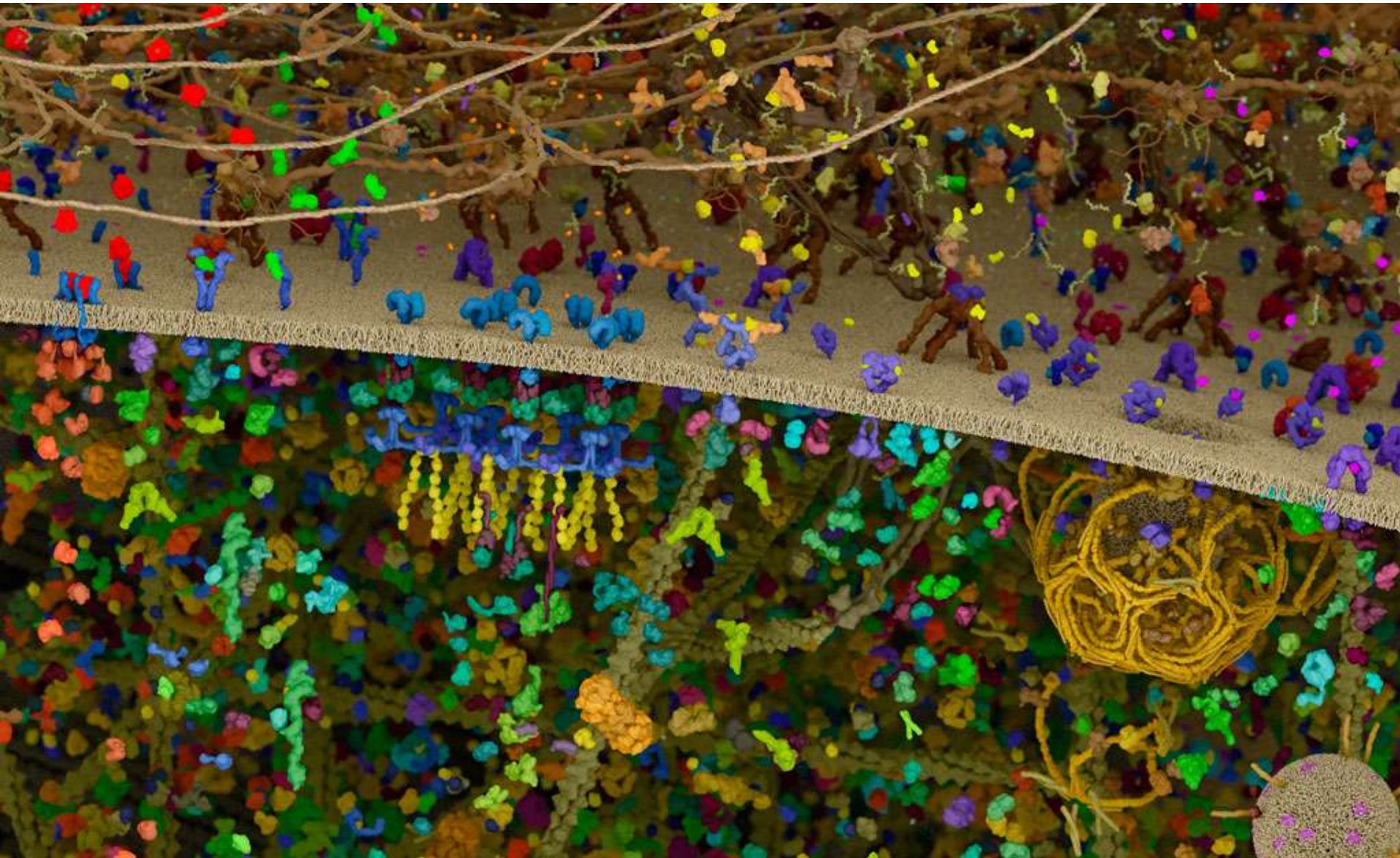
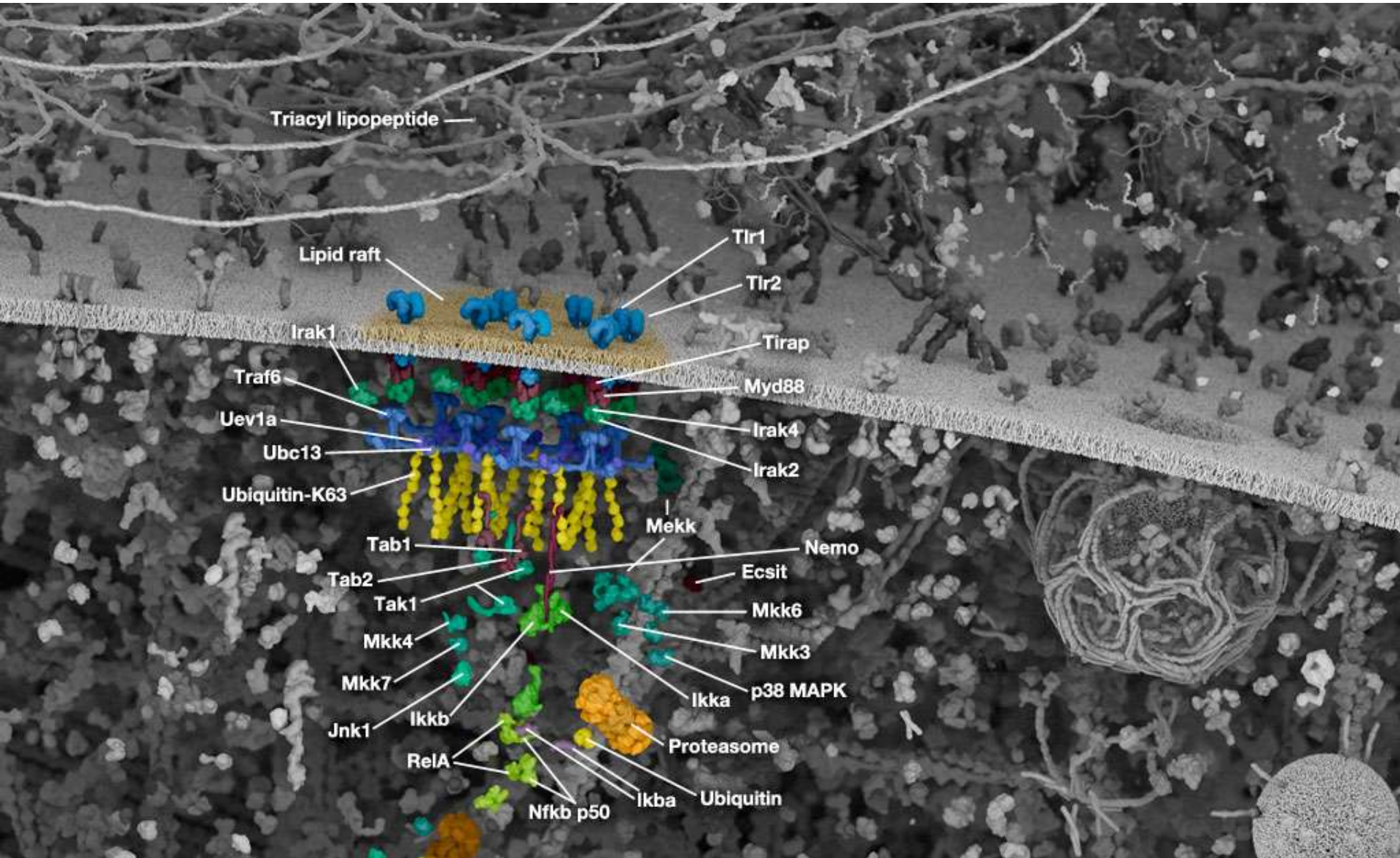
NFκB ELEMENTS IN CANCER PROGNOSIS AND THERAPY

