10th International Global Virus Network Meeting: Eradication and Control of (Re-)Emerging Viruses

"Nightmares of a Viral Oncologist"

November 9, 2018

Annecy, France

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Remarkable Biases of the Recent Past (1970's)

"Serious Epidemic infectious diseases are over in the industrialized world, therefore . ."

"Retroviruses do not infect humans and there are many reasons for this . . ."

"No viruses cause cancer in man."

In the early 1980's the biases were shattered

- Viruses shown to be the cause of about 20% of human cancers.
- Retroviruses discovered in humans, shown to cause some leukemias and neurologic diseases HTLV-1, 1980 and HTLV-2, 1982.
- One of the great pandemics of history (AIDS) appears and is caused by another retrovirus.

now a look at infectious causes of cancer…

List of known infectious causes of human cancer:

Infectious organism	Global burden (% in population)	Life time risk of malignancy development	Oncogenic mechanism
Epstein Barr virus (EBV/HHV-4)	>90%	0.3~0.4 %	Requires cofactors
Papilloma virus (HPVs)	5.2%	~0.3%	Direct
Hepatitis viruses (HCV+ HBV)	4.9%	HCV; 1~3%, HBV; < 1%	Inconclusive
Kaposi sarcoma virus (HHV-8)	2~5%	Minimum	Requires cofactors (HIV)
Human T-cell leukemia virus-1 (HTLV-1)	0.3% (45%, indigenous communities in Central Australia)	5~10% (~20% of infection at birth)	Direct (Tax / HBZ)
H. Pylori	~50%	0.3%	Direct (Cag A)

What were the keys to discovery of the HTLVs and then for the discovery of HIV? The story of HIV science and discovery is intricately related to the earlier discoveries of the HTLVs

- Sensitive and specific assays for virus – based on **reverse transcriptase** (RT) discovered in animal viruses by the late Howard Temin and by David Baltimore (1970).
- My colleagues and I, as well as D. Baltimore, made tests for **RT very sensitive** and sufficiently **specific** so it could be used as a surrogate marker for a retrovirus (1970-1978).
- We discovered **T-Cell Growth Factor - now known as Interleukin-2** (IL-2) - enabling us and others to grow human T cells in culture for the 1st time - a requisite for us in finding human retroviruses, - including for all labs in the finding of HIV. IL-2 was the 1st lymphokine and one of the 1st cytokines.

SUMMARY OF SOME NOTABLE ASPECTS of HTLV-1

- First Human Retrovirus; only known Human Leukemia Virus. Causes ATL a disease described (before the virus was discovered) in epidemic form by Takatsuki and Yodoi.
- Directly transforms target cells. Not known to need any co-factor.
- Can provide continuous growth of any mature CD4+ T Cell. (useful in the lab)
- Insights into the mechanisms of leukemogenesis – different from animal retroviruses.
- Also can cause serious central nervous system disease-(Gessaine/deThe—Osame)
- Also can cause immune disorder resulting in serious infections (many observers)
- **Provided impetus to search for other retroviruses leading to the discoveries of HTLV-2 and HIV and predicted TAT and rev of HIV.**

  More carcinogenic than any known human tumor virus and overall one of the strongest carcinogens known

- An important public health problem in S. America, Caribbean Islands, parts of Africa, Indonesia, Japan, Iran, Romania, and Australia, yet severely underfunded and understudied..

Dogma fills the air too often---

In 1980 I submitted a paper with the discovery of the FIRST human retrovirus, and the virus that gave us our ideas and background for the discovery of HIV. It was outright rejected by the J. of Virology –more or less because no-one believed it !!!!

Later after human retroviruses were accepted, M. Essex and I postulated that AIDS was most likely caused by another human retrovirus (1982). This too was heavily criticized by scientists who said “retroviruses never cause immune deficiency”.

The answer to such nonsense is to have science expertise in all types of viruses in a joined force—i.e., the GVN.

JOURNAL OF VIROLOGY

A publication of the American Society for Microbiology

September 15, 1980

Dr. Robert C. Gallo
Laboratory of Tumor Cell Biology
National Cancer Institute
Building 37, Room 6B06
Bethesda, Maryland 20205

RE: JVI 417

Dear Bob:

I regret that your paper on the T-cell retrovirus is not acceptable for publication in the JOURNAL OF VIROLOGY.

Enclosed are the comments of two reviewers, both of whom expressed grave doubts about the evidence that your protein is really analogous to a retroviral structural protein. I completely agree with reviewer #1 that there is little point in perpetuating this controversy about "the presumed viral nature of this material".

I hope you can understand that we can only accept definitive data to resolve this question. Therefore, I have no alternative but to reject this paper outright and must advise you that we cannot consider the present manuscript in any form.

Sincerely yours,

Robert R. Wagner

RRW/mc
enc.

cc: Mrs. Gisella Pollock

Now--- New findings and the nightmares

- Not a virus but a bacterium
- Hit and Run or Hit and Hide

Bacteria and cancer

- Many that commonly infect us or that we live with have been associated with cancer
- But other than Helicobacter pylori-- none are definitive—lacking specific mechanisms, animal models, or sufficiently tight association
- Many other bacteria are not associated. We hypothesize that one major mechanism for the carcinogenicity of some bacteria depends upon a common gene with a highly related sequence. This came out of a study of some mycoplasma isolates.

Some reports of associations of Mycoplasmas with human cancers

Hindawi Publishing Corporation
Infectious Diseases in Obstetrics and Gynecology
Volume 2011, Article ID 824627, 10 pages
doi:10.1155/2011/824627

Clinical Study

Chlamydia trachomatis and Mycoplasma genitalium Plasma Antibodies in Relation to Epithelial Ovarian Tumors

Annika Idahl,[1] Eva Lundin,[2,3] Margaretha Jurstrand,[4] Urban Kumlin,[5] Fredrik Elgh,[5] Nina Ohlson,[2] and Ulrika Ottander[1]

www.impactjournals.com/oncotarget/ Oncotarget, April, Vol.2, No 4

Association of *Mycoplasma hominis* infection with prostate cancer

Yulia A. Barykova[1], Denis Yu. Logunov[1], Maxim M. Shmarov[1], Andrei Z. Vinarov[2], Dmitry N. Fiev[2], Natalia A. Vinarova[2], Irina V. Rakovskaya[1], Patricia Stanhope Baker[3], Inna Shyshynova[3,5], Andrew J. Stephenson[4], Eric A. Klein[4], Boris S. Naroditsky[1], Alexander L. Gintsburg[1] and Andrei V. Gudkov[3,5]

Received: March 23, 2011, **Accepted:** April 4, 2011, **Published:** April 4, 2011

Received 15 March 2011; Revised 28 April 2011; Accepted 9 May 2011

Apostolou *et al. Journal of Cardiothoracic Surgery* 2011, **6**:137
http://www.cardiothoracicsurgery.org/content/6/1/137

JCTS JOURNAL OF CARDIOTHORACIC SURGERY

RESEARCH ARTICLE Open Access

Bacterial and fungal microflora in surgically removed lung cancer samples

Panagiotis Apostolou[1], Aggeliki Tsantsaridou[2], Ioannis Papasotiriou[1], Maria Toloudi[1], Marina Chatziioannou[1] and Gregory Giamouzis[3*]

RESEARCH PAPER

Epigenetics 10:4, 303–318; April 2015; © 2015 Taylor & Francis Group, LLC

Mycoplasma CG- and GATC-specific DNA methyltransferases selectively and efficiently methylate the host genome and alter the epigenetic landscape in human cells

Andrei V Chernov[1,*], Leticia Reyes[2], Zhenkang Xu[3], Beatriz Gonzalez[4], Georgiy Golovko[3], Scott Peterson[1], Manuel Perucho[1,4], Yuriy Fofanov[3], and Alex Y Strongin[1,*]

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World J Gastroentero, 2001;7(2):266 - 269
World Journal of Gastroenterology

ISSN 1007 - 9327

Mycoplasma infections and different human carcinomas

Su Huang, Ji You Li, Jan Wu, Lin Meng and Cheng Chao Shou

American Journal of Epidemiology

Vol. 162, No. 7
Printed in U.S.A.
DOI: 10.1093/aje/kwi261

Associations between Three Types of Maternal Bacterial Infection and Risk of Leukemia in the Offspring

Matti Lehtinen[1,2], Helga M. Ögmundsdottir[3,4], Aini Bloigu[1], Timo Hakulinen[5], Elina Hemminki[6], Margret Gudnadottir[4], Anne Kjartansdottir[4], Jorma Paavonen[7], Eero Pukkala[5], Hrafn Tulinius[3,4], Tuula Lehtinen[2], and Pentti Koskela[1]

CAN MYCOPLASMA-MEDIATED ONCOGENESIS BE RESPONSIBLE FOR FORMATION OF CONVENTIONAL RENAL CELL CARCINOMA?

