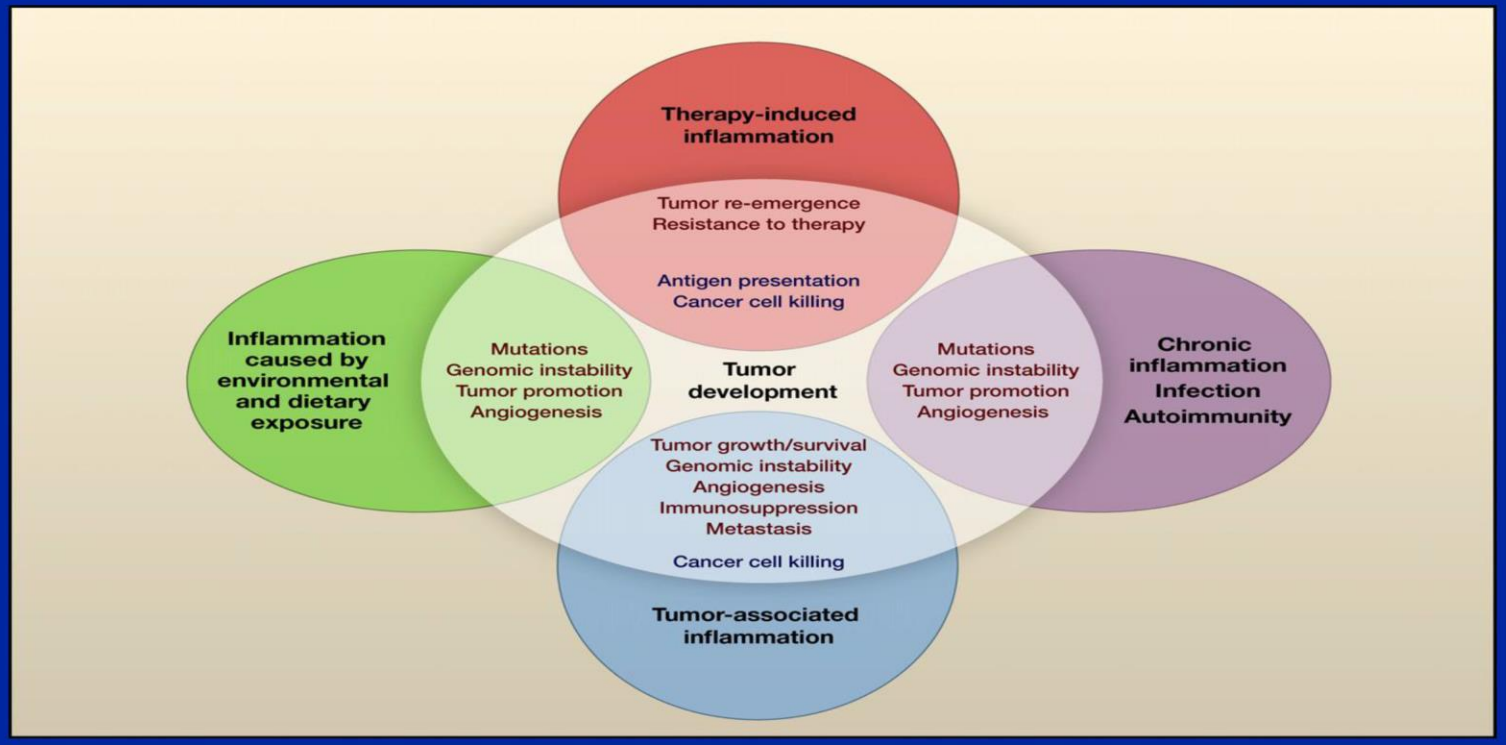
Inflammation Contributes to Various Stages of Tumorigenesis



Grivennikov and Karin, Curr. Opinion in Genet. Dev., 2010

Inflammation Types

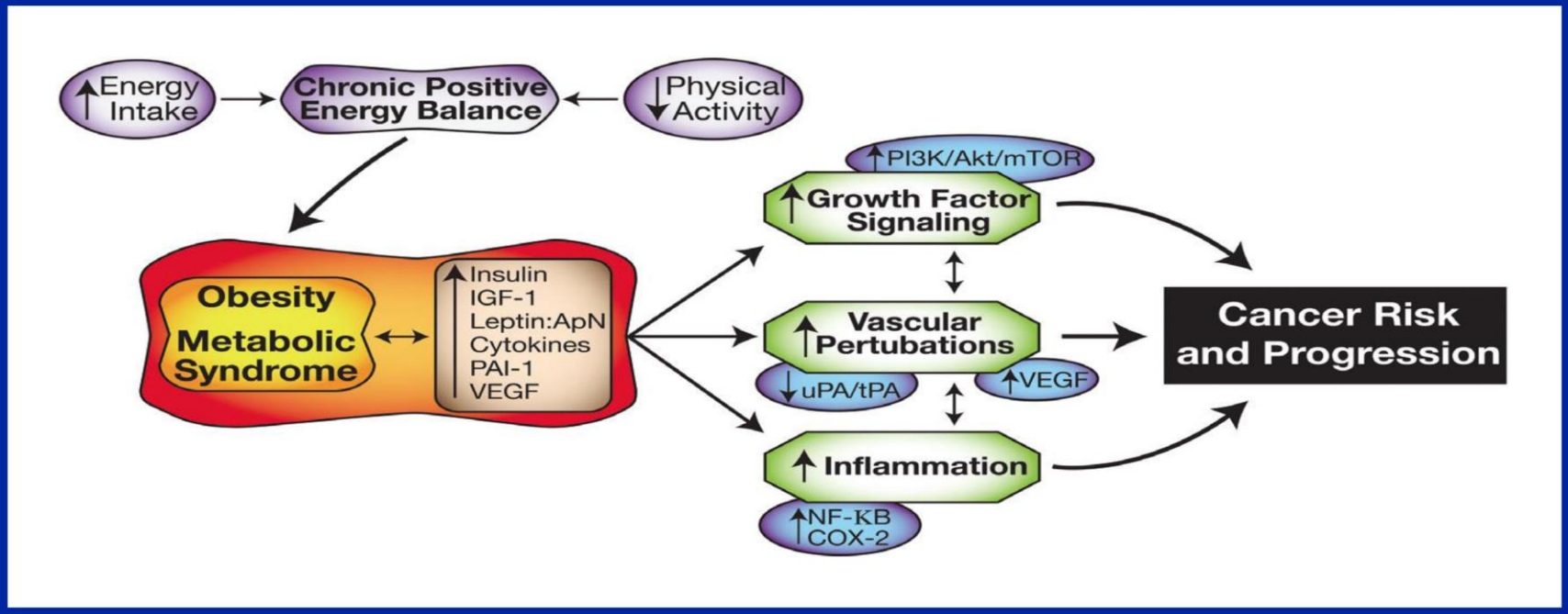
Types of Inflammation in Tumorigenesis and Cancer



Grivennikov, Greten and Karin, Cell, 140, 2010

Obesity, Metabolic Syndrome and Cancer

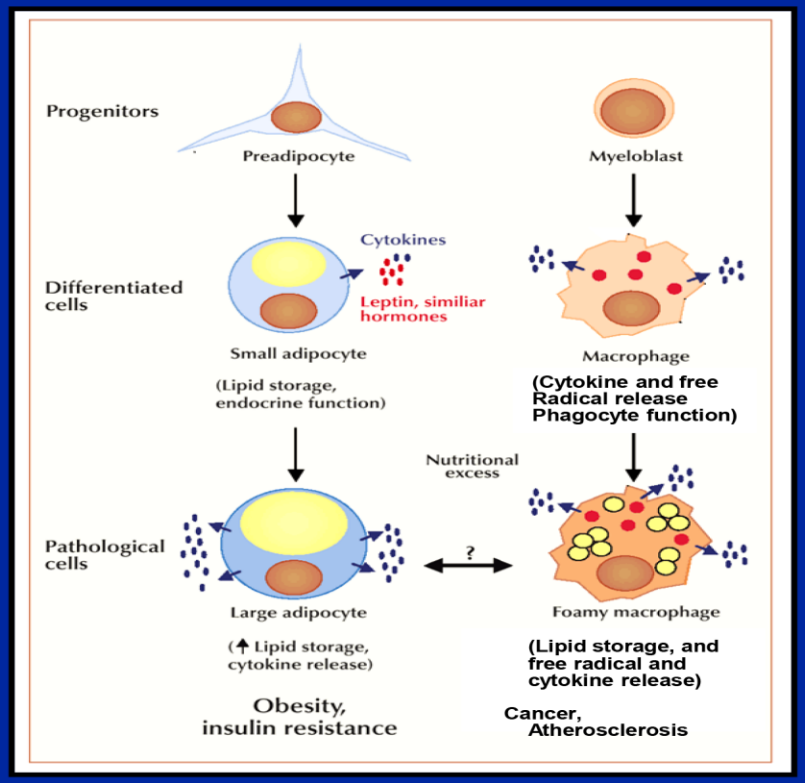
Obesity, Metabolic Syndrome and Cancer



Hursting and Hursting, *Arterioscler. Vasc. Biol., 2012*

Macrophage and Adipocyte Functions

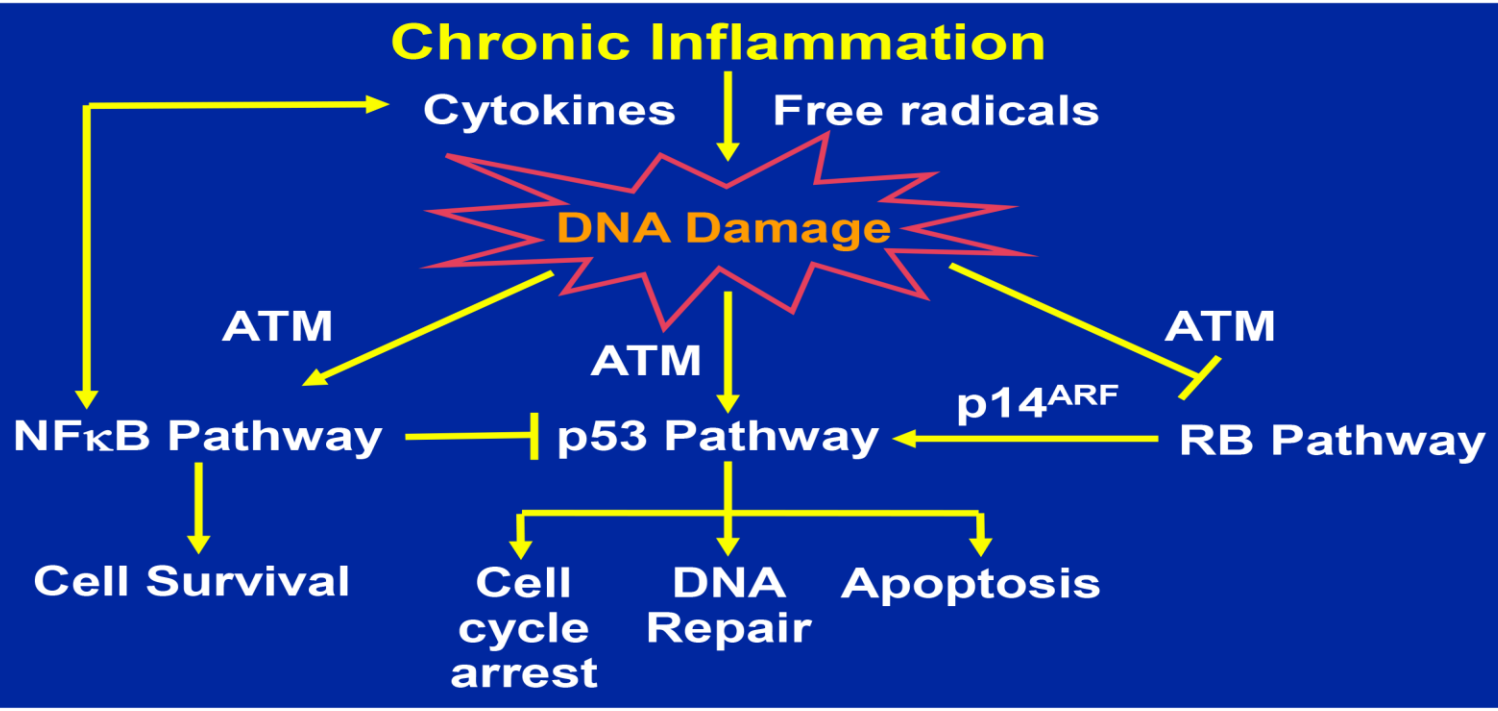
CONVERGENCE OF MACROPHAGE AND ADIPOCYTE FUNCTIONS IN OBESITY AND METABOLIC SYNDROME