Grup de Recerca en Cèl-lules Mare i Càncer: NF-κB section

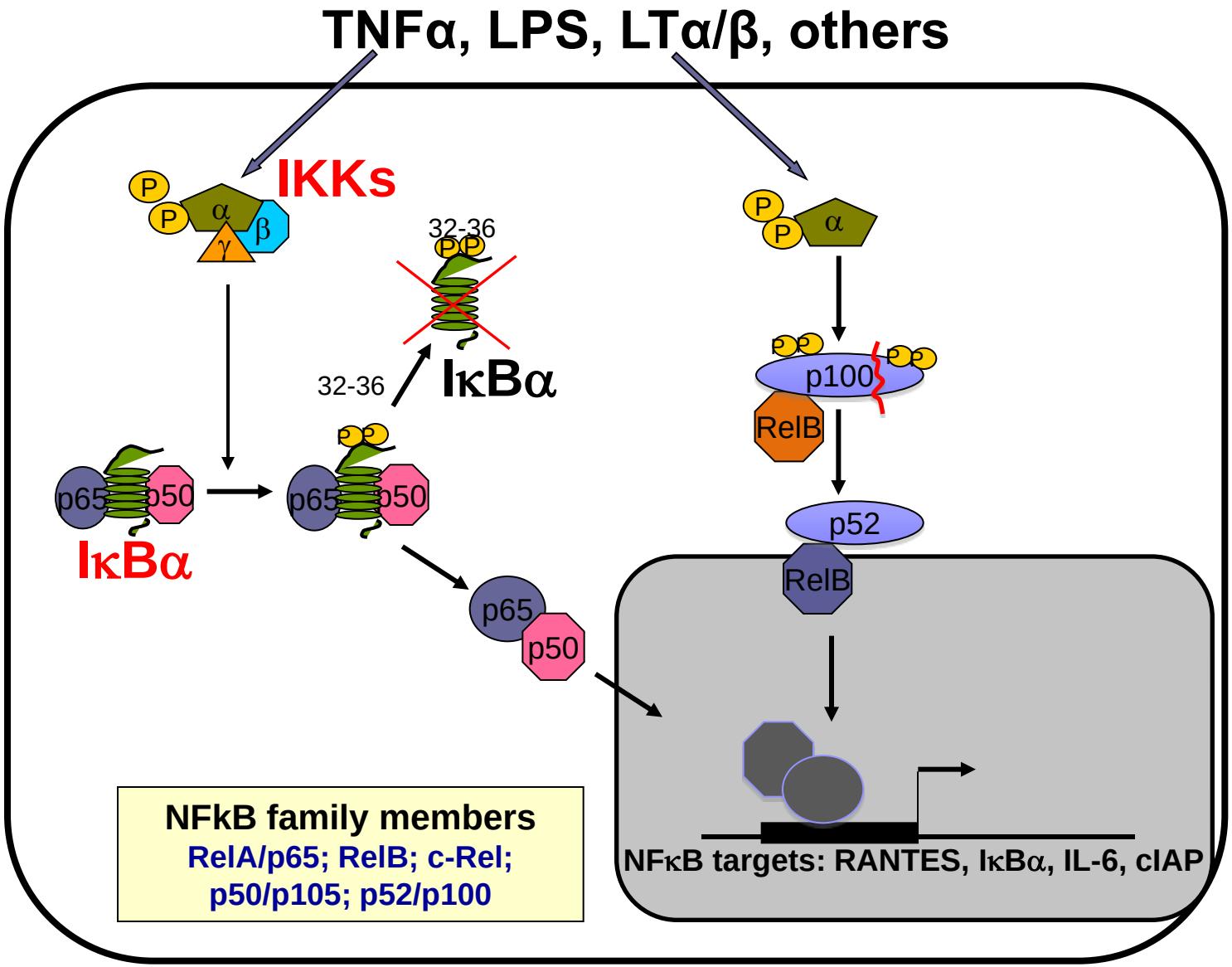
Cells are in a constant dialogue with their environment



Limited number of signaling pathways mediate this interaction



NFκB PATHWAY ACTIVATION



NFκB plays and essential role in inflammation…

…and INFLAMMATION IS RELATED WITH CANCER IN MOST OF THE TISSUES:

- **SMOKING AND LUNG CANCER**
- **HEPATITIS, CIRROSIS AND LIVER CANCER**
- **UNHEALTHY DIET AND COLON CANCER**
- **UV EXPOSURE AND SKIN CANCER…**


COGDE-501; NO OF PAGES 8 ARTICLE IN PRESS

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Current Opinion in Genetics & Development

ELSEVIER

NF-κB and cancer — identifying targets and mechanisms

Willscott E Naugler[1] and Michael Karin[2*]

A connection between inflammation and carcinogenesis has long been known, but the precise mechanisms are just

have emerged over the last couple of years implicating NF-κB signaling pathways and downstream targets in


Research article

NF-κB is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression

Margit A. Huber,[1,2,3] Ninel Azoitei,[1] Bernd Baumann,[1] Stefan Grünert,[2] Andreas Sommer,[2] Hubert Pehamberger,[2] Norbert Kraut,[4] Hartmut Beug,[2] and Thomas Wirth[1]

[1]Department of Physiological Chemistry, Ulm University, Ulm, Germany. [2]Institute of Molecular Pathology, Vienna, Austria. [3]Department of Dermatology, Vienna Medical University, Vienna, Austria. [4]Department of New Chemical Entity Lead Discovery, Boehringer Ingelheim Austria GmbH, Vienna, Austria.

REVIEWS


NF-κB: LINKING INFLAMMATION AND IMMUNITY TO CANCER DEVELOPMENT AND PROGRESSION

Michael Karin and Florian R. Greten‡*

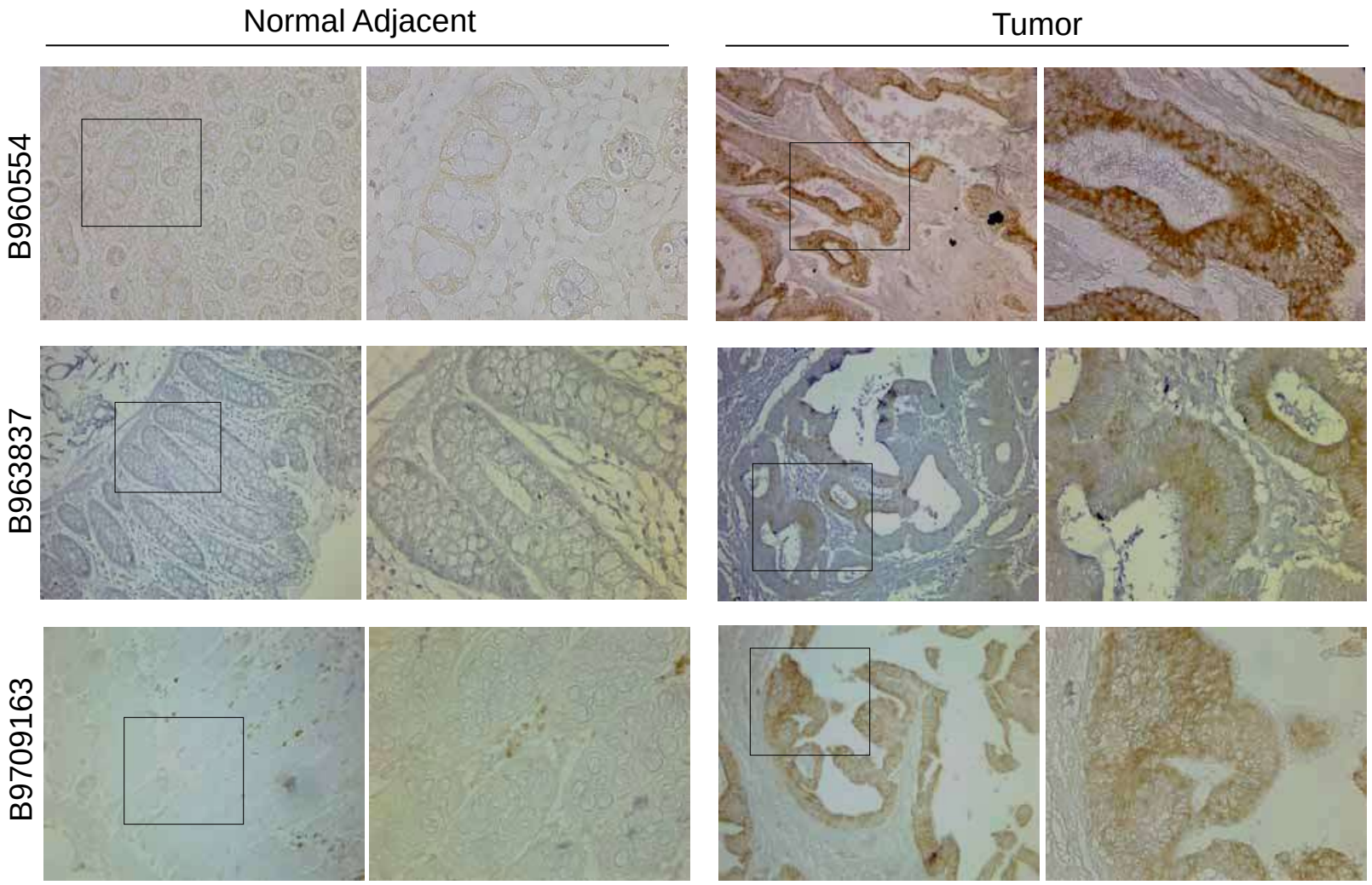
Abstract | There has been much effort recently to probe the long-recognized relationship between the pathological processes of infection, inflammation and cancer. For example, epidemiological studies have shown that ~15% of human deaths from cancer are associated