MUSTAFA PEHLIVAN, SACIDE PEHLIVAN, HUSEYIN ONAY, MERAL KOYUNCUOGLU, AND ZIYA KIRKALI

UROLOGY **65:** 411- 414, 2005.

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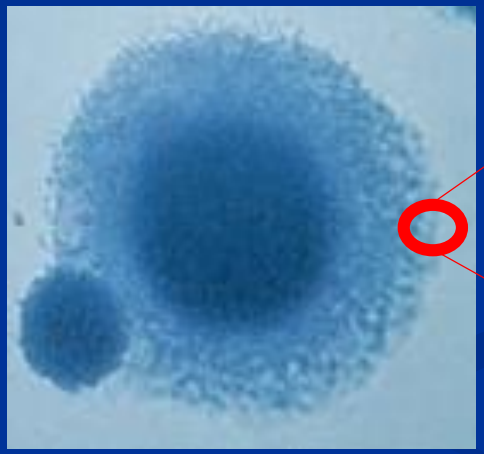
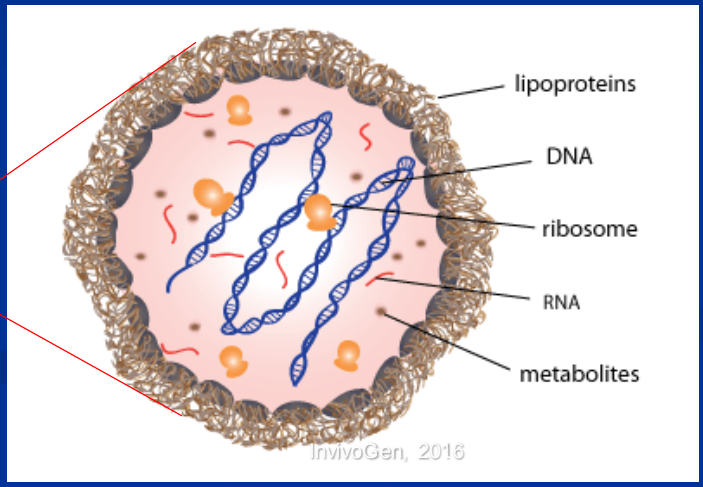
Typical Mycoplasma morphology and structure

- At least 400 species; widespread in nature as parasites of mammals, reptiles, fish, arthropods and plants.
- Wall-less bacteria, about 0.1mm in diameter, genome length: 0.5-2.0 Mbp.
- Immuno-suppression may lead to uncontrolled replication of Mycoplasmas.
- Some can be intracellular

Mycoplasma colony



Single Mycoplasma



Mahon C.R. *et al*., Atlas of Mycoplasma and Ureaplasma, 2011

An association of disseminated Mycoplasma fermentans in HIV-1 positive patients with non-Hodgkin's lymphoma.

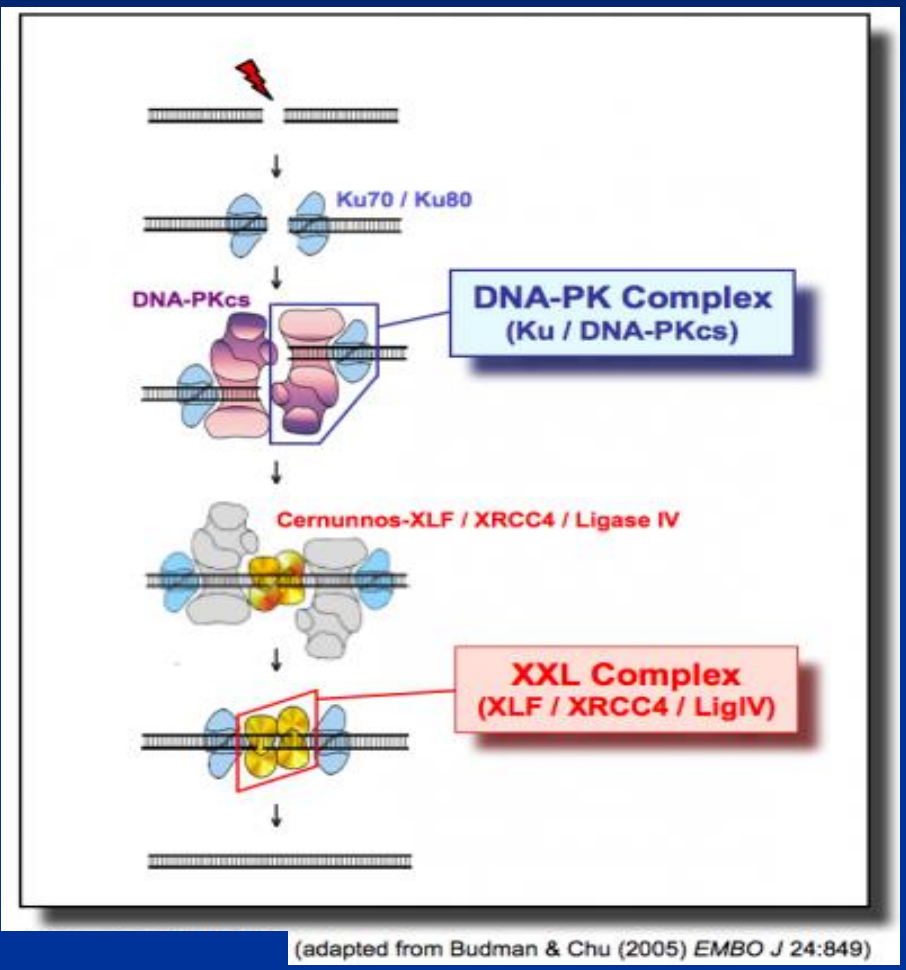
Ainsworth JG, *et al*.

Int. J. STD AIDS (12), 499, 2001.

We turned to a mouse model –the SCID mouse.

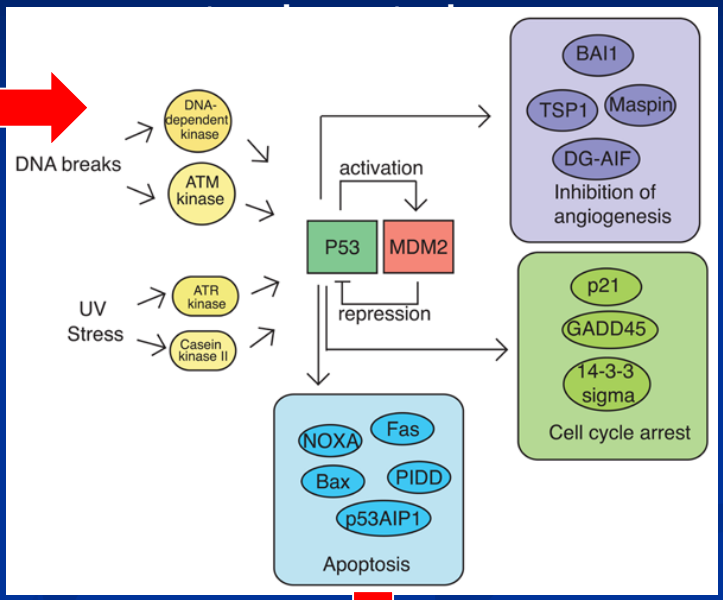
The Severe Combined Immuno-Deficient (SCID) mouse model

Model of DNA-PK-dependent Double Strand Breaks (DSBs) repair



(adapted from Budman & Chu (2005) *EMBO J* 24:849)