M Lehrke and Lazar MA, Nature Medicine,10: 126, 2004

Chronic Inflammation

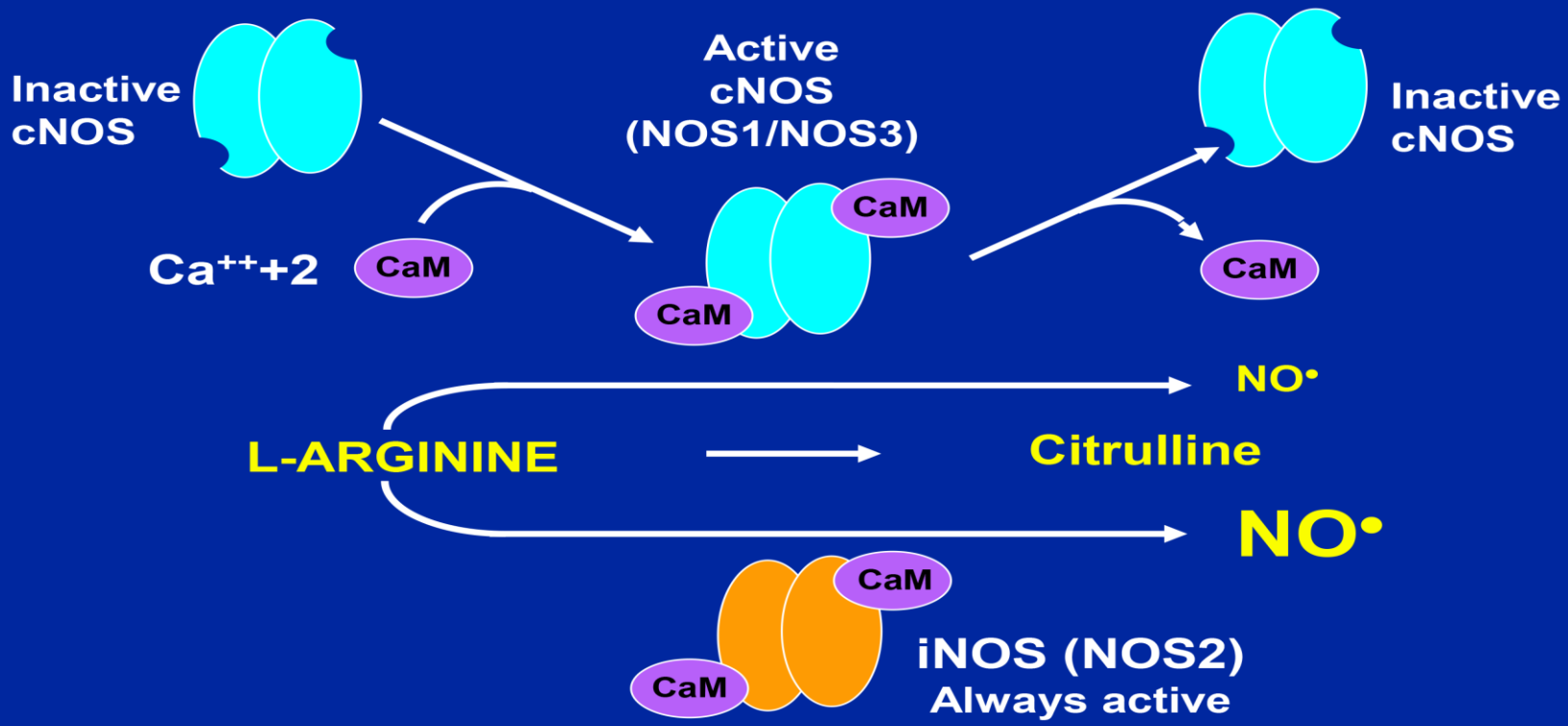
CHRONIC INFLAMMATION AFFECTS MULTIPLE PATHWAYS



Hussain, Hofseth and Harris., *Nature Rev. Cancer*, 3, 276-285, 2003

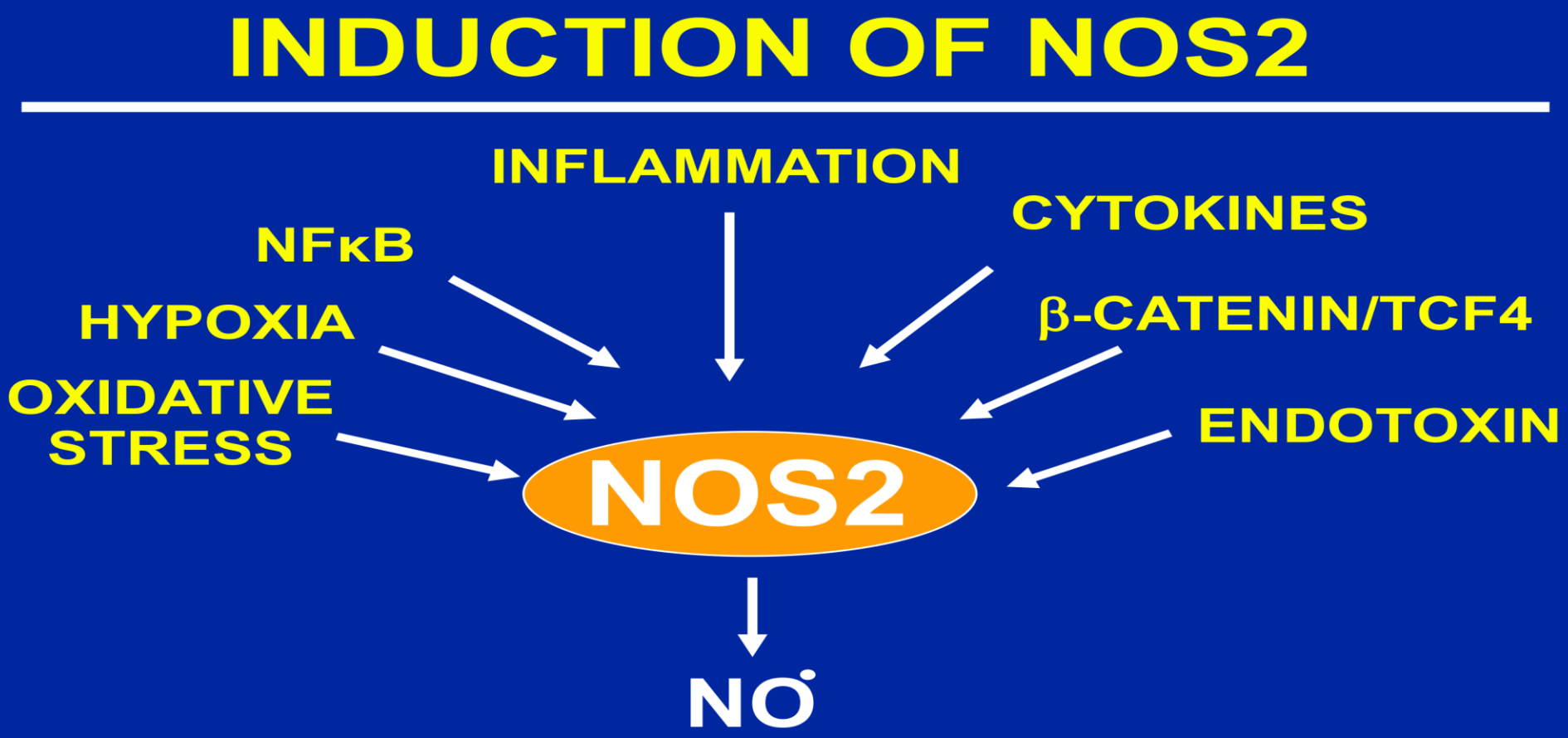
Nitric Oxide Synthase

NITRIC OXIDE SYNTHASE



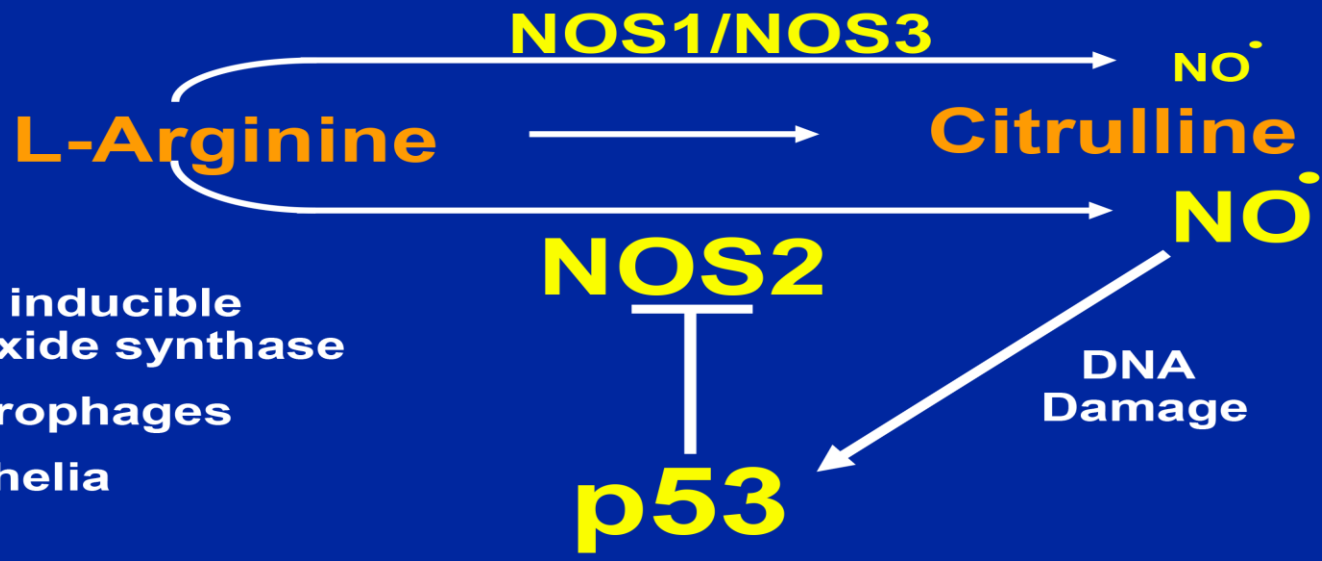
Billiar

NOS2 Induction



p53 Transrepresses NOS2

p53 TRANSREPRESSES NOS2: EXAMPLE OF p53 NEGATIVE FEEDBACK LOOP



- NOS2 - inducible nitric oxide synthase
  - Macrophages
  - Epithelia

Forrester et al., PNAS 93: 2442, 1996
Ambs et al., PNAS 95: 8823, 1998

Ulcerative Colitis Colon

ULCERATIVE COLITIS COLON

Normal

UC Lesions

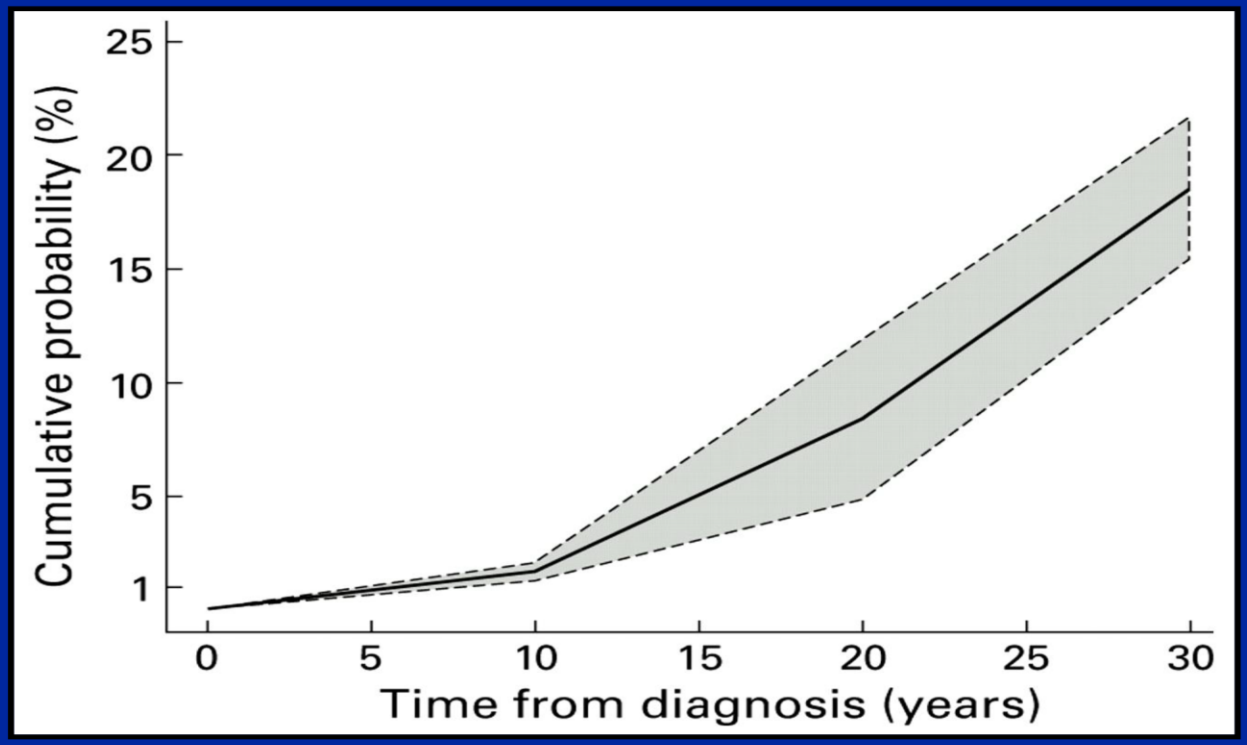
Ulceration

UC Cancer

Cancer

Colorectal Cancer and Ulcerative Colitis

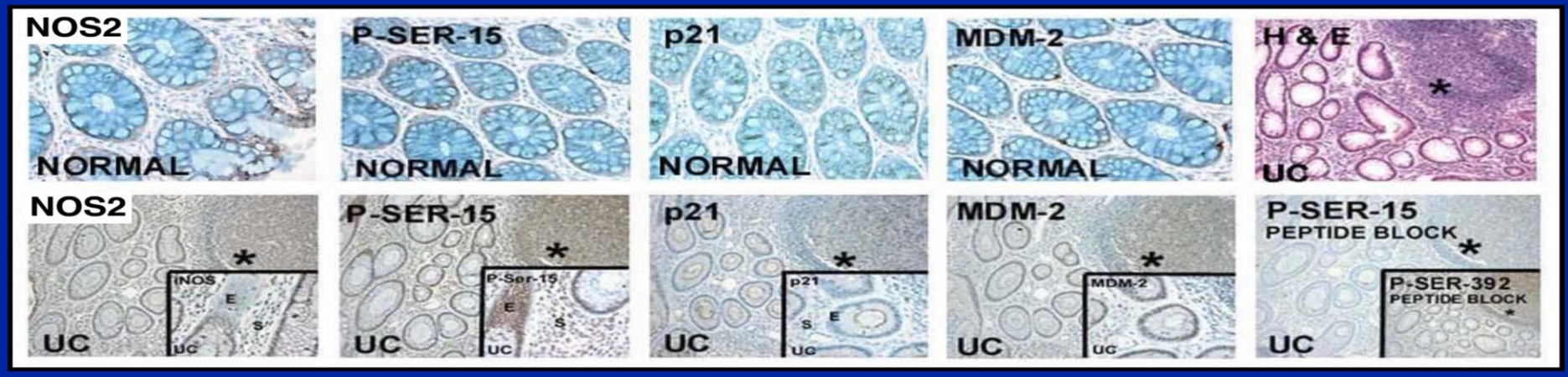
CUMULATIVE RISK OF DEVELOPING COLORECTAL CANCER FOR A PATIENT WITH ULCERATIVE COLITIS



JA Eaden et al., Gut, 48: 526, 2001

NOS2 Expression

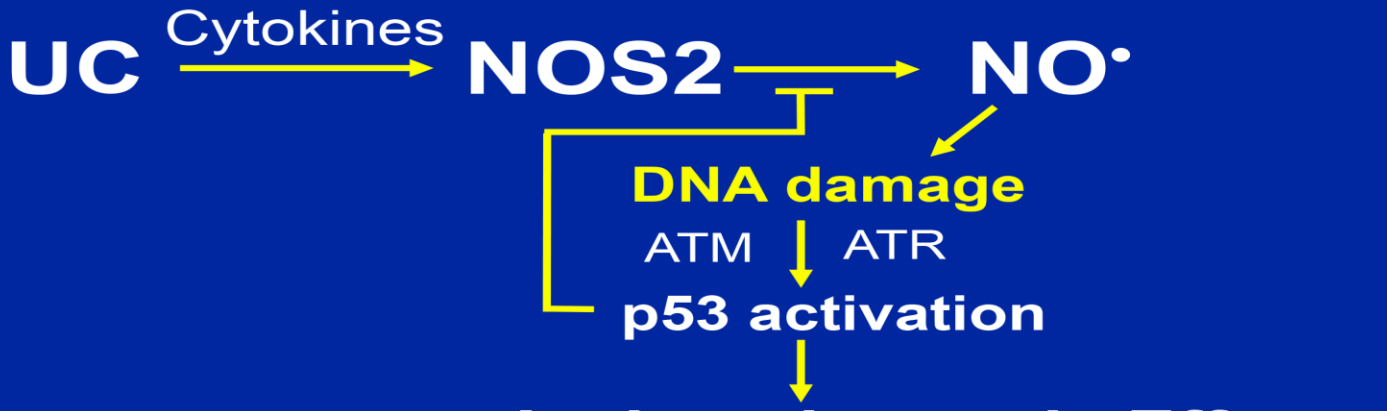
NOS2 EXPRESSION CORRELATES WITH p53 SER15 PHOSPHORYLATION AND EXPRESSION OF p21 and MDM2 IN ULCERATIVE COLITIS



Hofseth et al., PNAS, 2003

Nitric Oxide

NITRIC OXIDE CAN ACTIVATE THE PROTECTIVE p53 STRESS RESPONSE PATHWAY