Nuclear IKK activity leads to dysregulated Notch-dependent gene expression in colorectal cancer

V. Fernández-Majada*, C. Aguilera*, A. Villanueva†, F. Vilardell†, A. Robert-Moreno*, A. Aytés†, F. X. Real‡, G. Capella†, M. W. Mayo§, L. Espinosa*¶, and A. Bigas*¶

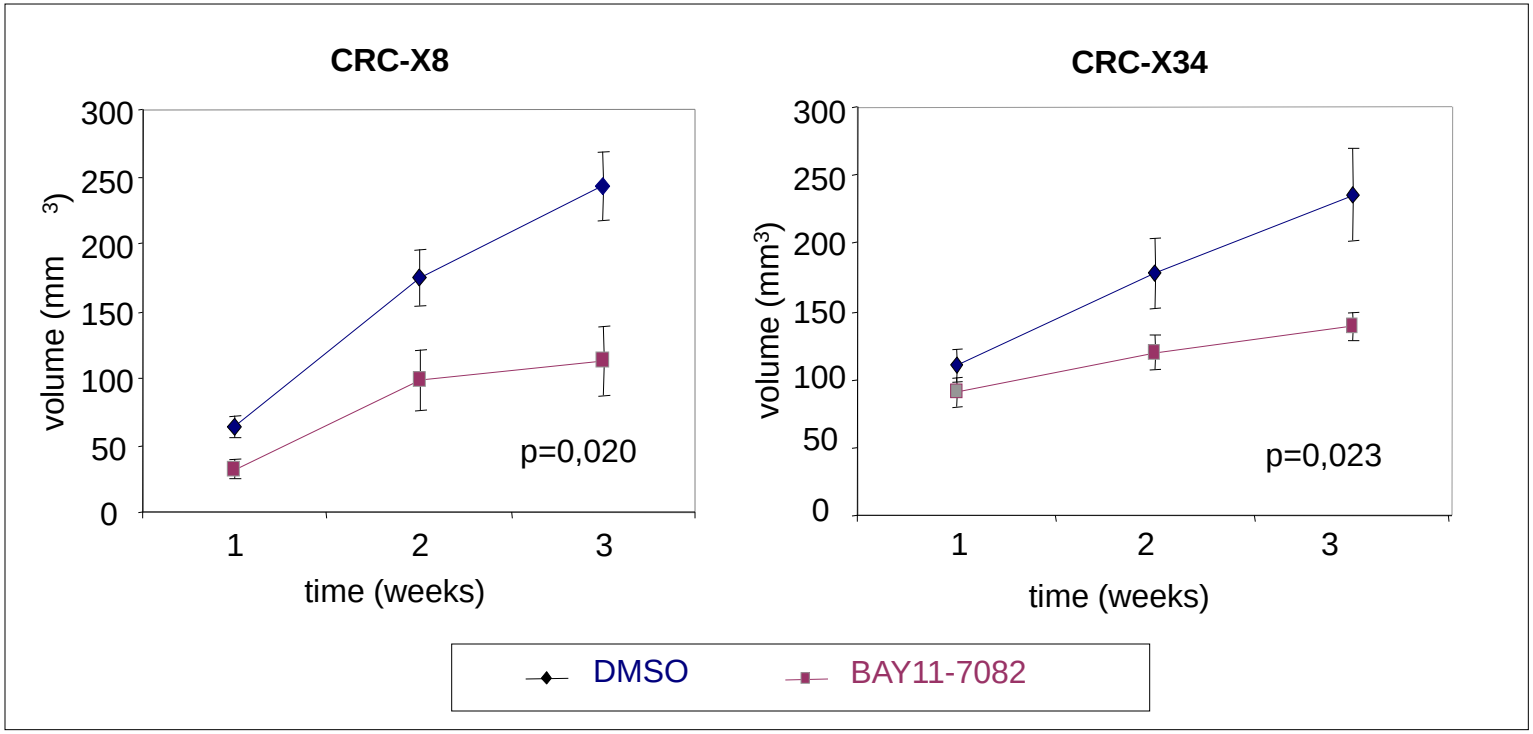
*Centre Oncologia Molecular, Institut d'Investigació Biomèdica de Bellvitge, Gran Via Km 2.7, Hospitalet, 08907 Barcelona, Spain; †Laboratori de Recerca Translacional, Institut d'Investigació Biomèdica de Bellvitge-Institut Català de Oncologia, Gran Via Km 2.7, Hospitalet, 08907 Barcelona, Spain; ‡Unitat de Biologia Celular i Molecular, Institut Municipal d'Investigació Mèdica, Universitat Pompeu Fabra, 08003 Barcelona, Spain; and §Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, VA 22908

IKKS ARE ACTIVATED IN COLORECTAL CANCER CELLS



α-P-IKKα/β STAINING

TREATMENT WITH THE IKK INHIBITOR BAY 11-7082 REDUCES TUMOR GROWTH "IN VIVO"