Involvement of DNA-PK and P53 in DNA damage-induced cell cycle



Lack of B and T cells: Severe Combined Immunodeficiency

P53$^{-/-}$ /SCID	14 weeks
P53$^{-/-}$	19 weeks
SCID	30 weeks

Nacht M. *et al.*, Genes Devel., 1996

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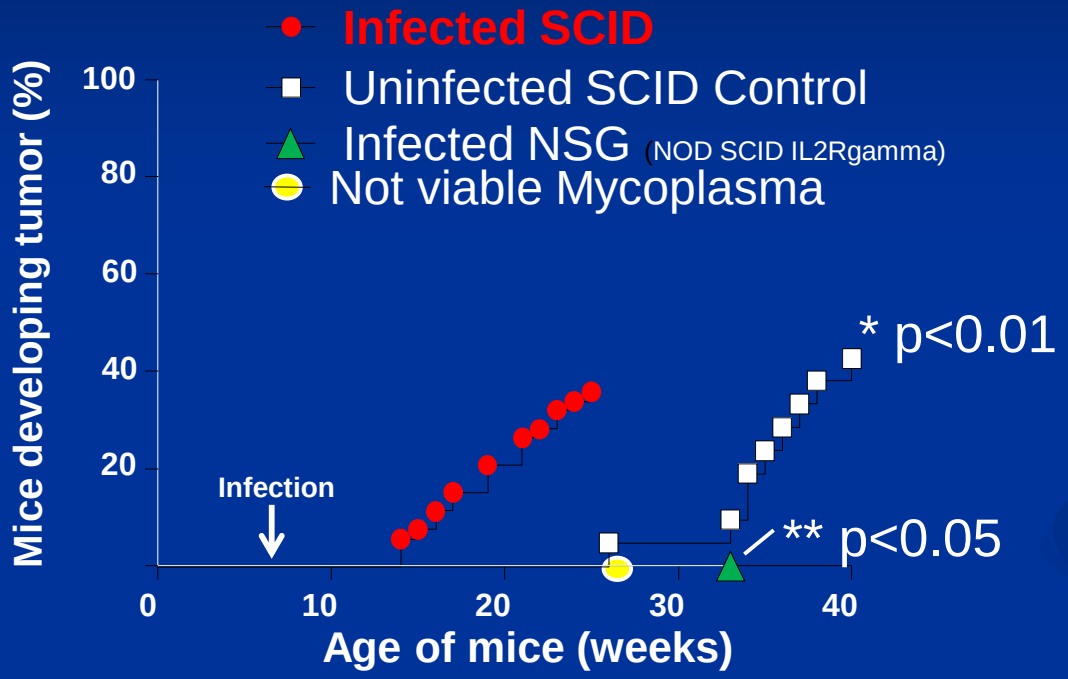
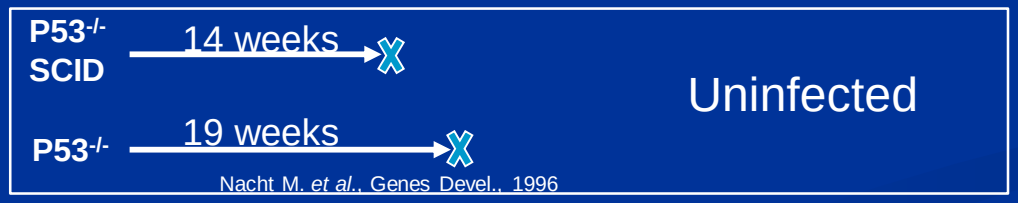
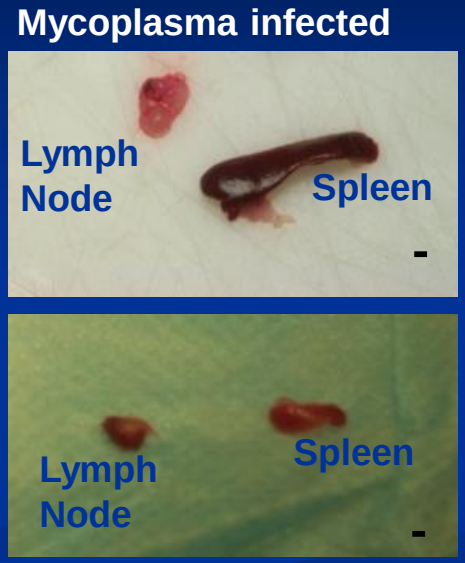
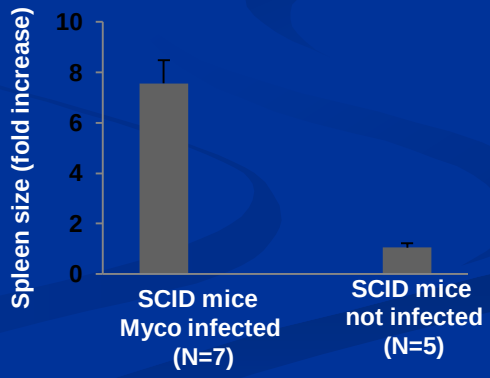
Mycoplasma infection induces tumorigenesis in SCID mice









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Real-time PCR amplification of mycoplasma sequences in transformed cells (secondary tumors).

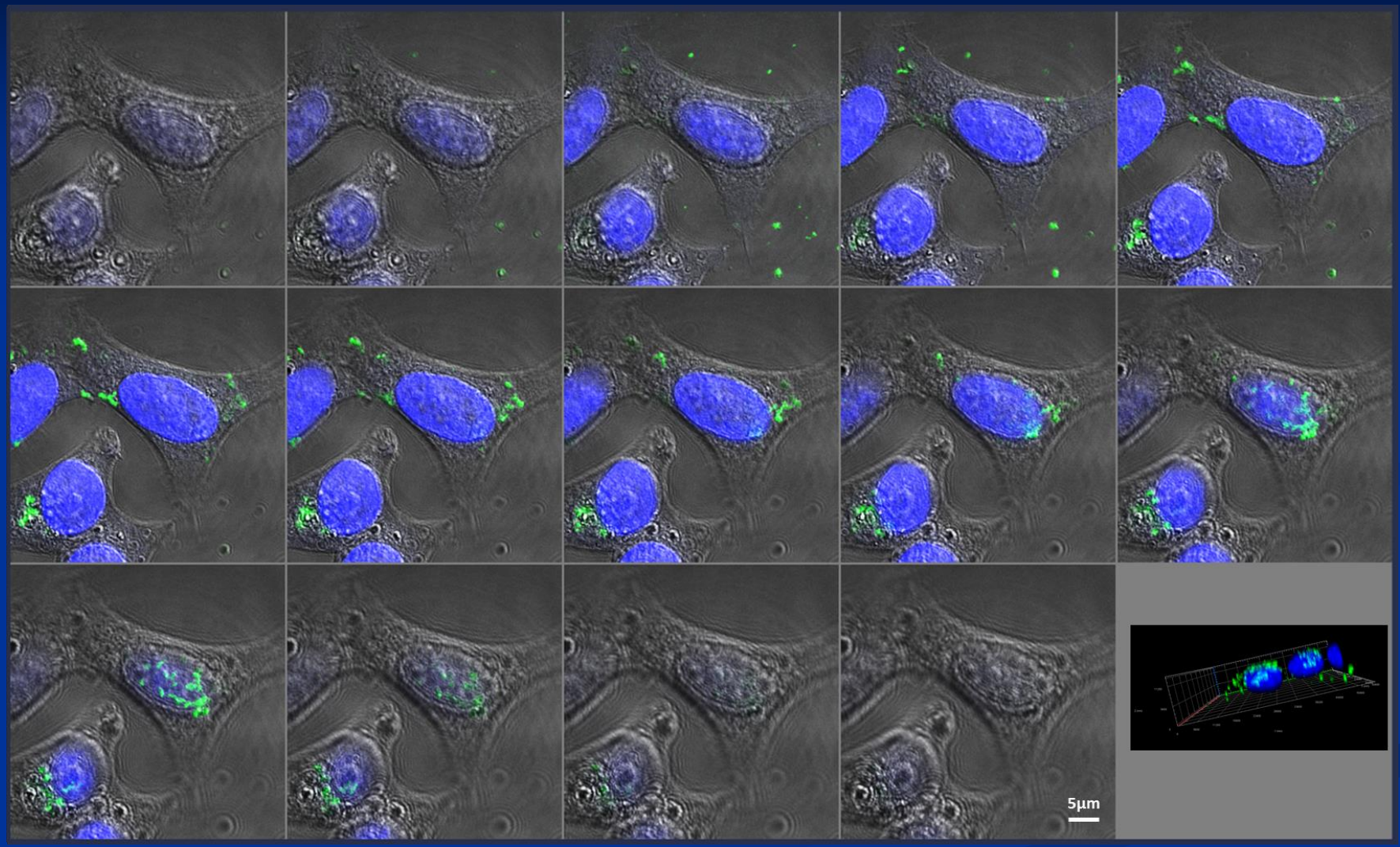
	DnaK 368-462	DnaK 367-716	DnaK 367-954	DnaK 688-1069	DnaK 1037-1508	R1	R2	R3	R4	R5
T1a	+	+	+	+	+	-	-	-	-	-
T1b	+	-	-	+	-	-	-	-	-	-
T2	+	-	+	-	-	-	-	-	+	-
T3	+	+	+	+	-	-	-	-	+	-