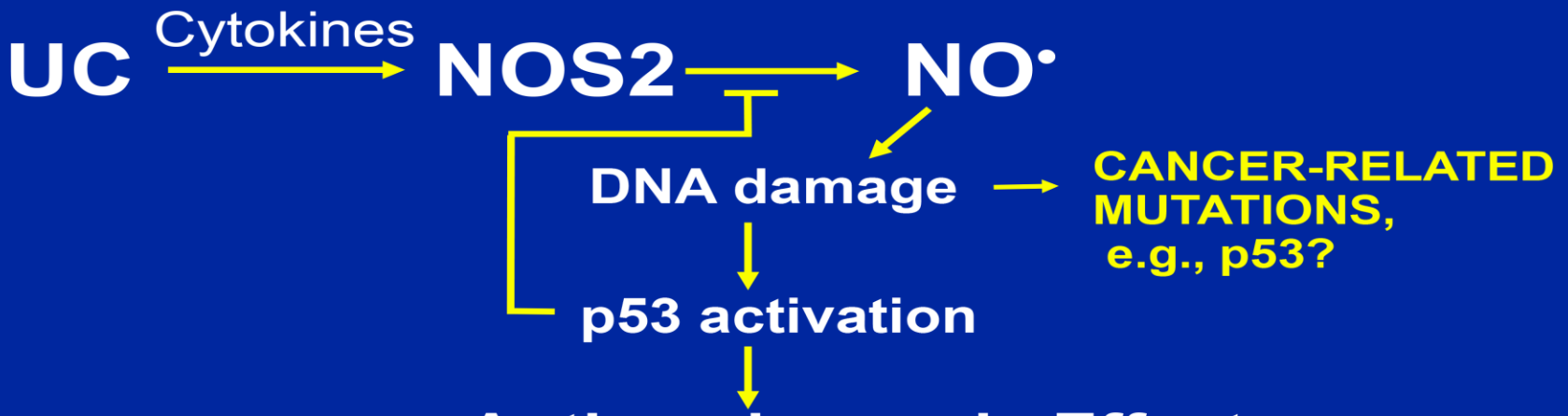
Anticarcinogenic Effects

- Growth arrest
- DNA repair
- Apoptosis
- Anti-oxidative and -nitrosative stress*

* S. P. Hussain et. al., Cancer Res., 64, 2004

Hypothesis

HYPOTHESIS: NITRIC OXIDE AND OXYRADICALS ASSOCIATE WITH CANCER-RELATED MUTATIONS IN CHRONIC INFLAMMATORY DISEASES PRIOR TO CANCER



Anticarcinogenic Effects

- Growth arrest
- DNA repair
- Apoptosis
- Anti-oxidative and -nitrosative stress

p53 Mutation Load Assay: Hussain et al., PNAS 97: 12770, 2000

p53 Mutation

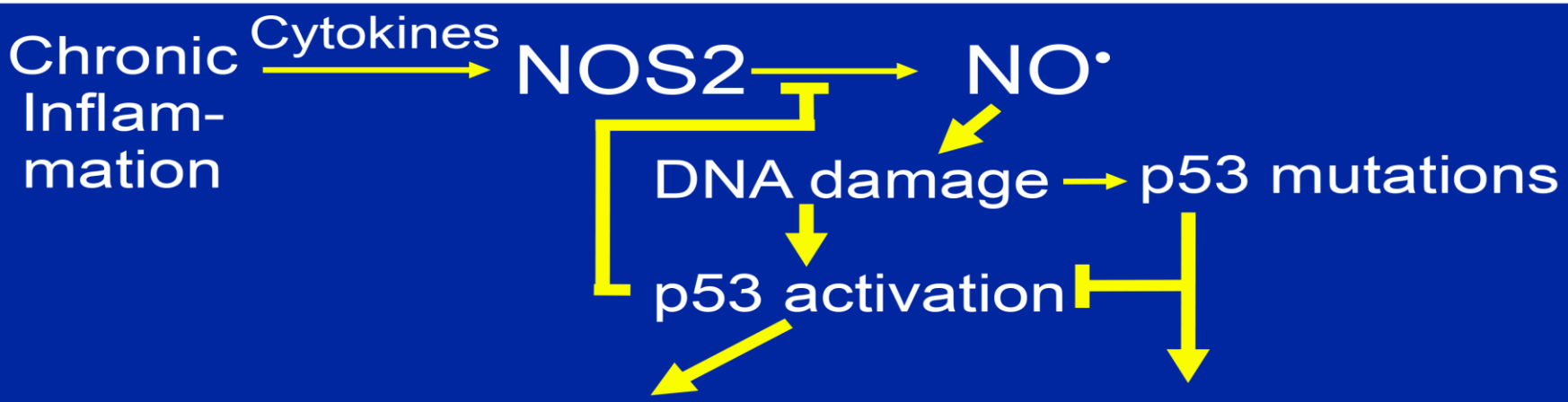
INCREASED TISSUE p53 MUTATION LOAD IN CHRONIC INFLAMMATORY AND OXYOVERLOAD CONDITIONS

- Ulcerative Colitis
- Hemochromatosis
- Wilson Disease
- Lungs from Tobacco Smokers
- Chronic Pancreatitis ?

Hussain et al., Cancer Res. 60: 333, 2000
Hussain et al., Proc. Natl. Acad. Sci. 97: 12770, 2000
Hussain et al., Cancer Res. 61: 6350, 2001
Hagiwara et al., Cancer Res., 66:8309, 2006

Stress Response Pathway

NITRIC OXIDE CAN ACTIVATE THE PROTECTIVE p53 STRESS RESPONSE PATHWAY AND INDUCE ONCOGENIC p53 MUTATIONS

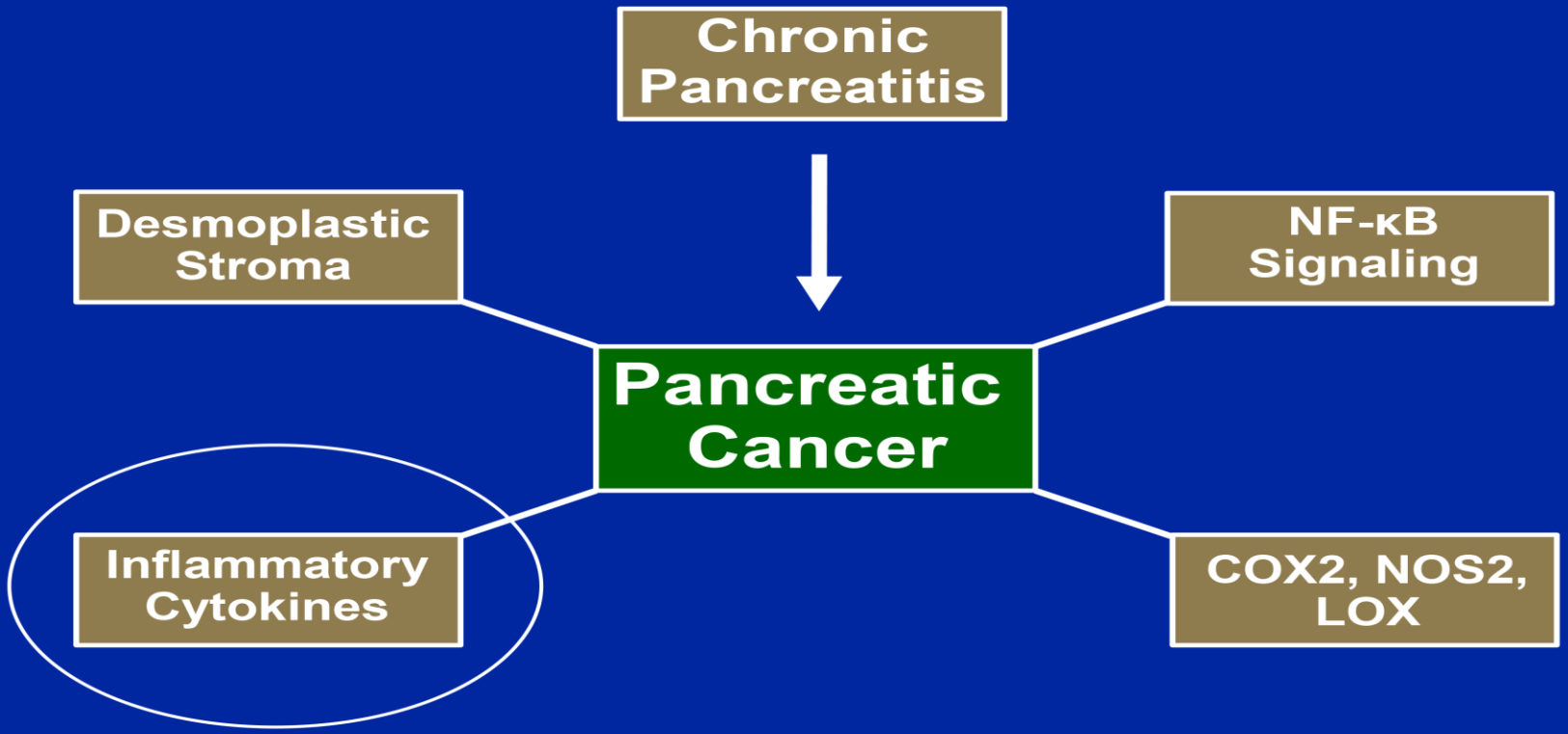


Anti-carcinogenic Effects
- Growth arrest
- DNA repair
- Apoptosis
- Anti-oxidative and -nitrosative stress