… however general NFκB inhibition leads to severe side effects…

Cell PRESS

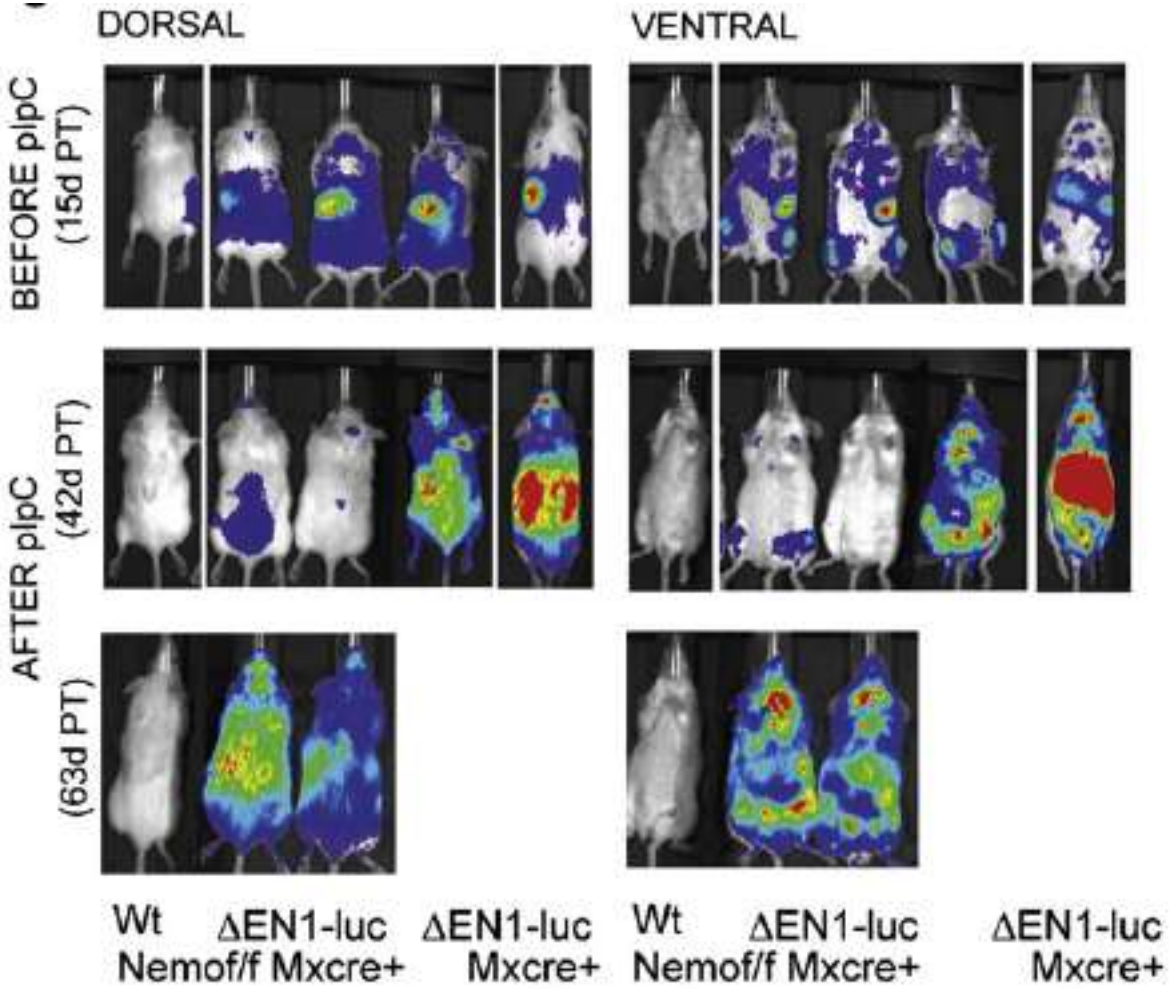
Cancer Cell
Article

The Notch/Hes1 Pathway Sustains NF-κB Activation through *CYLD* Repression in T Cell Leukemia

Lluis Espinosa,[1,12,*] Severine Cathelin,[2,12] Teresa D'Altri,[1] Thomas Trimarchi,[2] Alexander Statnikov,[3] Jordi Guiu,[1] Veronica Rodilla,[1] Julia Inglés-Esteve,[1] Josep Nomdedeu,[4] Beatriz Bellosillo,[5] Carles Besses,[6] Omar Abdel-Wahab,[7] Nicole Kucine,[7,8] Shao-Cong Sun,[9] Guangchan Song,[10] Charles C. Mullighan,[10] Ross L. Levine,[7] Klaus Rajewsky,[11] Iannis Aifantis,[2,13,*] and Anna Bigas[1,13,*]

[1]Cancer Research Program, Institut Municipal d'Investigacions Mèdiques, (IMIM), Hospital del Mar, 08003 Barcelona, Spain
[2]Howard Hughes Medical Institute and Department of Pathology

ABROGATING NFκB LEADS TO THE CLEARANCE OF TUMOR CELLS IN ALREADY ESTABLISHED LEUKEMIA



NF-κB is not a common target for anti-cancer therapies!!!!!

… and IKK activation is not used as a biomarker for cancer diagnosis

THE NEXT 10 YEARS

The diverse and complex roles of NF-κB subunits in cancer

Neil D. Perkins

… and in specific physiological functions…

Please cite this article in press as: Margalef et al., A Truncated Form of IKKα Is Responsible for Specific Nuclear IKK Activity in Colorectal Cancer, Cell Reports (2012), http://dx.doi.org/10.1016/j.celrep.2012.08.028

Cell Reports

Article

Cell PRESS

Open ACCESS

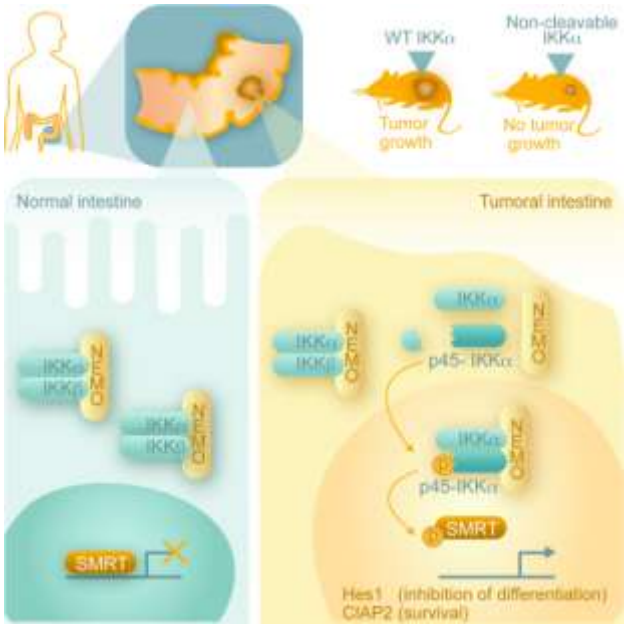
A Truncated Form of IKKα Is Responsible for Specific Nuclear IKK Activity in Colorectal Cancer

Pol Margalef,[1,8] Vanessa Fernández-Majada,[1,8,9] Alberto Villanueva,[3] Ricard Garcia-Carbonell,[1,2] Mar Iglesias,[2] Laura López,[2] María Martínez-Iniesta,[3] Jordi Villà-Freixa,[4] Mari Carmen Mulero,[1] Montserrat Andreu,[5] Ferran Torres,[6] Marty W. Mayo,[7] Anna Bigas,[1] and Lluis Espinosa[1,*]

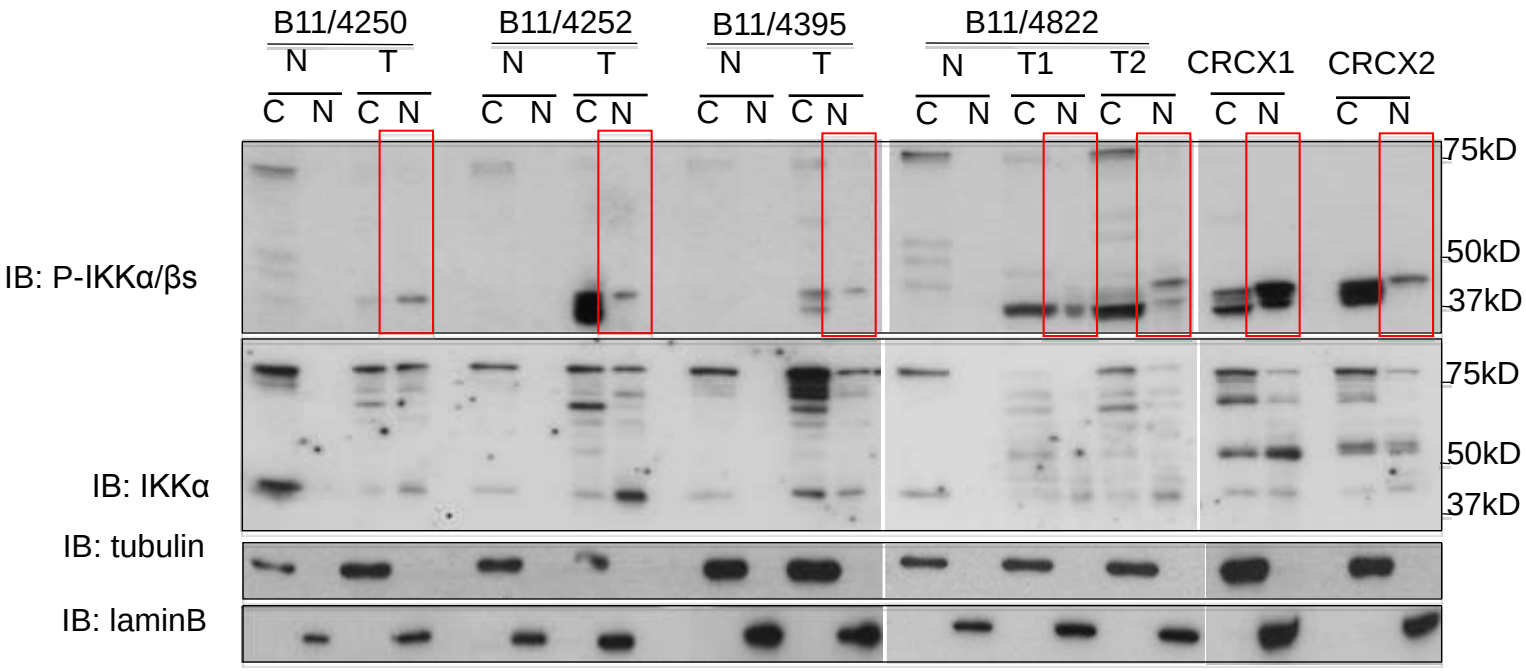
[1]Institut Municipal d'Investigacions Mèdiques (IMIM)