Single-cell suspension was obtained from enlarged lymph nodes from SCID mice and cells injected into three NOD/SCID mice. Extra-nodal tumors were collected and analyzed by real-time PCR with the indicated primers. T1-3: secondary tumor from animal 1-3. DnaK: primers in the DnaK region. R1-4 are different regions we selected from mycoplasma genome.

Hit and run/hide

Mycoplasma was detected early in the infected mice, but only low copy numbers of Mycoplasma DnaK DNA sequences were found in some primary and secondary tumors, pointing toward a “hit and run/hide” mechanism of transformation.

Intracellular uptake of exogenous DnaK-V5 protein by Mycoplasma-free HCT116 cells



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Turning to the mechanism of Mycoplasma Induced Lymphoma– the SCID model itself and the following report focused us on p53:

Mycoplasma infection suppresses p53, activates NF-kB and cooperates with oncogenic Ras in rodent fibroblast transformation.

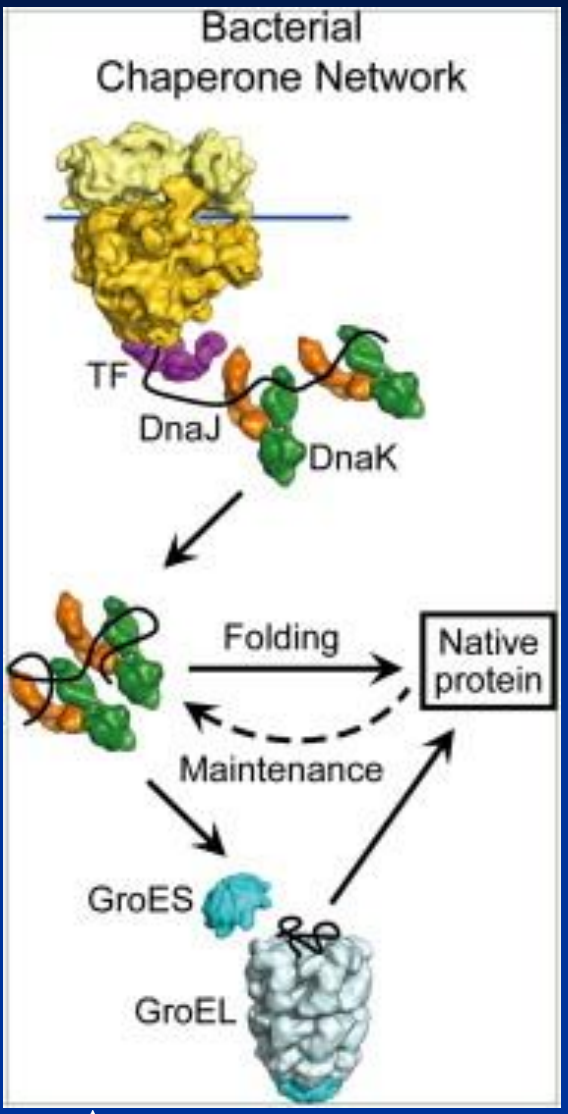
Logunov DY, *et al.*
Oncogene (27), 4521, 2008.

Anti-p53 mAb immuno-precipitate proteins from cells* infected with Mycoplasma

Identified proteins
HSP 70 family (DnaK)
Thiamine pyrophosphate (TPP) Family
ATP synthase Family
Enolase
Arginyl-tRNA synthetase Family
Glyceraldehyde

* HCT116: colon adenocarcinoma cell line

DnaK and p53



- Member of the Heat Shock Protein family (HSP70);
- Expressed under stress;
- Chaperone activity.

Cell Reports
Resource

Cell PRESS
Open ACCESS

DnaK Functions as a Central Hub in the *E. coli* Chaperone Network

Giulia Calloni,[1,4] Taotao Chen,[1,4] Sonya M. Schermann,[1,5] Hung-chun Chang,[1,6] Pierre Genevaux,[2] Federico Agostini,[3] Gian Gaetano Tartaglia,[3] Manajit Hayer-Hartl,[1,*] and F. Ulrich Hartl[1,*]
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[2]Laboratoire de Microbiologie et Génétique Moléculaire, Centre National de la Recherche Scientifique and Université Paul Sabatier, F-31000 Toulouse, France
[3]Centre for Genomic Regulation and Universitat Pompeu Fabra, 08003 Barcelona, Spain
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*Correspondence: mhartl@biochem.mpg.de (M.H.-H.), uhartl@biochem.mpg.de (F.U.H.)
DOI 10.1016/j.celrep.2011.12.007

DnaK from E. *coli* studied as prototype protein. It interacts with human and murine p53, and increases the p53 activities, although the significance of these interactions is not clear (Pinhasi-Kihmi. O. et al., Nature, 1986; Hinds P.W. et al., Mol. Cell Biol., 1987; Sturzbecher H.W. et al., Oncogene, 1987; Clarke C.F. et al., Mol. Cell Biol. 1988; Hupp T.R. et al., Cell 1992; Nihei T. et al.,Cancer Res., 1993).

DnaK and p53

- Previous data showed that DnaK from E. *coli* interacts and increases the activity of human and murine p53 (Pinhasi-Kihmi. O. et al., Nature, 1986; Hinds P.W. et al., Mol. Cell Biol., 1987; Sturzbecher H.W. et al., Oncogene, 1987; Clarke C.F. et al., Mol. Cell Biol. 1988; Nihei T. et al.,Cancer Res., 1993, Hupp T.R. et al., Cell 1992).

- In contrast, our data show that DnaK from M. fermentans inhibits p53 functions.

Mycoplasma DnaK: 1) directly impairs DNA repair and 2) indirectly suppresses p53 activities

1) Immuno-precipitation analysis shows interaction with a complex of proteins involved in DNA repair (PARP1 and DNA-PK)

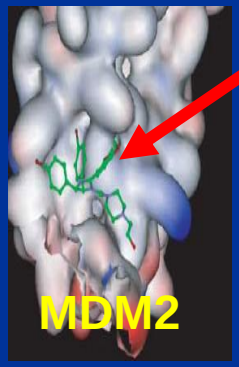
2) Indirectly reduces p53 activity by interacting with USP10, a protein which de-ubiquinitates p53. The downstream effects of diminished p53 include reduced:

- PARP1 activity
- p21 activity (cell cycle regulator)
- Bax (Bcl-2 associated X protein) expression (mediator of apoptosis)
- PUMA (P53 Upregulated Mediator of Apoptosis) expression