Pro-carcinogenic Effects
- Genomic instability
- Decrease cell cycle checkpoints, apoptosis and DNA repair
- Pro-oxidant and -nitrosative stress

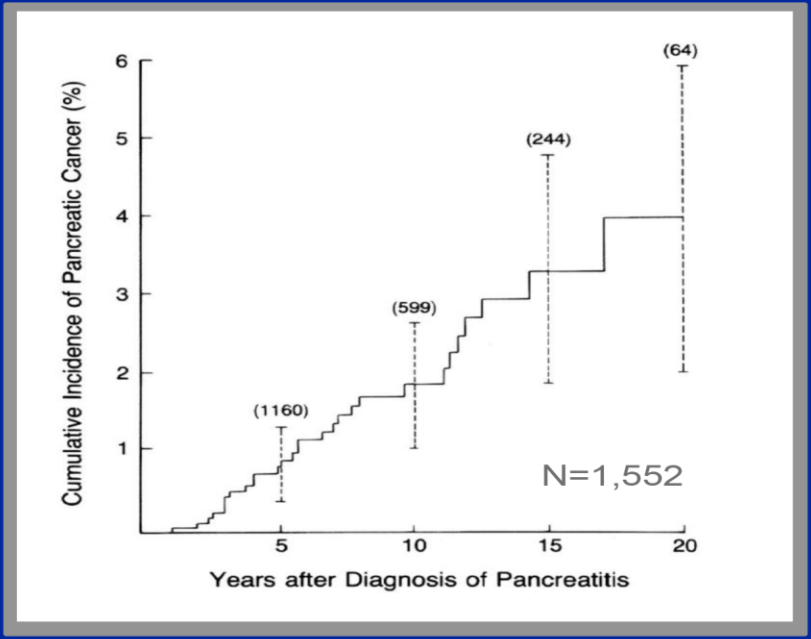
Inflammation and Pancreatic Cancer

Inflammation and Pancreatic Cancer



Chronic Pancreatitis

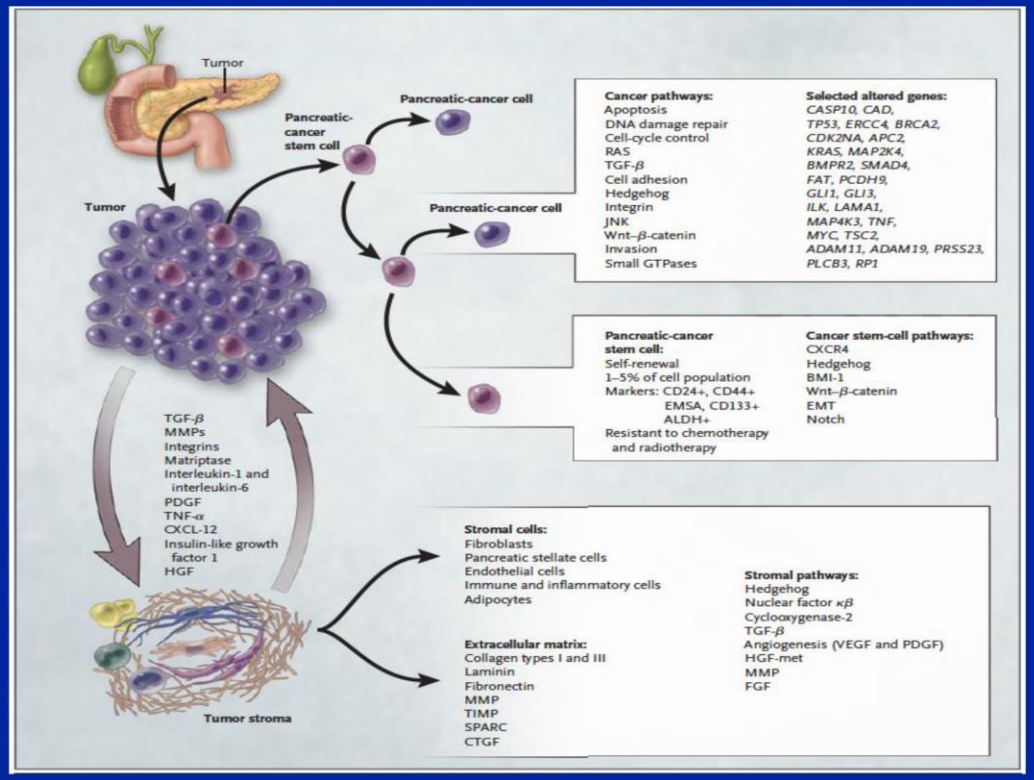
Increased Risk of Pancreatic Cancer in Patients with Chronic Pancreatitis

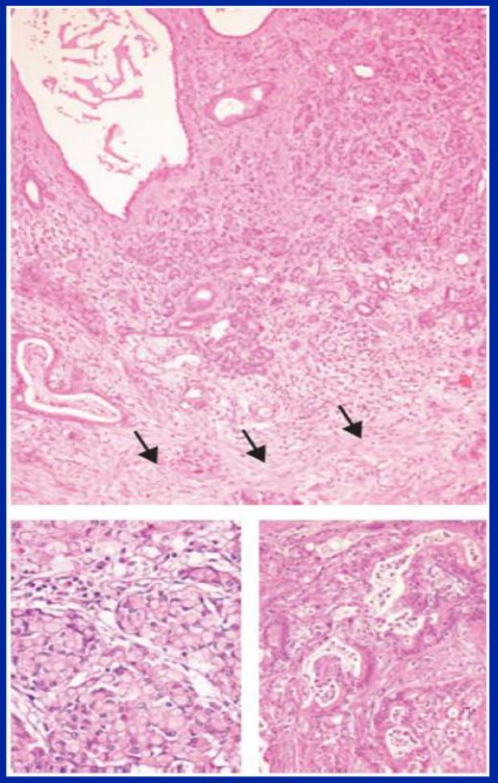


Lowenfels, A.B., et. al., NEJM, 328, 1993

Components of Pancreatic Cancer

COMPONENTS OF PANCREATIC CANCER



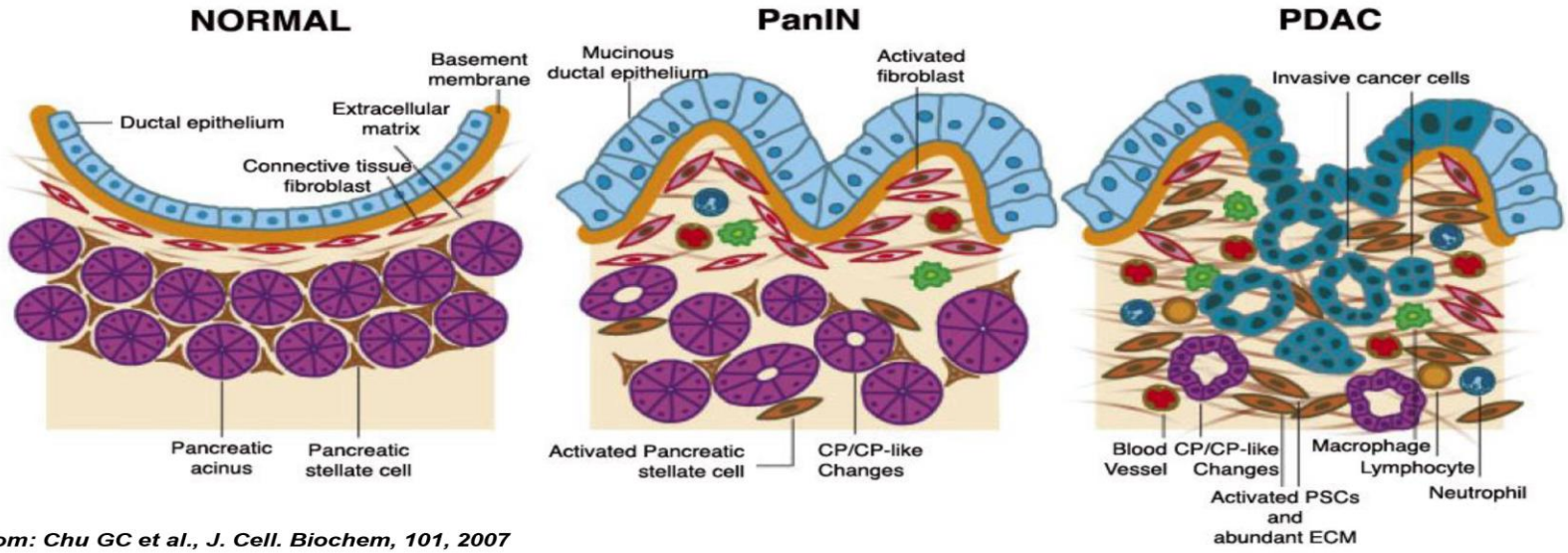


H/E

From: Hidalgo, M., *N Engl J Med, 2010*

Inflammatory Changes

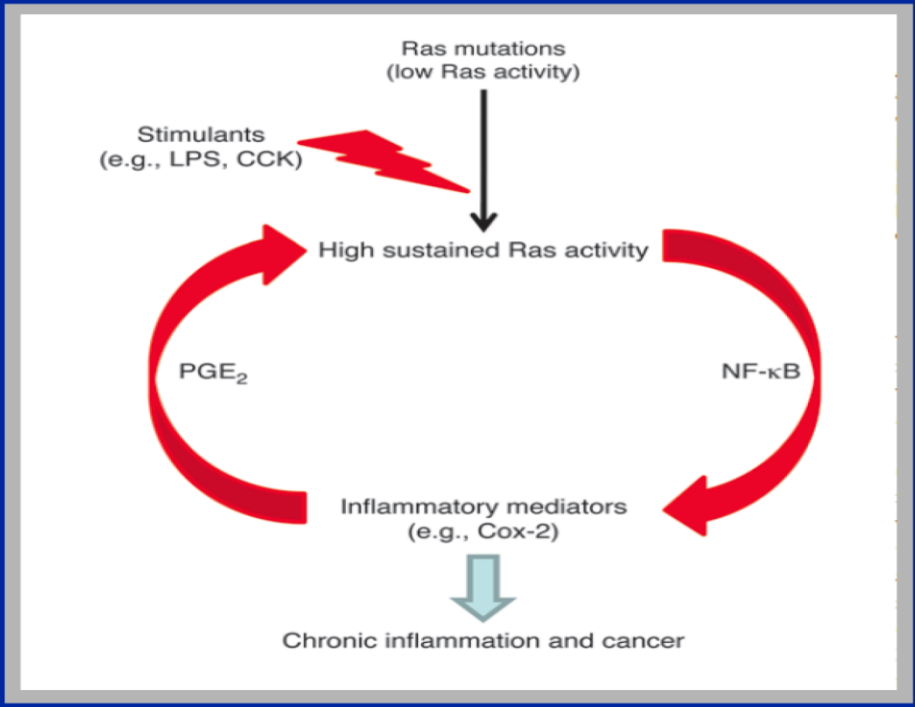
INFLAMMATORY CHANGES DURING DEVELOPMENT AND PROGRESSION OF PANCREATIC CANCER



From: Chu GC et al., J. Cell. Biochem, 101, 2007

Oncogenic KRAS

Inflammation enhances and maintains a pathologic level of oncogenic KRAS in pancreatic cancer



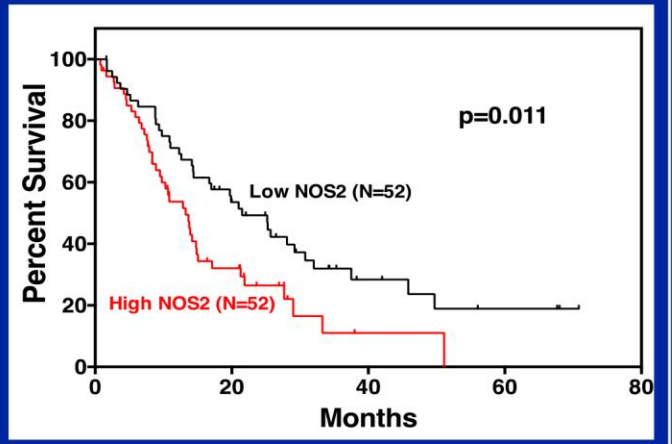
Daniluk et. al.,
JCI, 2012

NOS2 expression

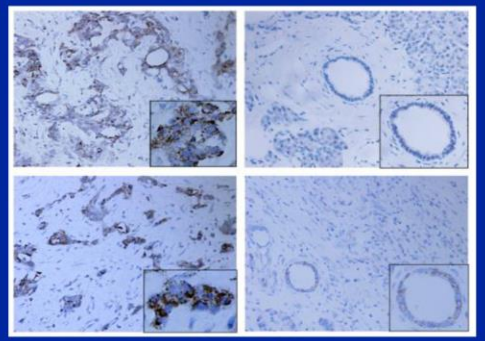
Increased NOS2 expression is associated with poor survival of resected pancreatic cancer patients (Stage I/II).