[2]Department of Pathology

Institut Hospital del Mar d'Investigacions Mèdiques, Parc de Recerca Biomèdica de Barcelona, Barcelona 08003, Spain

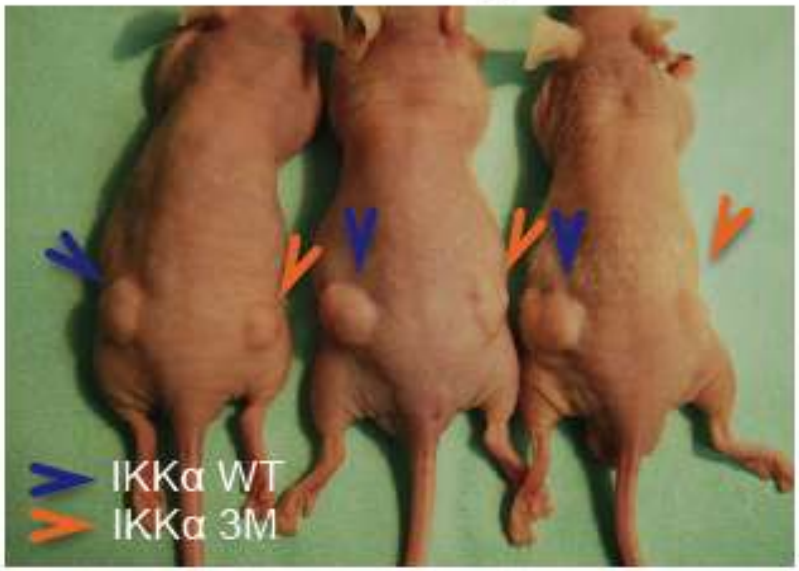


NUCLEAR IKK FROM HUMAN CRC SAMPLES CORRESPONDS TO A 45kD IKKα MOLECULE (also found in cell lines)

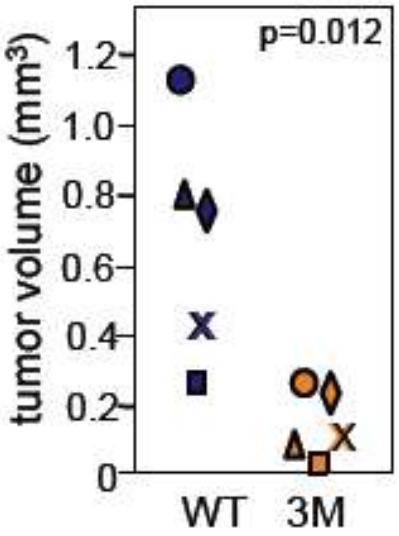


… AND TO PROMOTE TUMOR CELL GROWTH

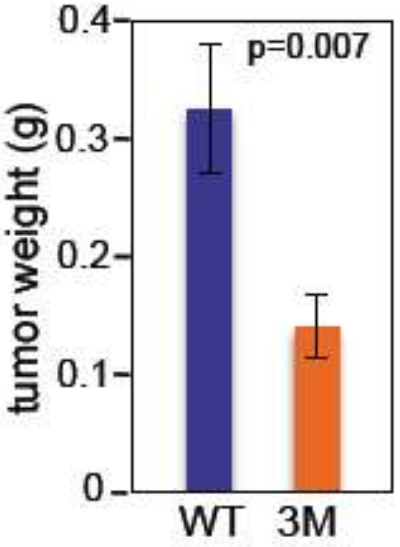
E

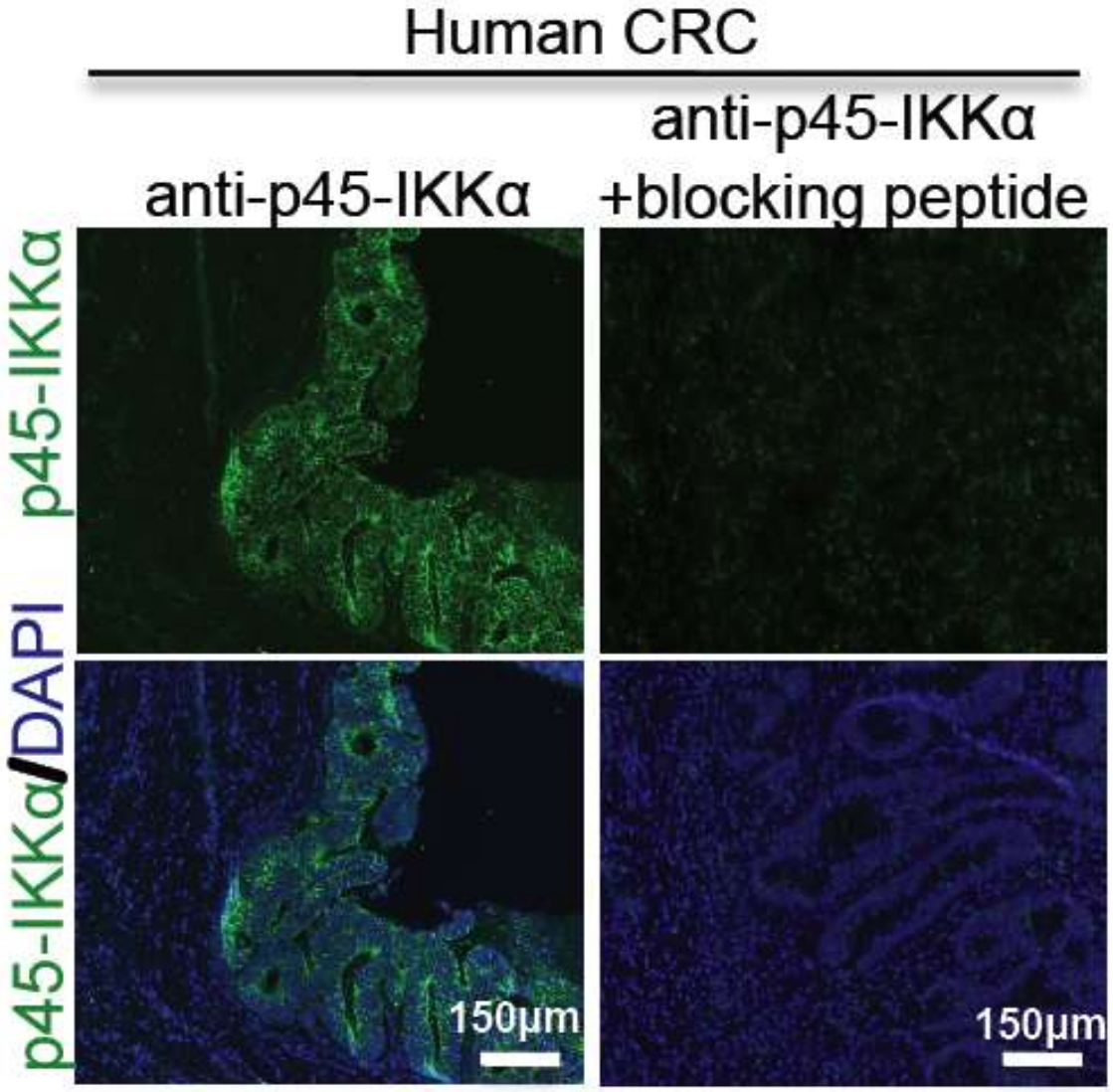


F



G




Human CRC
anti-p45-IKKα
anti-p45-IKKα
+blocking peptide
p45-IKKα
p45-IKKα/DAPI
150μm
150μm

- **Inhibiting p45-IKK activity would potentially prevent cancer progression (in selected patients and tumor types) without affecting normal cell physiology**