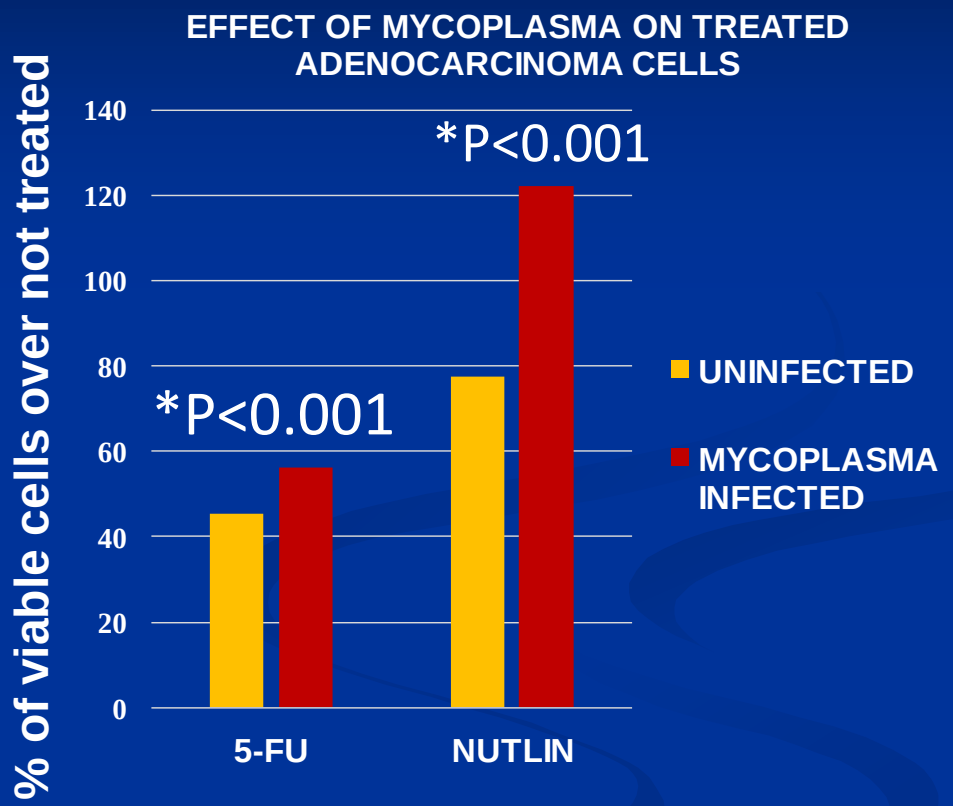
- RESULT—impaired DNA repair and apoptosis of DNA altered cells is ineffective

Mycoplasma infection reduces the activity of the anticancer drugs 5-FU and Nutlin

5-FU blocks DNA replication.
It is currently used to treat several types of cancers, including colon, esophageal, stomach, pancreatic, breast and cervical cancer.



Nutlin activates p53 by binding to its inhibitor, MDM2. Nutlin analogs are currently undergoing clinical trials for the treatment of several cancers, including hematological cancers and prostate cancer (Roche).



Mean difference is shown.

*: calculated using Poisson regression

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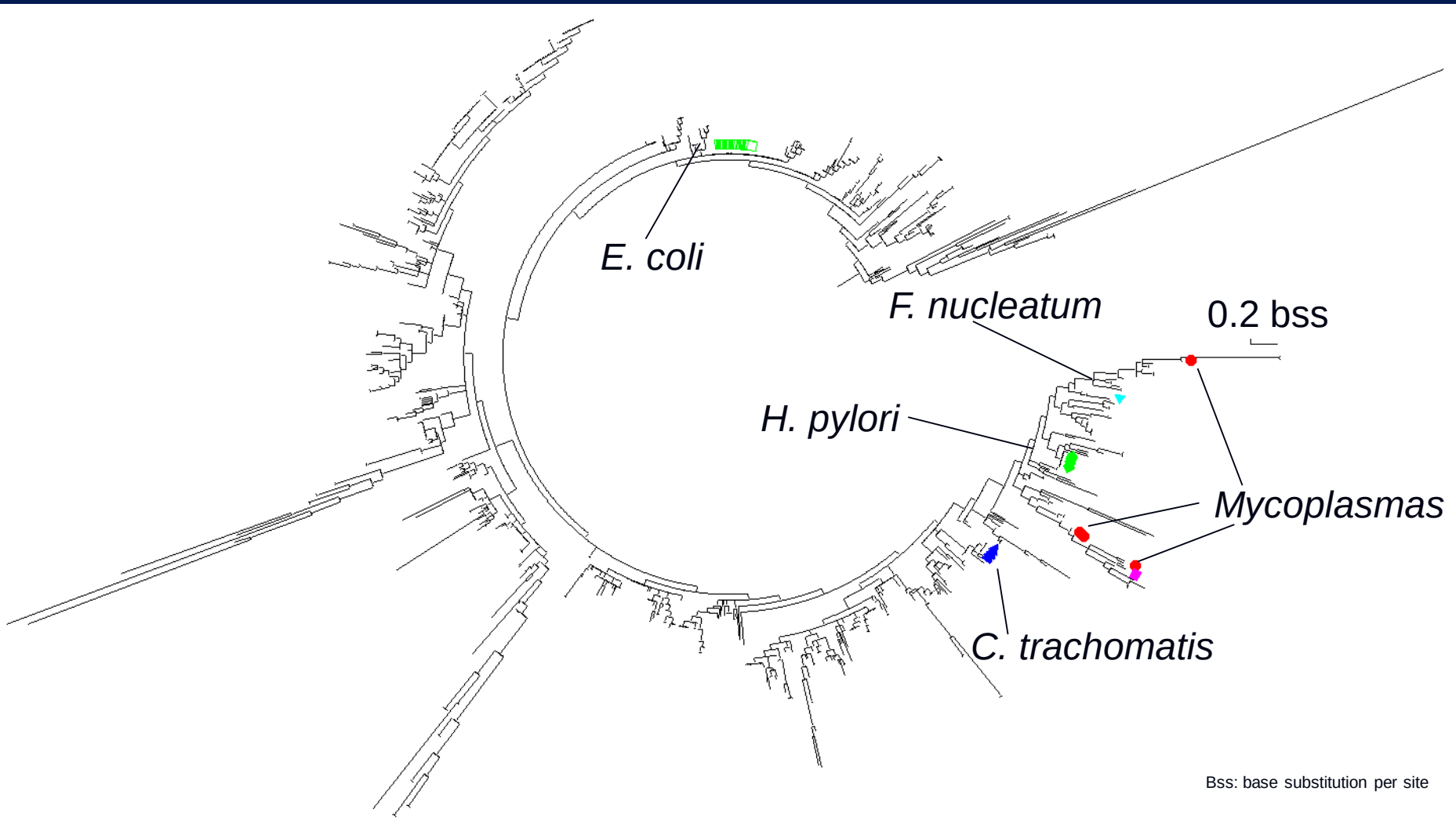
These data demonstrate that a Mycoplasma protein (DnaK) interacts with proteins involved in DNA repair and hampers cellular p53 functions.

In addition to these pro-carcinogenic effects the mycoplasma infection of cells also results in resistance to anti-cancer drugs dependent on p53.

What about other bacteria?

Phylogenetic analysis of bacterial DnaKs



In mycoplasma induced lymphoma of mice the Mycoplasma DNA is found only in a very small number of tumor cells.

Preliminary studies indicate similar sequences are also found in some human tumors--- also in very few cells and also include the DnaK gene.

Detection of Mycoplasma DNA sequence of DnaK (588bp) in PBLs of different human samples

Lymphomas	Total PBLs	PBLs positive	PBLs pos/tot	Other solid tissues
A) Diffuse Large B-cell lymphomas				
- Germinal Center (p=0.0001)	6	5	5/6	1/2
- Non Germinal Center	2	0	0/2	1/6
B) Follicular	12	2	2/12	0/1
C) Burkitt's	1	1	1/1	3/12
D) Mantle Cell	10	3	3/10	1/1
- Total lymphomas	31	11	11/31	6/22
Adult T-cell Leukemia (HTLV-1)	3	0	0/3	
Healthy donors (no cancer)	57	4	4/57	3/9 tonsils

…But how does this “fragment” persist (replicate)?

Summary

A bacterium capable of intracellular infection, a type of Mycoplasma fermentans related to the incognitos strain, infects mouse and human lymphocytes and produces lymphoma in SCID mice.

No evidence of the Mycoplasma is found after tumor development except for small (less than 1KB) DNA fragments in a very small number of tumor cells.