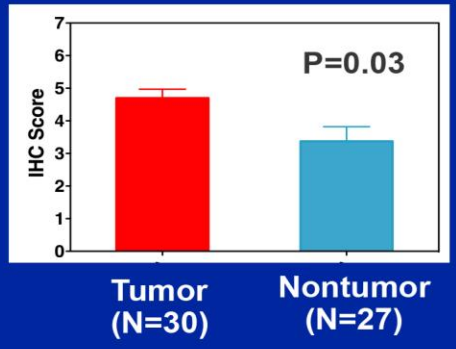
Human Pancreatic Ductal Adenocarcinoma

K/M Survival Curve



NOS2 (IHC)



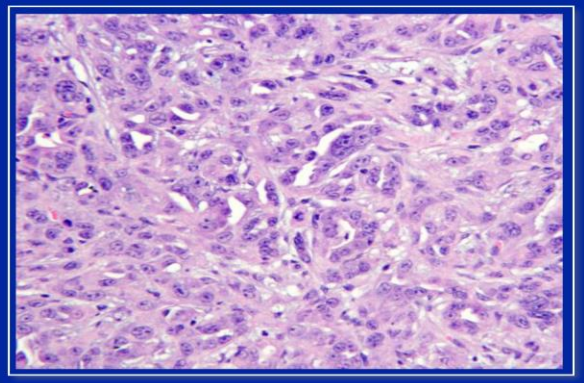


Pancreatic cancer mouse model

Genetically Engineered Mouse Model of Pancreatic Cancer

*LSL-Kras-G12D X p53 LSL R172H X Pdx-Cre 1 (KPC)

Pancreatic Ductal Adenocarcinoma (PDAC)
(Median Survival = 4-5 months)



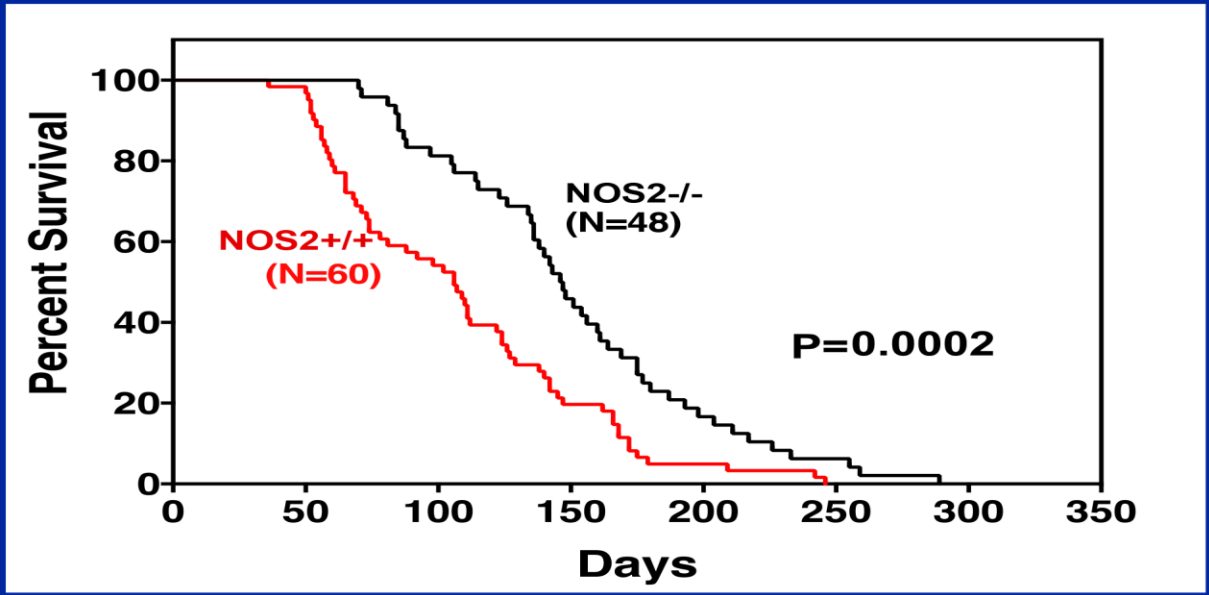
H/E

*Hingorani, S.R. et al., Cancer Cell, 2005

NOS2 knockout mouse

HYPOTHESIS: NO• Enhances Pancreatic Cancer Progression

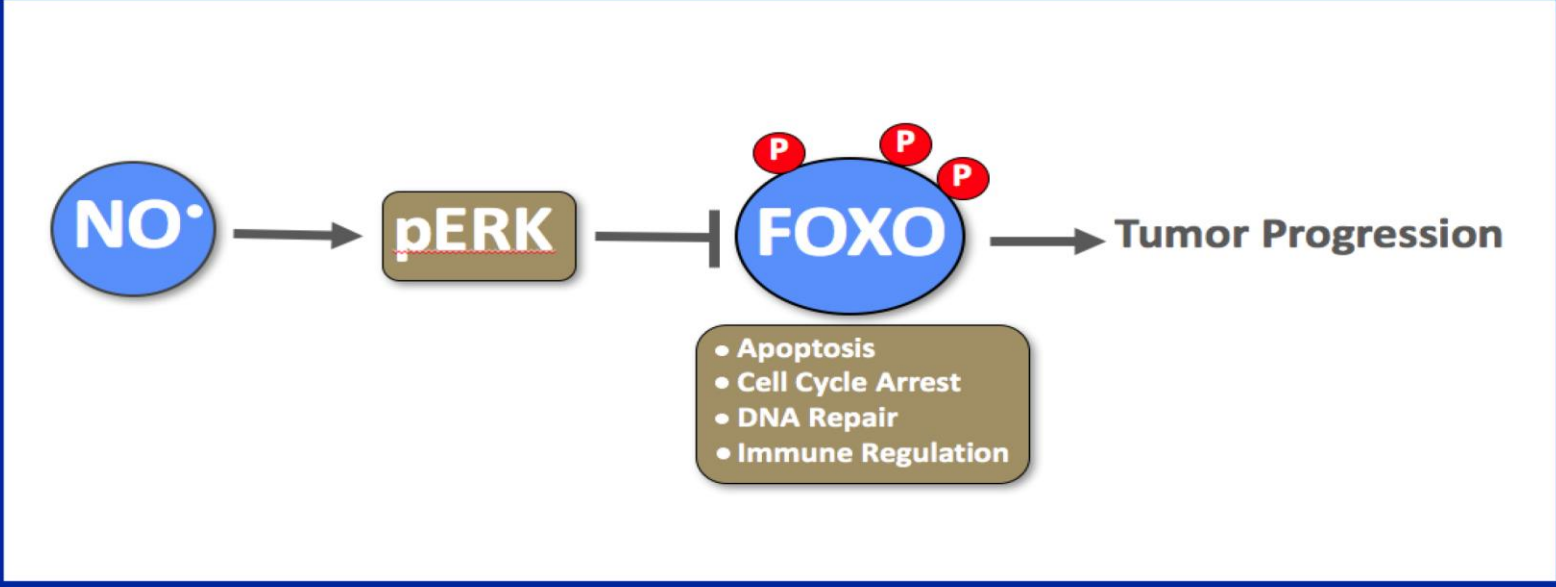
- NOS2-deficiency Enhances Survival in KPC Mice



NOS2 deletion in genetically engineered mouse model of pancreatic cancer

Nitric oxide and pancreatic cancer

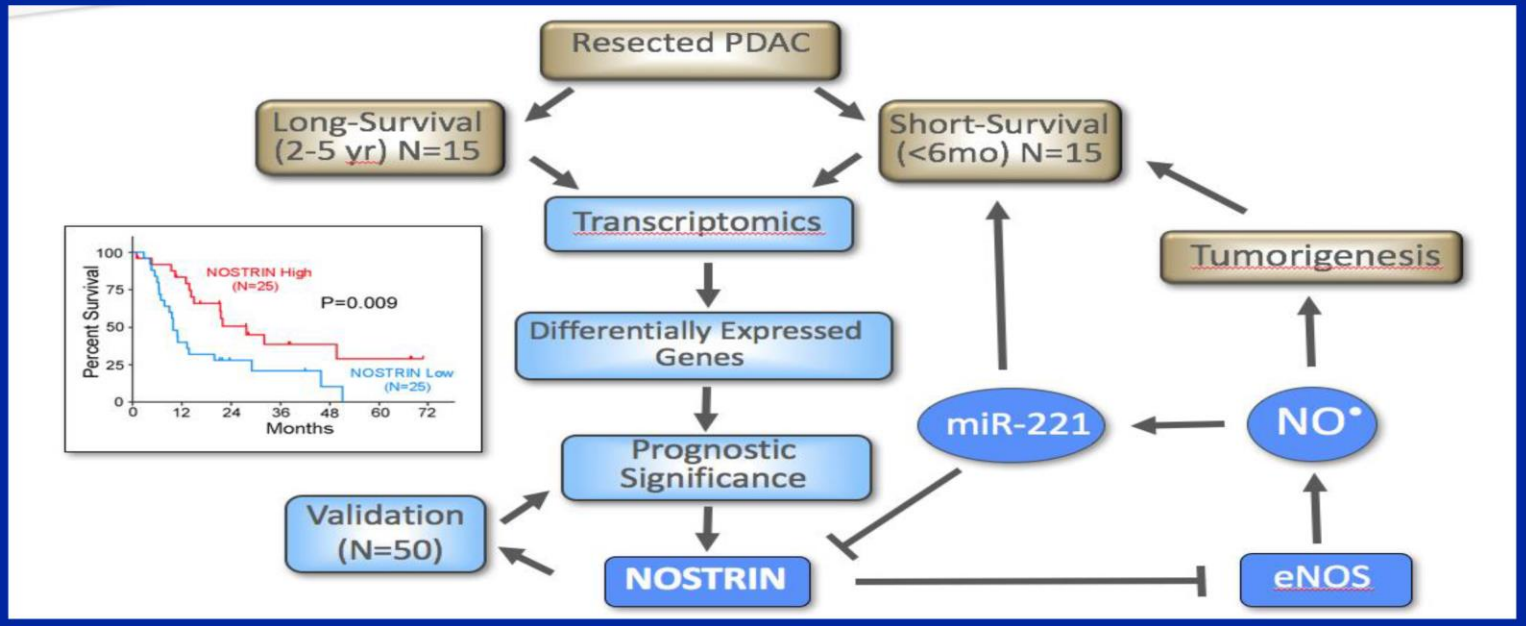
$NO^{\bullet}$ and Pancreatic Cancer



FOXO: Fork-head box transcription factor (subclass O)

Nostrin

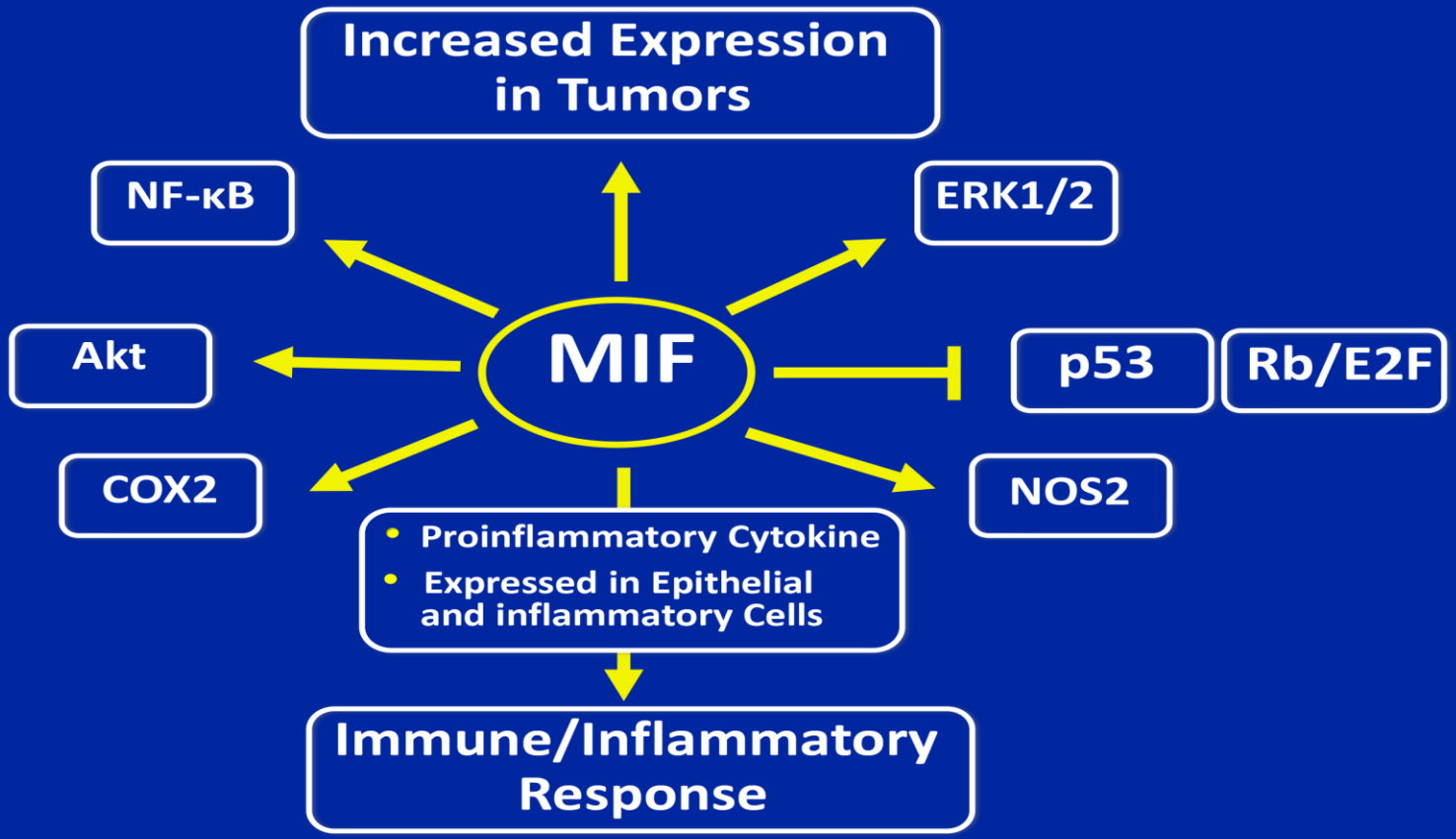
NOSTRIN is a Negative Regulator of Disease Aggressiveness