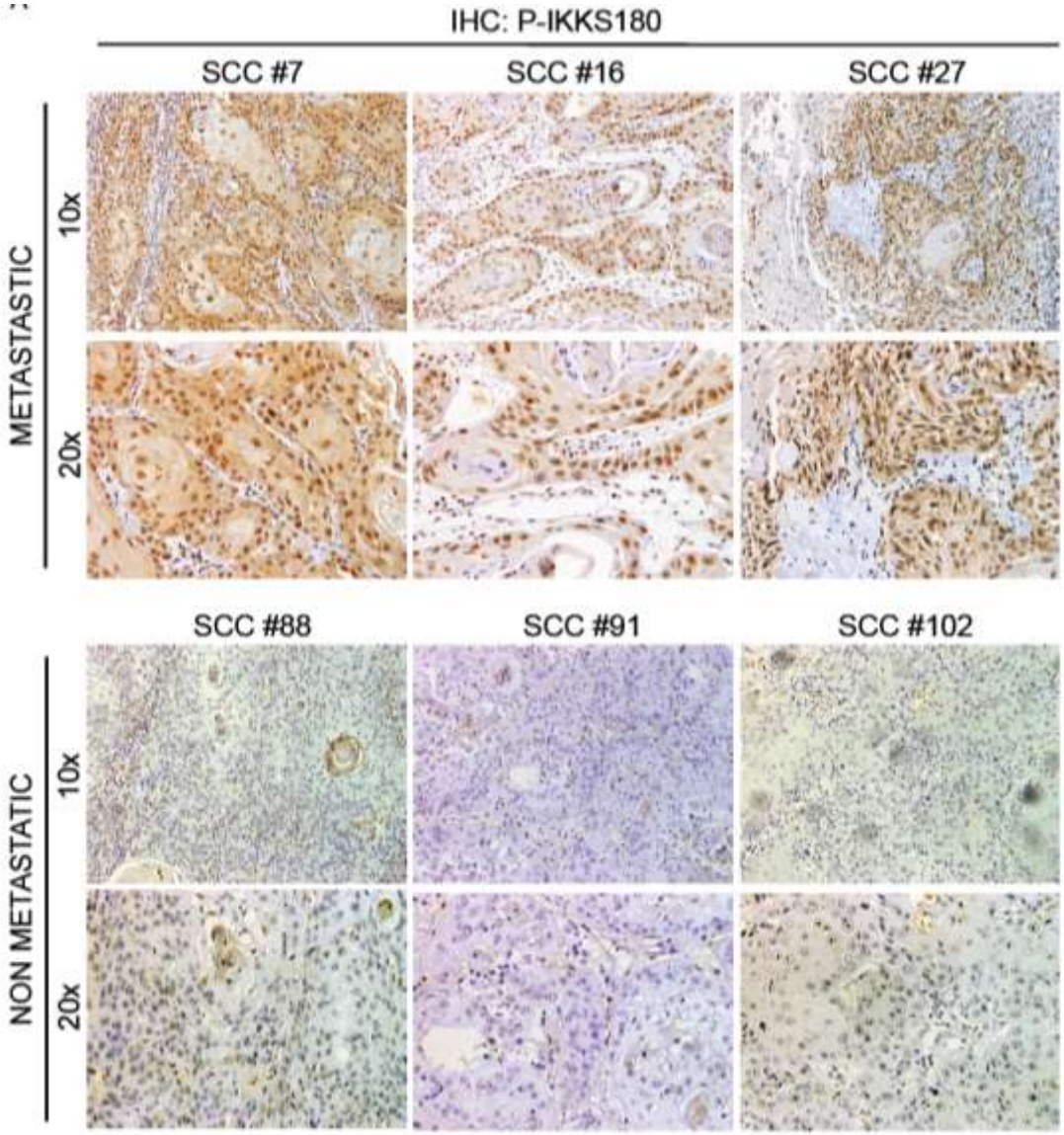
- **We need to further study the contribution of p45-IKK to cancer progression and therapy response…**

… NEXT????

- **Determine the specific types of cancer that depend on p45-IKK and which are the signals that induces p45-IKK in cancer.**

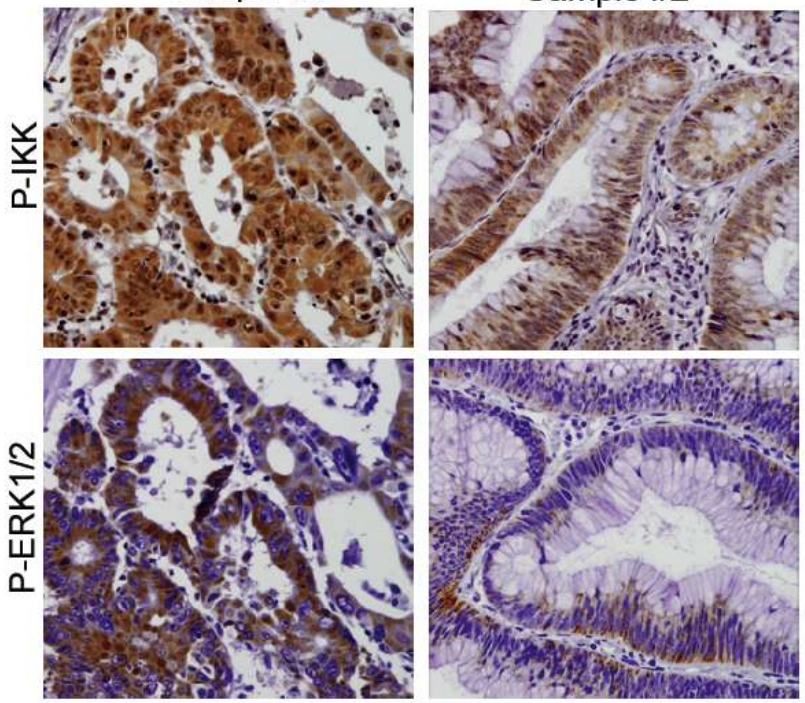
- **This will help to design/identify compounds that specifically target p45-IKK activity and classify those patients or tumor types that would benefit of future anti-p45-IKK therapies**

Nuclear IKK is an independent biomarker that predicts SCC prognosis and stratify patients that will benefit from future anti-p45-IKK treatments