The fragments include a component of DnaK the protein of which markedly reduces pro-apoptotic p53 activity and interacts with proteins of the DNA repair complex. This protein also impairs anti-cancer drugs depending upon p53 enhancement.

Exogenous DnaK protein can be taken up by nearby cells.

The same fragment (but with variable mutations not identical to that found in the mice) has been discovered in some human lymphomas, and that fragment has mutations allowing its translation in human cells.

Summary (continued)

- DnaKs from cancer-associated bacteria are very similar;
- DnaK reduces the same anti-cancer cellular pathways affected by oncogenic viruses

("Mycoplasma promotes malignant transformation in vivo, and its DnaK has broad oncogenic properties": Proceedings of the US National Academy of Sciences, Zella et al. in press).

Hypothesis and Predictions

- A mycoplasma bacterial protein DnaK can foster cancer development.
- It does so by both impairing DNA repair and reducing p53.
- Several other bacteria have similar DnaK sequences.
- Most of these bacteria are associated with several different human cancers but no evidence of mechanism or convincing causality.
- **These bacteria with similar DnaK that are carried by or chronically infect humans, particularly but not necessarily also having an intracellular presence, can cause cancer and can diminish efficacy of some anti-cancer drugs.

**Prediction based on some preliminary results*

Acknowledgments

Institute of Human Virology
School of Medicine - University of Maryland, Baltimore

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- **F. Cocchi**
- **S. Krishnan**

Initial observations and Imaging analysis
- F. Romerio
- O. Latinovic
- F. Denaro (Morgan State University)

Statistical analysis
- M. E. Charurat

IHV-Animal Model Division
- J. Bryant

Institute for Genome Sciences
School of Medicine -University of Maryland, Baltimore

Sequencing and Genomic analysis of Mycoplasmas
- **H. Tettelin**

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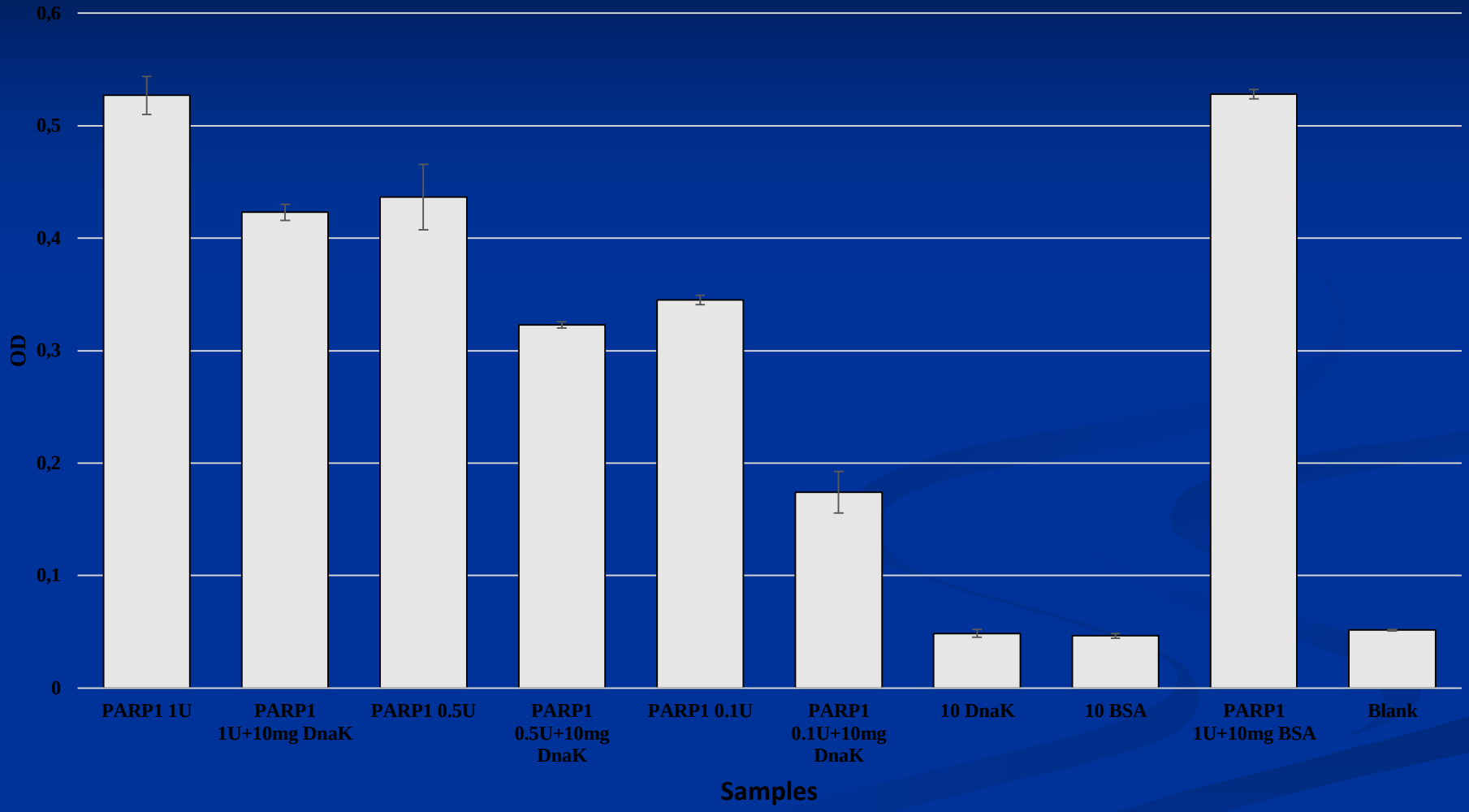
Real-time PCR amplification of Mycoplasma sequences in enlarged lymph nodes and spleens from *Mycoplasma*-infected SCID mice (Primary tumors)

Infected SCID mice -primary tumor	DnaK primers 368-462	Other region of Mycoplasma specific primers
LN (N=5)	Pos=1 Neg=4	Pos=0 Neg=5
Spleen (N=7) * **	Pos=3 Neg=4	Pos=0 Neg=7

SCID mice were injected intra-peritoneally with 1 X 10^7 CFU of *Mycoplasma fermentans* MF-I1. Injected mice were sacrificed and spleen and lymph nodes were collected. Pos: Positive test for real-time PCR. Neg: Negative test for real-time PCR. Numbers in parentheses indicate the number of organs analyzed. DnaK: primers in the DnaK region. Amplified products were confirmed by sequencing. Fisher's two-tailed T test analysis was used to analyze statistical correlation between different sets of primers. *: Significant; **:p=0.19.

Measurement of catalytic activity of PARP1 shows reduction of histone-PARylation in the presence of DnaK



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USP10 Regulates p53 Localization and Stability by Deubiquitinating p53

Jian Yuan,[1] Kuntian Luo,[1] Lizhi Zhang,[2] John C. Cheville,[2] and Zhenkun Lou[1,*]
[1]Division of Oncology Research, Department of Oncology
[2]Department of Pathology
Mayo Clinic, Rochester, MN 55905, USA

Cell *140*, 384–396, February 5, 2010

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Dissecting the contribution of external agents to different stages of cellular transformation and tumor growth

- UV light exposure
- Ionizing radiation
- Chemical exposure
- Reactive Oxygen Species (ROS)
- Other DNA damaging agents

- Immune system response
- Cytokines
- Viral and bacterial proteins

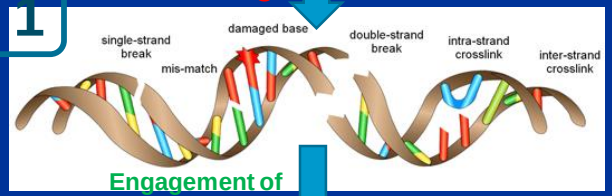
Tumor growth

Microenvironment

Cell

1

DNA damage



Engagement of cellular pathways

- DNA repair (i.e., PARP1, DNA-PK)
- Transcriptional program activation (p53)
- Cell cycle checkpoint activation (p21)
- Apoptosis (Bax, PUMA)