Wang, J. et. al., Clin Cancer Res., 2016

MIF

Macrophage Migration Inhibitory Factor (MIF)



MIF, Inflammation, and Cancer

MIF, Inflammation and Cancer

Immunity, 26, 2007

Perspective

Cell PRESS

Macrophage Migration Inhibitory Factor: A Probable Link between Inflammation and Cancer

Richard Bucala[1,*] and Seamas C. Donnelly[2,*]

The pleiotropic effects of macrophage migration inhibitory factor (MIF) place it in a central position in the immunopathogenesis of many diseases. Here we discuss the current understanding of MIF's role and highlight it as a potential link between inflammatory activation and malignant progression.

J. Exp. Med., 190, 1999

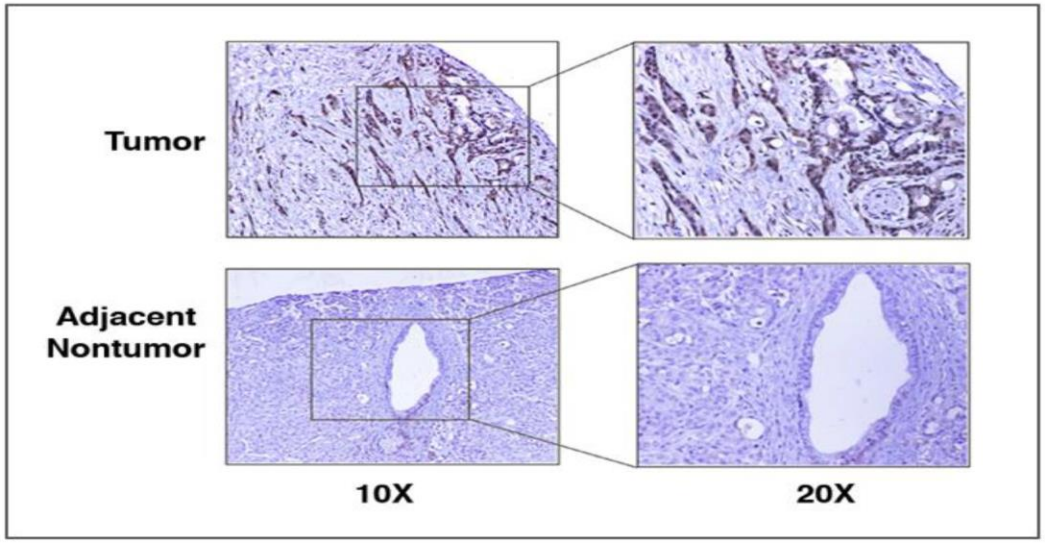
At the Crossroads of Inflammation and Tumorigenesis

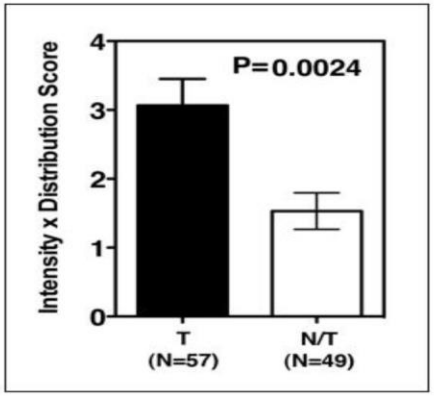
By Carlos Cordon-Cardo* and Carol Prives‡

*From the *Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021; and the ‡Department of Biological Sciences, Columbia University, New York, New York 10027*

MIF expression

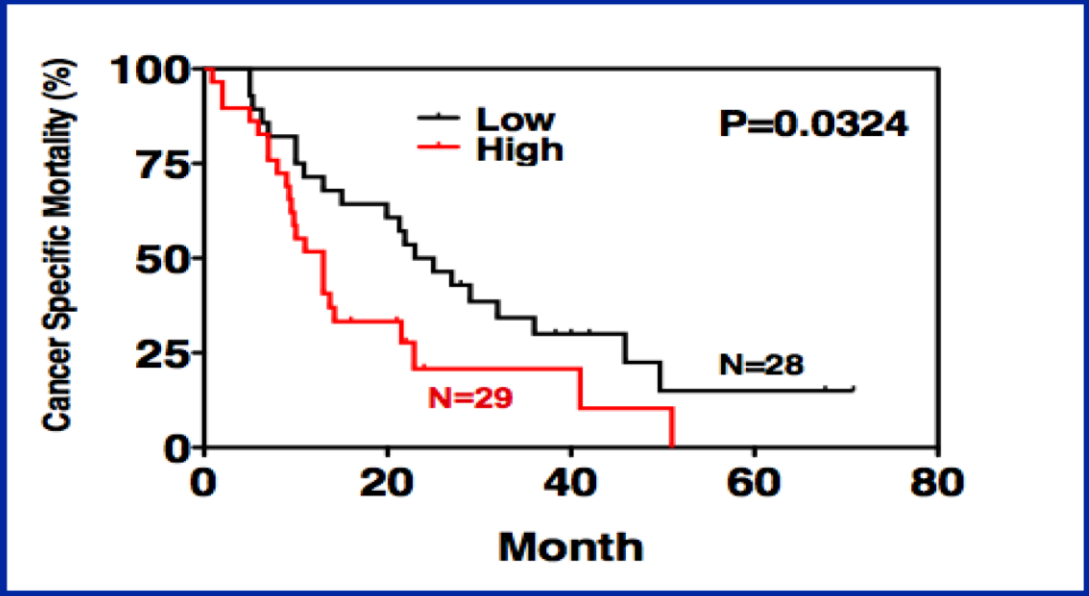
Increased expression of MIF in tumors from pancreatic ductal adenocarcinoma cases





Higher MIF Expression and PDAC

A Higher MIF Expression is Associated with Poorer Survival in Resected PDAC Cases

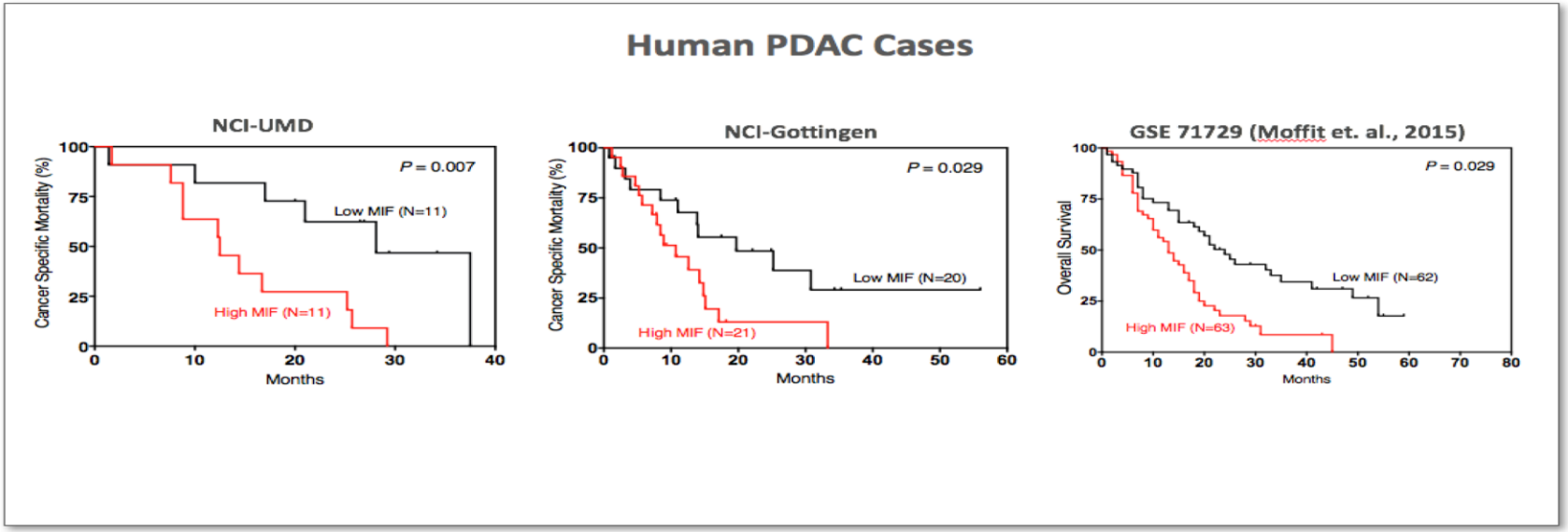


Funamizu et al., Int. J. Cancer , 2012

MIF expression

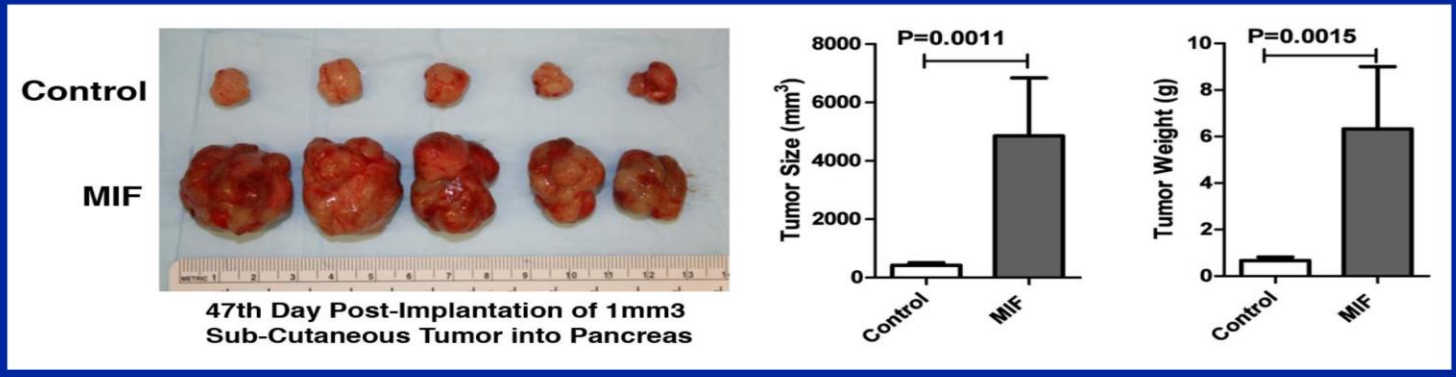
A higher expression of MIF is associated with poor survival in human PDAC

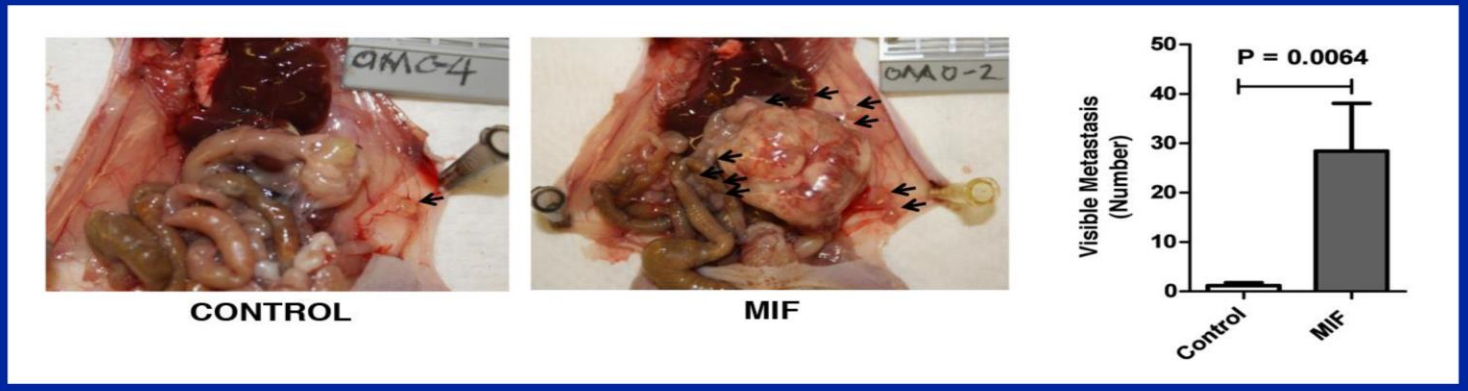
Validation in Independent Cohorts



MIF Overexpression

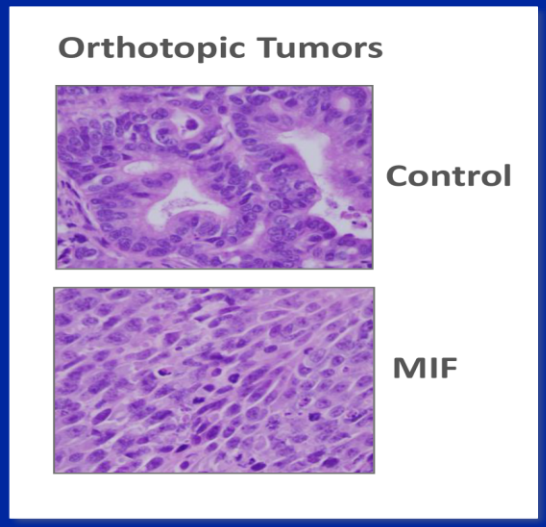
MIF-Overexpression Enhanced Tumor Growth and Metastasis in Orthotopic Mouse Model