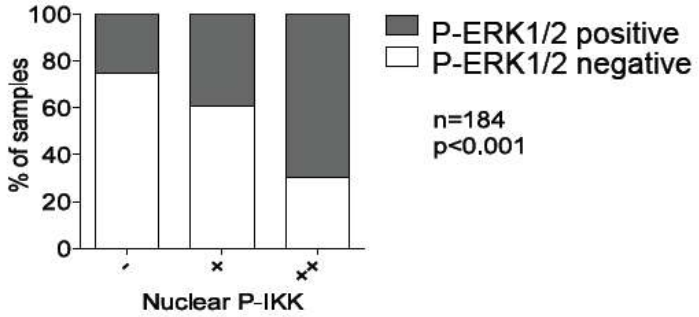


Active nuclear IKK associates with active MAPK pathway and BRAF mutations in CRC

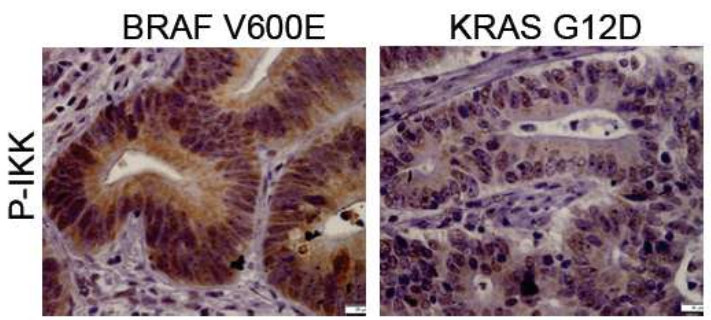
A



B



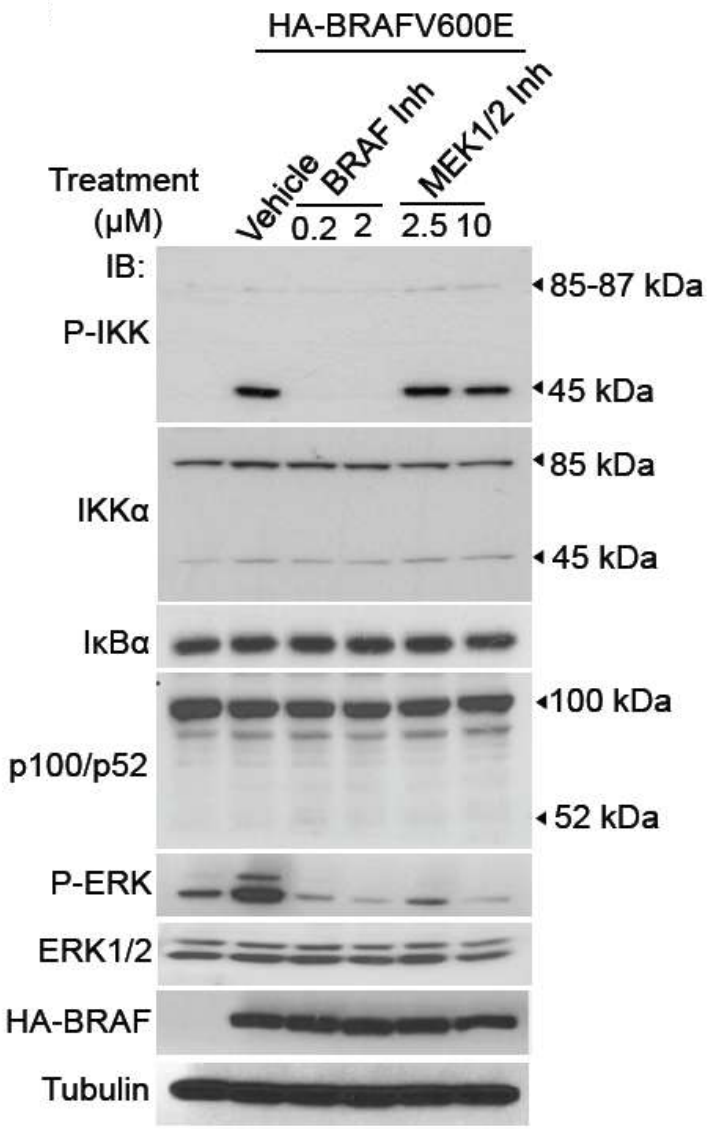
C



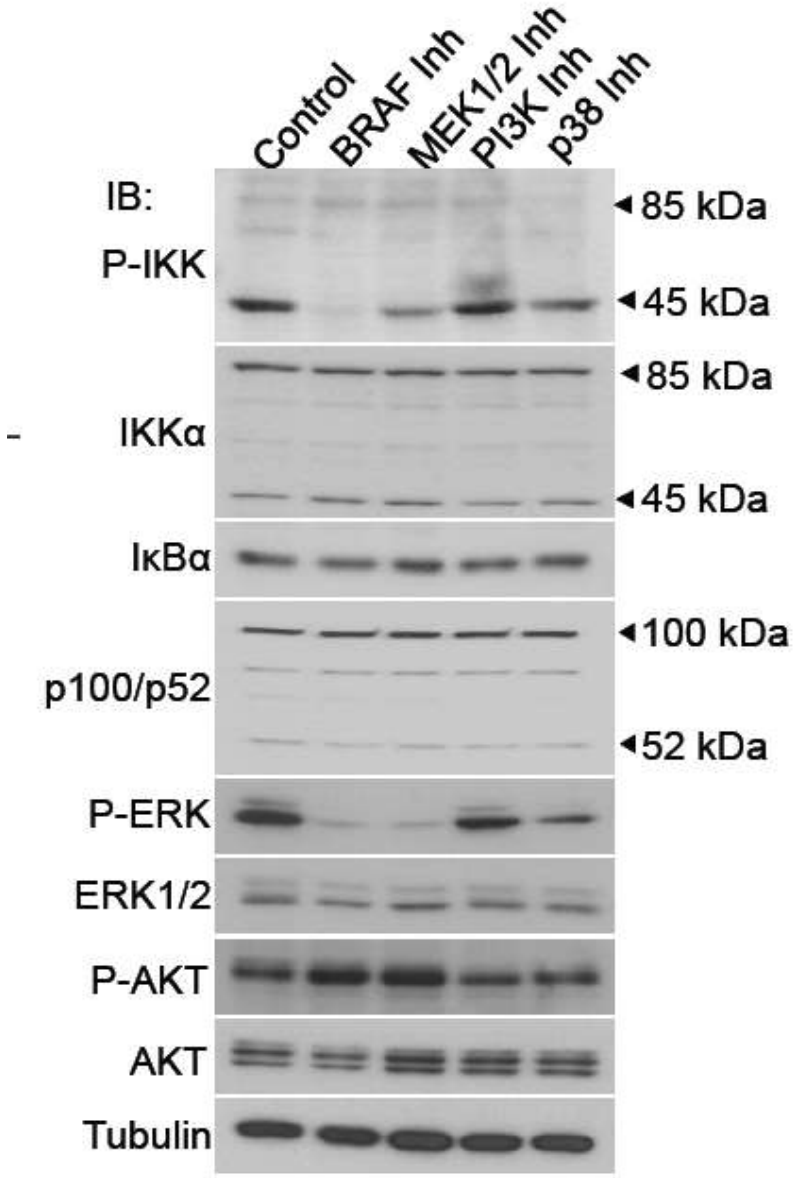
Nuclear P-IKK	negative	low	high	TOTAL
WT	5 (6.2)	68 (62.6)	9 (13.2)	82
Mutant	2 (0.8)	3 (8.4)	6 (1.8)	11
TOTAL	7	71	15	93