Correct execution of cellular pathways

Repair of DNA damage or cell death

2

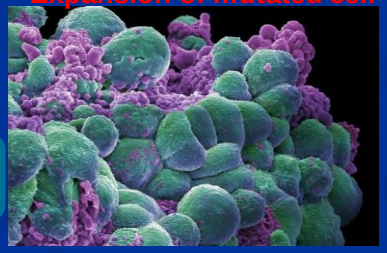
- Interaction with cellular proteins
- reduction of cellular pathways activity

3

4

Transformation (Tumor)

Expansion of mutated cell



Proliferation

Growth and differentiation pathways

Incorrect execution of cellular pathways
Mutation fixed

Accumulation of mutations

- Viral proteins: HTLV, EBV, HPV, HBV, HCV, KSHV, HIV (p53, DNA repair)
- Bacterial proteins: CagA (p53), DnaK (p53, DNA repair)

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Listing of demonstrable infectious causes of cancer and note highest malignancy development associated with HTLV-1 in comparison with other oncogenic microorganisms

Infectious organism	Global burden (% in population)	Lifetime risk of malignancy development following infection
H. Pylori	5.5%	3%
HPV	5.2%	0.29%
HCV + HBV	4.9%	HCV, 1~3% / HBV, < 1%
HHV-8	2~5%	Minimally oncogenic by itself
EBV	>90%	0.3~0.4%
HTLV-1	0.3% (~40% in central Australian aboriginals)	5~10%

List of infectious causes of cancer and the high malignancy development associated with HTLV-1, in comparison with other oncogenic microorganisms

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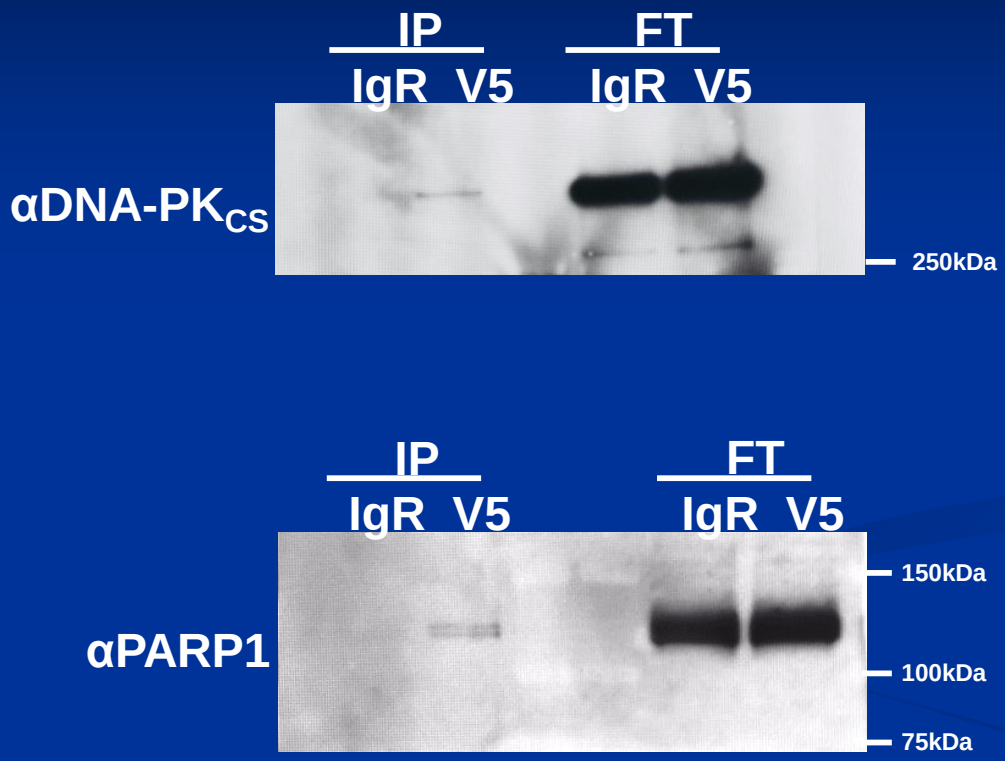
EBV	>90%	0.3~0.4%
HTLV-1	0.3% (~40% in central Australian aboriginals)	**5~10% and 25% in infected infants**
MCV	0.06%	??

DnaK immunoprecipitates DNA-PK$_{CS}$ and PARP1



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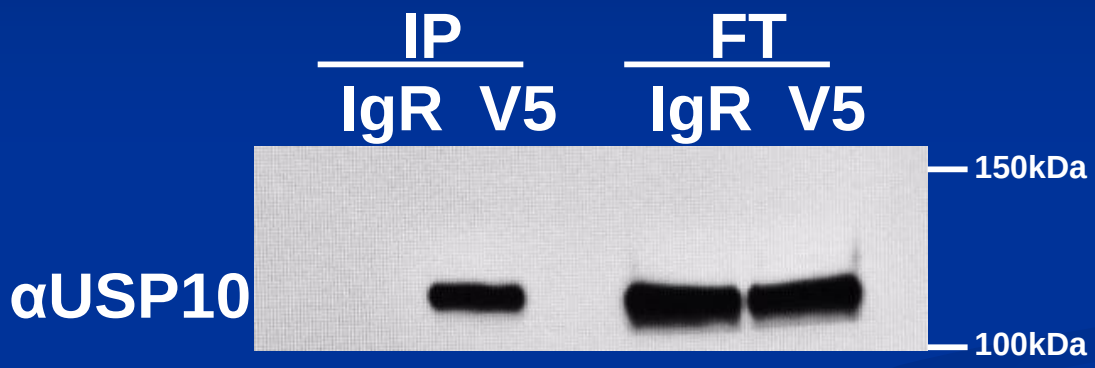
Localization of the two specific mutations in the 2F/7R region of Mycoplasma DnaK

The mutations allow the gene to be potentially translated in the cell

DnaK immunoprecipitates USP10



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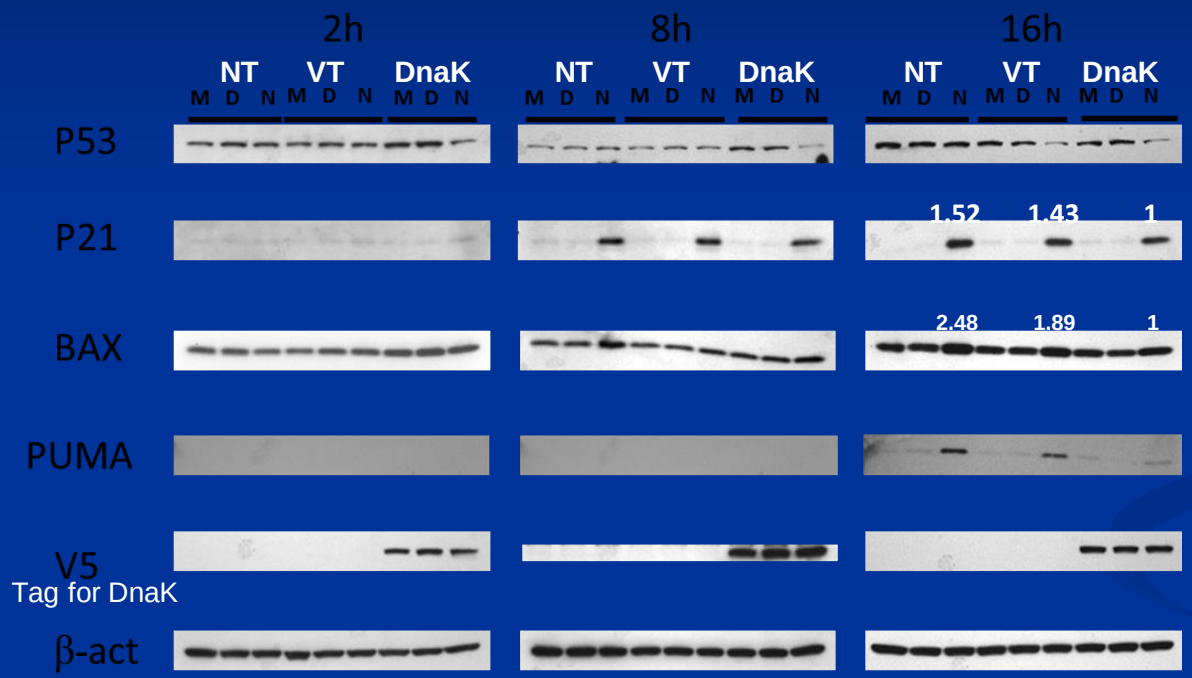
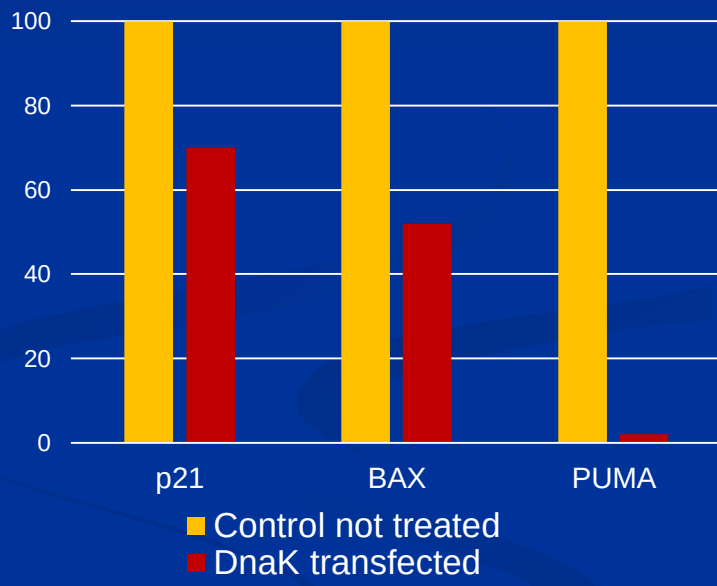
Mycoplasma DnaK affects p53-associated activities in human colorectal carcinoma cell line (HCT116)