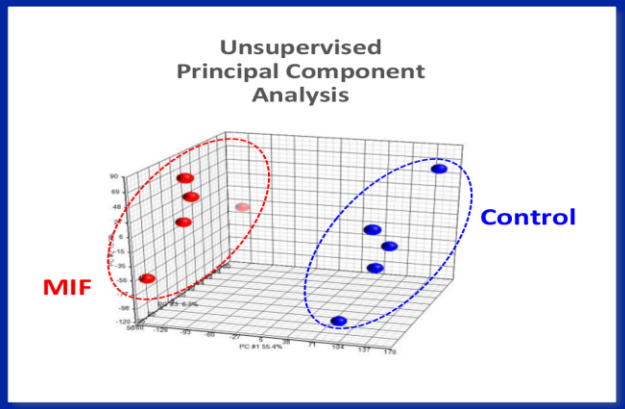


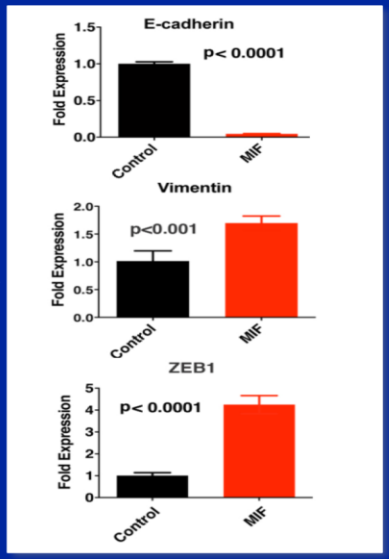


MIF and EMT-related genes

MIF Induces a Marked Change in Global Gene Expression Profile including EMT-related Genes in Orthotopic Tumors







- MIF over-expressing tumors are poorly differentiated.
- MIF induces a change in global gene expression profile.
- MIF over-expressing tumors showed expression of EMT-related genes.

MIF and liver metastasis

Exosomal MIF Enhances Liver Metastasis in PDAC

ARTICLES

nature cell biology

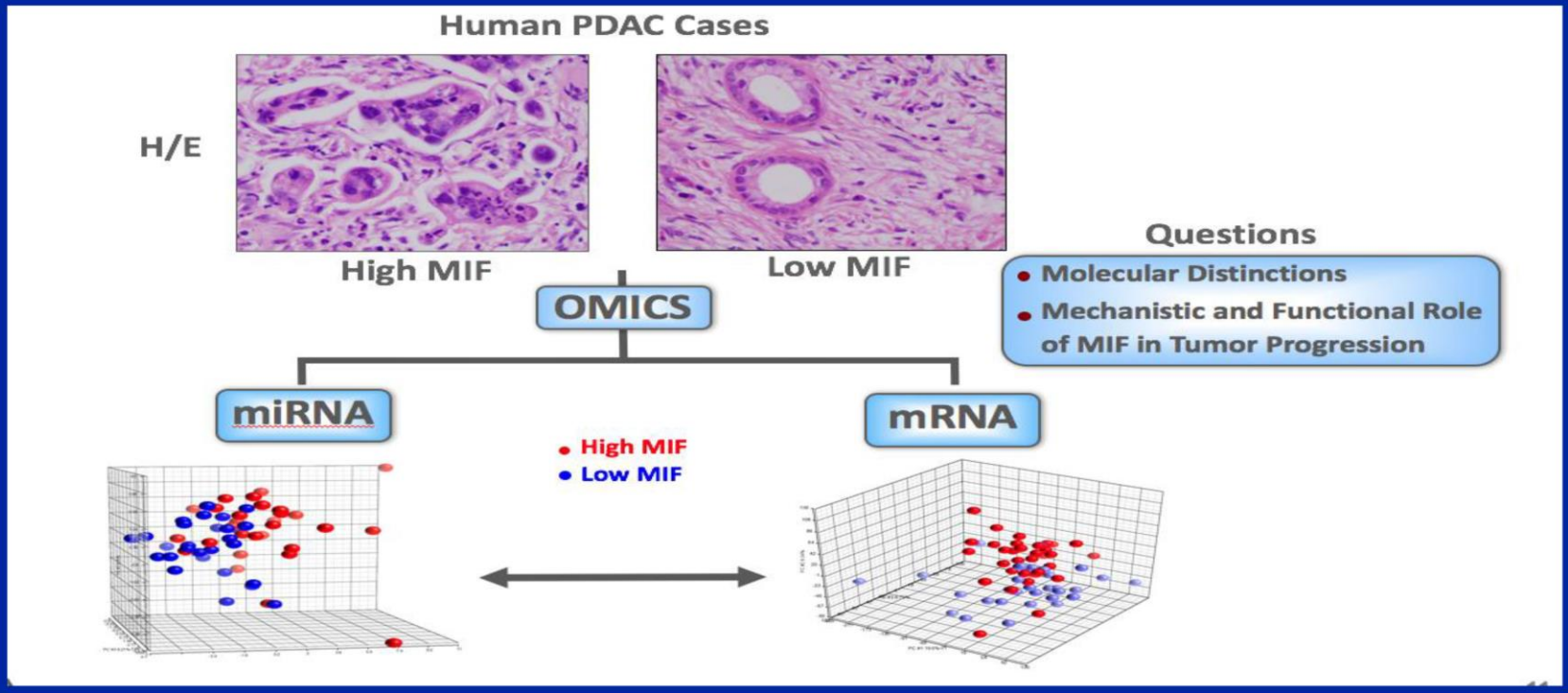
Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver

Bruno Costa-Silva[1], Nicole M. Aiello[2], Allyson J. Ocean[3], Swarnima Singh[1], Haiying Zhang[1], Basant Kumar Thakur[1,4], Annette Becker[1], Ayuko Hoshino[1], Milica Tešić Mark[5], Henrik Molina[5], Jenny Xiang[6], Tuo Zhang[6], Till-Martin Theilen[1], Guillermo García-Santos[1], Caitlin Williams[1], Yonathan Ararso[1], Yujie Huang[1], Gonçalo Rodrigues[1,7], Tang-Long Shen[8], Knut Jørgen Labori[9], Inger Marie Bowitz Lothe[10,11], Elin H. Kure[11], Jonathan Hernandez[12], Alexandre Doussot[12], Saya H. Ebbesen[1], Paul M. Grandgenett[13], Michael A. Hollingsworth[13], Maneesh Jain[14], Kavita Mallya[14], Surinder K. Batra[14], William R. Jarnagin[12], Robert E. Schwartz[15], Irina Matei[1], Héctor Peinado[1,16], Ben Z. Stanger[2,19], Jacqueline Bromberg[17,19] and David Lyden[1,18,19]

Pancreatic ductal adenocarcinomas (PDACs) are highly metastatic with poor prognosis, mainly due to delayed detection. We hypothesized that intercellular communication is critical for metastatic progression. Here, we show that PDAC-derived exosomes induce liver pre-metastatic niche formation in naive mice and consequently increase liver metastatic burden. Uptake of PDAC-derived exosomes by Kupffer cells caused transforming growth factor β secretion and upregulation of fibronectin production by hepatic stellate cells. This fibrotic microenvironment enhanced recruitment of bone marrow-derived macrophages. We found that macrophage migration inhibitory factor (MIF) was highly expressed in PDAC-derived exosomes, and its blockade prevented liver pre-metastatic niche formation and metastasis. Compared with patients whose pancreatic tumours did not progress, MIF was markedly higher in exosomes from stage I PDAC patients who later developed liver metastasis. These findings suggest that exosomal MIF primes the liver for metastasis and may be a prognostic marker for the development of PDAC liver metastasis.

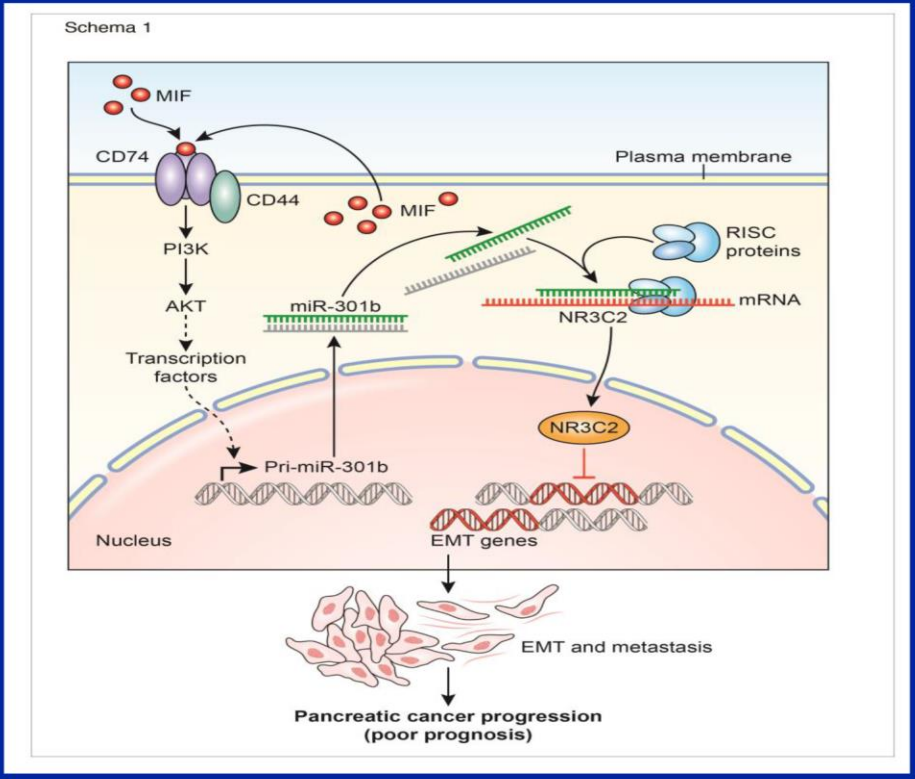
MIF and pancreatic cancer

MIF-induced disease aggressiveness in pancreatic cancer



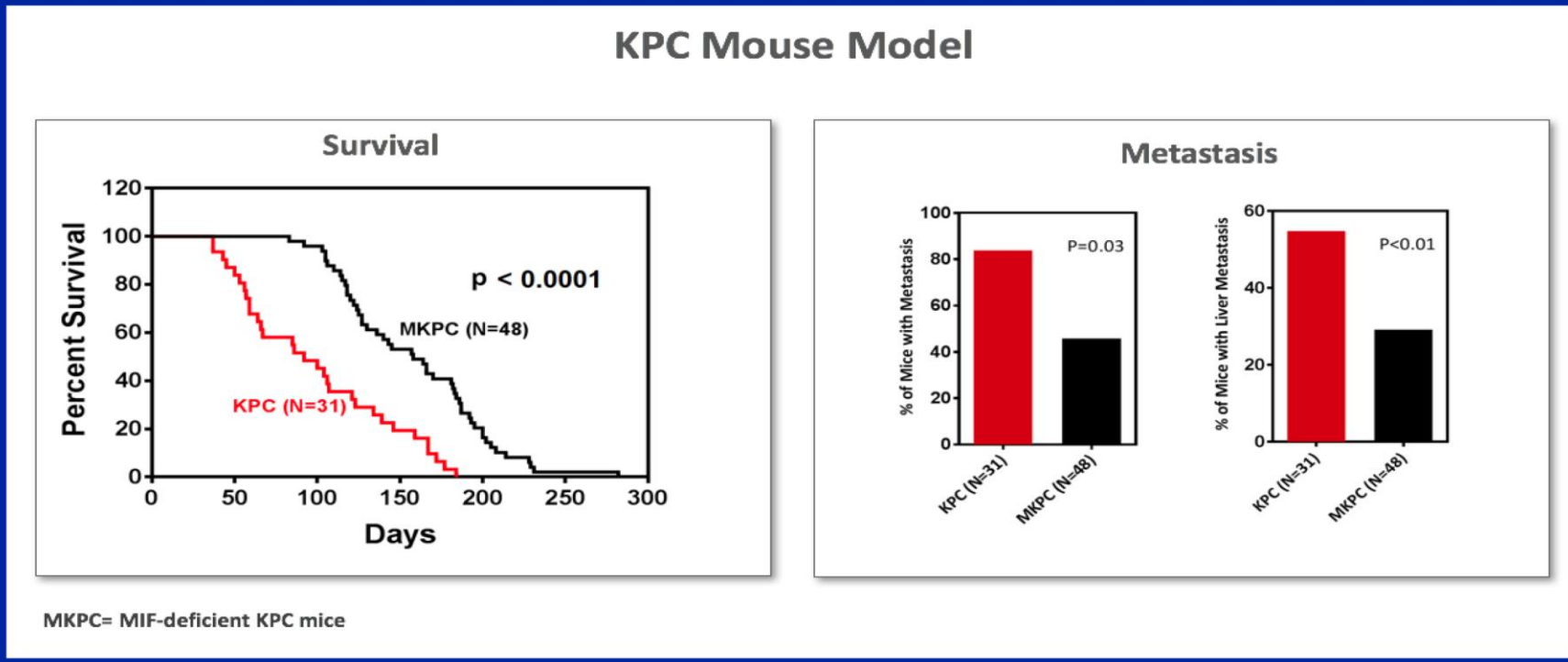
miR-301b and pancreatic cancer

MIF/miR-301b/NR3C2 Axis in Pancreatic Cancer



MIF deficiency

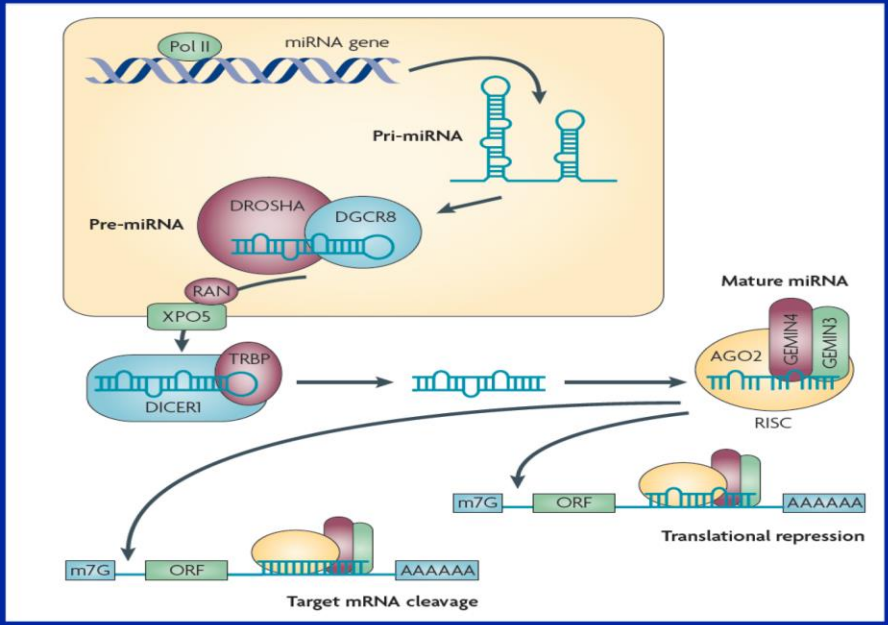
MIF-deficiency enhanced survival and reduced metastasis in KPC mice



MKPC= MIF-deficient KPC mice

miRNA and Cancer

miRNA and Cancer



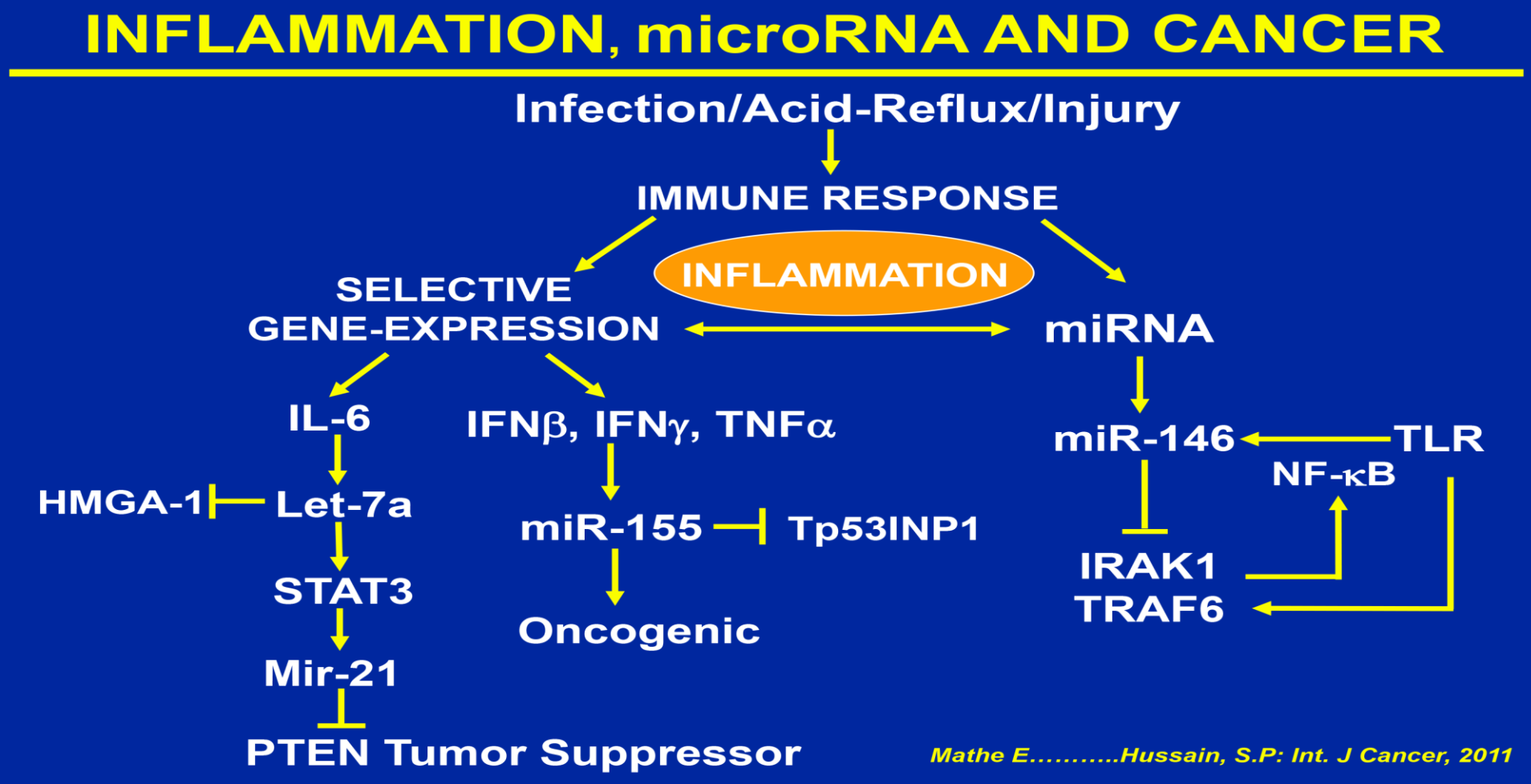
Ryan, Robles and Harris, Nat. Rev. Cancer, 2010

miR	*N*	Tumor type
miR-21	6	Breast, colon, lung, pancreas, prostate, stomach
miR-17-5p	5	Breast, colon, lung, pancreas, prostate
miR-191	5	Colon, lung, pancreas, prostate, stomach
miR-29b-2	4	Breast, colon, pancreas, prostate
miR-223	4	Colon, pancreas, prostate, stomach
miR-128b	3	Colon, lung, pancreas
miR-199a-1	3	Lung, pancreas, prostate
miR-24-1	3	Colon, pancreas, stomach
miR-24-2	3	Colon, pancreas, stomach
miR-146	3	Breast, pancreas, prostate
miR-155	3	Breast, colon, lung
miR-181b-1	3	Breast, pancreas, prostate
miR-20a	3	Colon, pancreas, prostate
miR-107	3	Colon, pancreas, stomach
miR-32	3	Colon, pancreas, prostate
miR-92-2	3	Pancreas, prostate, stomach
miR-214	3	Pancreas, prostate, stomach
miR-30c	3	Colon, pancreas, prostate
miR-25	3	Pancreas, prostate, stomach
miR-221	3	Colon, pancreas, stomach
miR-106a	3	Colon, pancreas, prostate

The list includes 21 commonly up-regulated microRNAs in 3 or more (*N*) types of solid cancers (*P* value = 2.5×10^{-3}).

Volinia et al., PNAS, 2006

Inflammation, miRNA, and Cancer



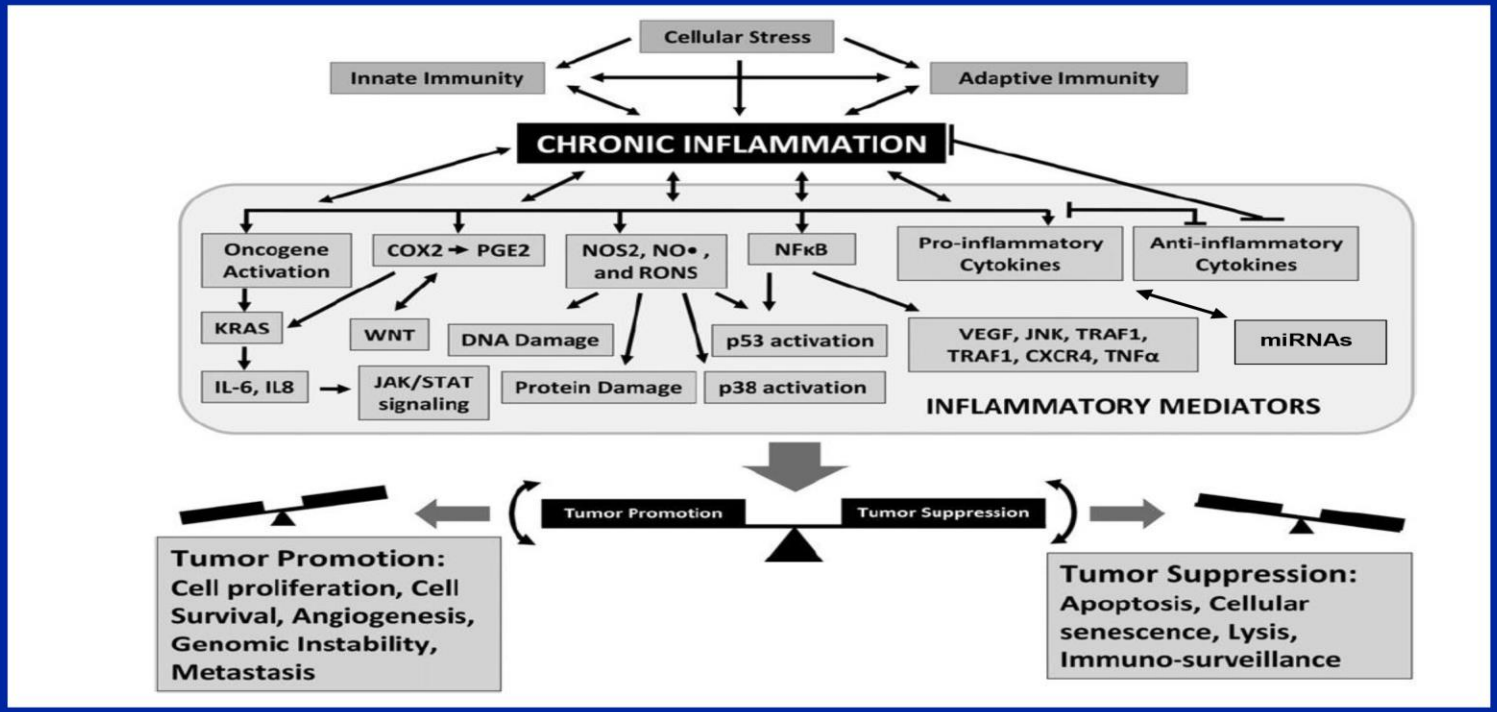
Chronic Inflammatory Diseases

Alterations in miRNA Expression in Cancer-Prone Chronic Inflammatory Diseases

Ulcerative Colitis	→	miR-21, miR-192, miR-375, miR-126,miR-195, miR-23a
Chronic Pancreatitis	→	miR-100, miR-10b, miR-125, miR-199, miR-99

Balance of Inflammatory Signals

Overall Balance of Inflammatory Signals Determine the Outcome



Schetter et. al., Carcinogenesiss, 31, 2009

Summary

Summary

- Many chronic inflammatory diseases increase cancer risk.
- Inflammatory and immune mediators contribute to different stages of tumor development and progression.
- NO can activate p53 stress response pathway and may also induce oncogenic p53 mutation in ulcerative colitis.
- Increased Expression of inflammatory mediators (e.g., MIF and NO) enhances disease aggressiveness in pancreatic cancer.
- Targeting MIF and NO-induced signaling pathways increased survival in mouse model with lethal pancreatic cancer.
- The highly complex interactions of immune and inflammatory signaling determines the overall effect of inflammation on tumorigenesis.