Numbers above bands represents fold over control=1



NT: Not Transfected
VT: Control Vector
DnaK: transfected with DnaK

M: media control
D: DMSO added to media
N: Nutlin

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Major findings

- Development of an in vivo model to study initial step(s) of lymphomagenesis induced by human Mycoplasma: **SCID-mouse model**;
- Identification of a Mycoplasma protein, **DnaK**, which **interacts with proteins of the DNA-repair complex** and **reduces pro-apoptotic p53 activities**;
- Exogenous DnaK can be taken-up by bystander cells;
- Other cancer-associated bacteria have DnaKs with similar AAs compositions: implications for origen/progression of some cancers and for anti-cancer therapies.

…But how does this “fragment” persist (replicate)?

- Some data implies that it integrates (paired-end sequence analysis)
- Possible integration sites identified by computer analysis
- It needs to be conclusively demonstrated by PCR of cell sequence junction sites (now in progress).

Oncogene (2008) 27, 4521–4531

www.nature.com/onc

ORIGINAL ARTICLE

Mycoplasma infection suppresses p53, activates NF-κB and cooperates with oncogenic Ras in rodent fibroblast transformation

DY Logunov[1], DV Scheblyakov[1], OV Zubkova[1], MM Shmarov[1], IV Rakovskaya[1], KV Gurova[2], ND Tararova[2], LG Burdelya[2,3], BS Naroditsky[1], AL Ginzburg[1] and AV Gudkov[2,3]

[1]Gamaleya Research Institute for Epidemiology and Microbiology, Moscow, Russia; [2]Cleveland BioLabs Inc., Buffalo, NY, USA and [3]Department of Cell Stress Biology, Roswell Park Cancer Institute, Buffalo, NY, USA

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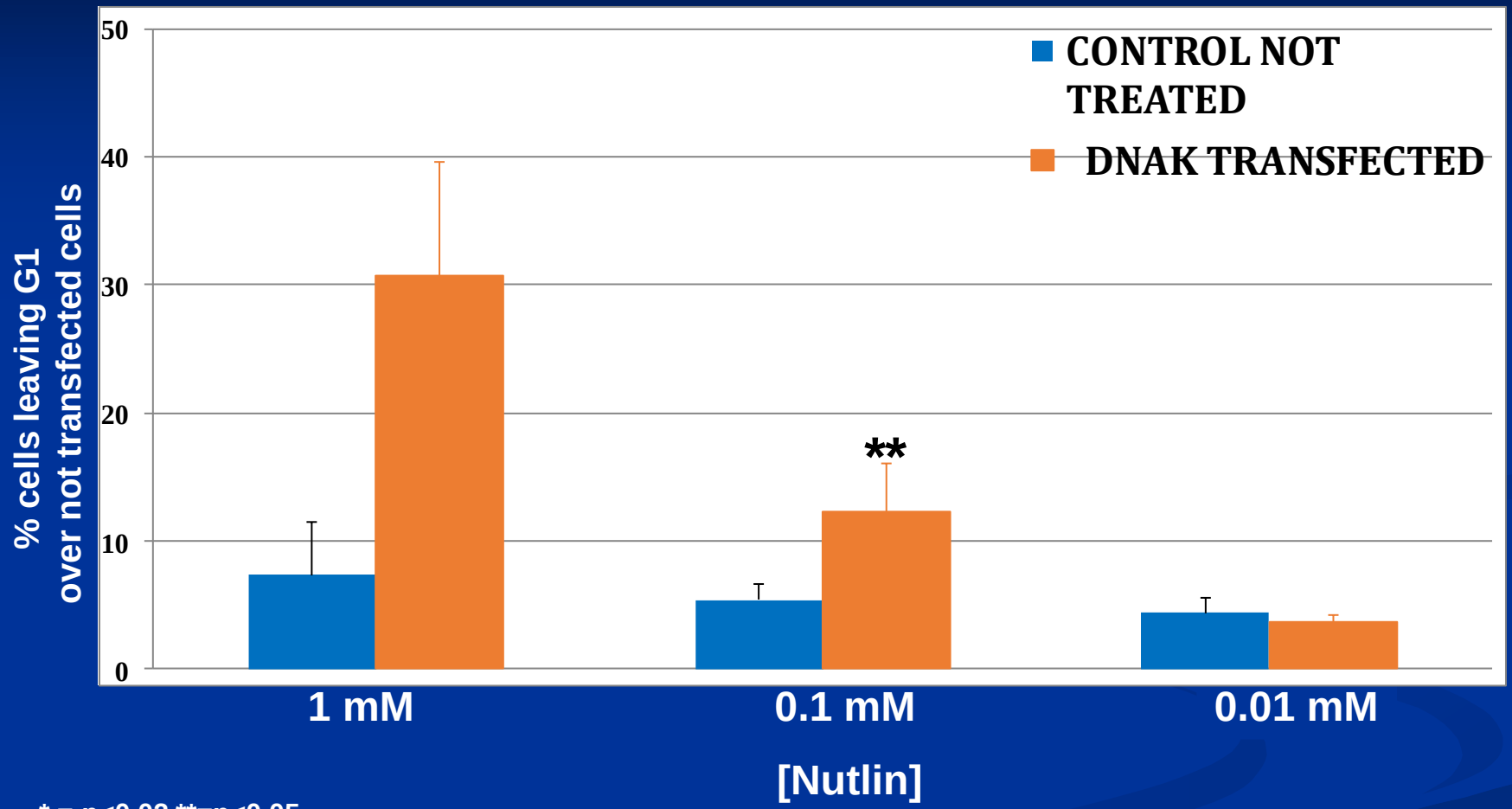
DnaK specifically binds to proteins critical to anti-cancer functions

Cellular proteins interacting with DnaK (IP analysis)	Protein function	Effect
PARP1	DNA-repair	Reduced DNA repair activity
DNA-PKcs	DNA-repair	Reduced DNA repair activity
USP10	De-ubiquinitates and regulates p53 stability	Reduced function of p53, resulting in low expression of Bax, PUMA and p21
DNAJa1 (HSP40)	HSP70 activator	Activation of HSP70 proteins

Proteins analyzed but found IP negative: BRCA2, HSP90b1, p53, HSP70, KU86, SP1, DDB1, ING1, DNAJA2, DNAJB1.

Increased cell cycle progression in adenocarcinoma cells transfected with DnaK



* = p<0.02 **=p<0.05

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