p<0.001

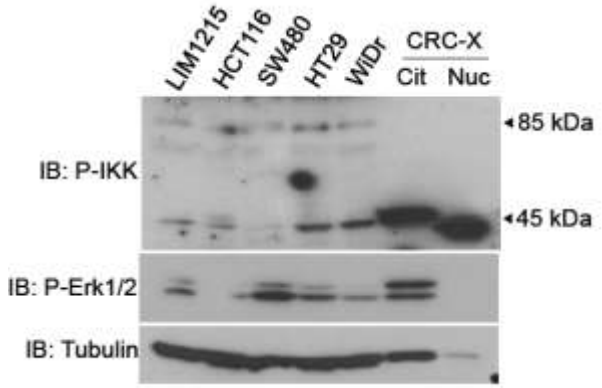
BRAF (and KRAS) INDUCES p45-IKKα

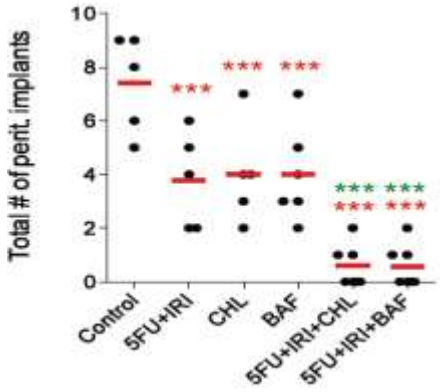


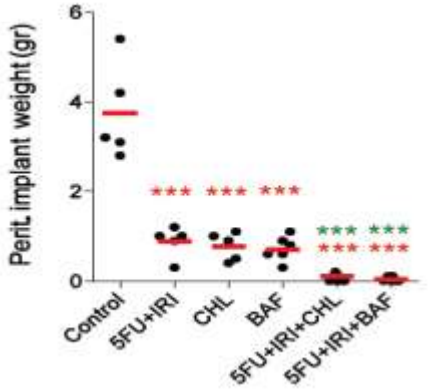
INHIBITION OF BRAF IN CANCER CELLS INHIBITS p45-IKKα ACTIVITY

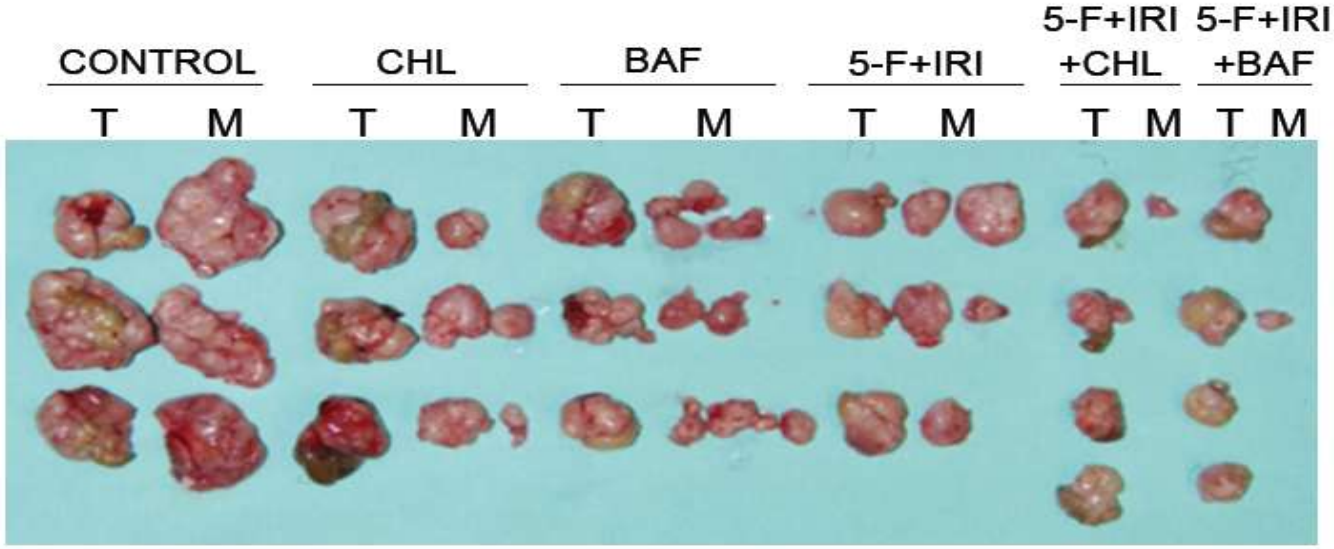


ENDOSOME INHIBITORS POTENCIATE THE EFFECT OF CHEMOTHERAPY (SPECIALLY ON PREVENTING METASTASIS)









WE KNOW THAT p45-IKK is also active in Melanoma Cell lines that are extremely sensitive to Bafilomycin A1 treatment.

We plan to test the possible use of p45-IKK inhibition in different in vivo models

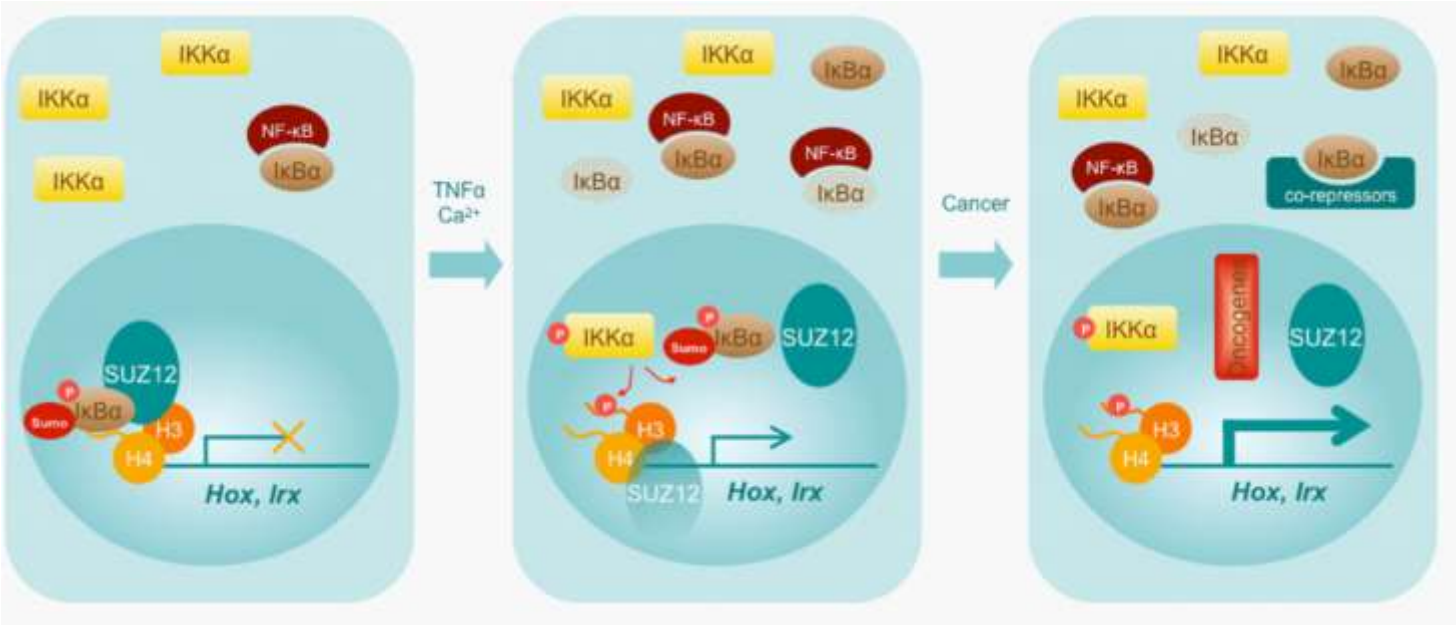
Please cite this article in press as: Mulero et al., Chromatin-Bound IκBα Regulates a Subset of Polycomb Target Genes in Differentiation and Cancer, Cancer Cell (2013), http://dx.doi.org/10.1016/j.ccr.2013.06.003

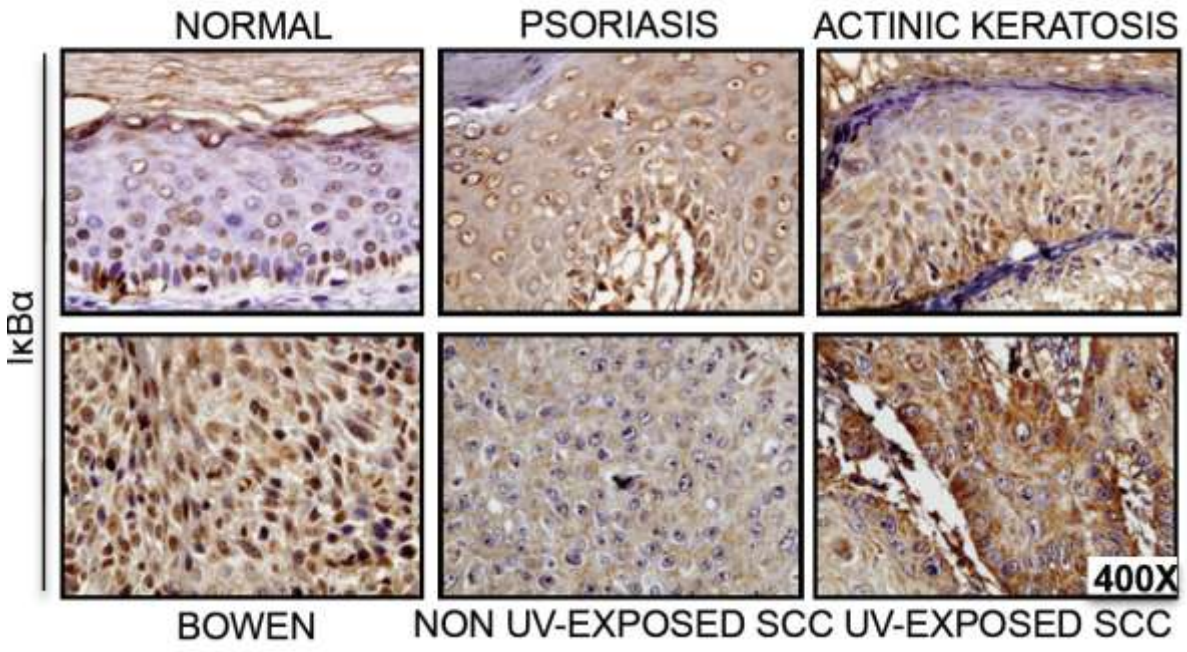
Cancer Cell

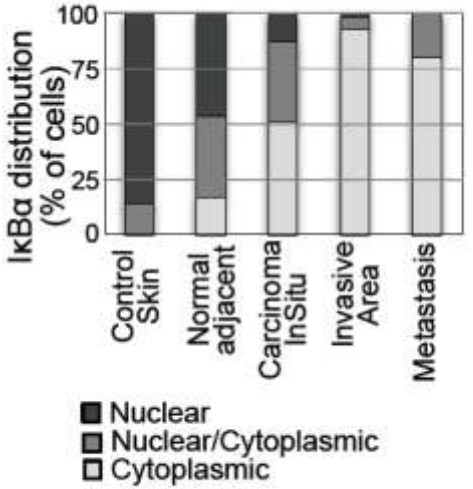
Article

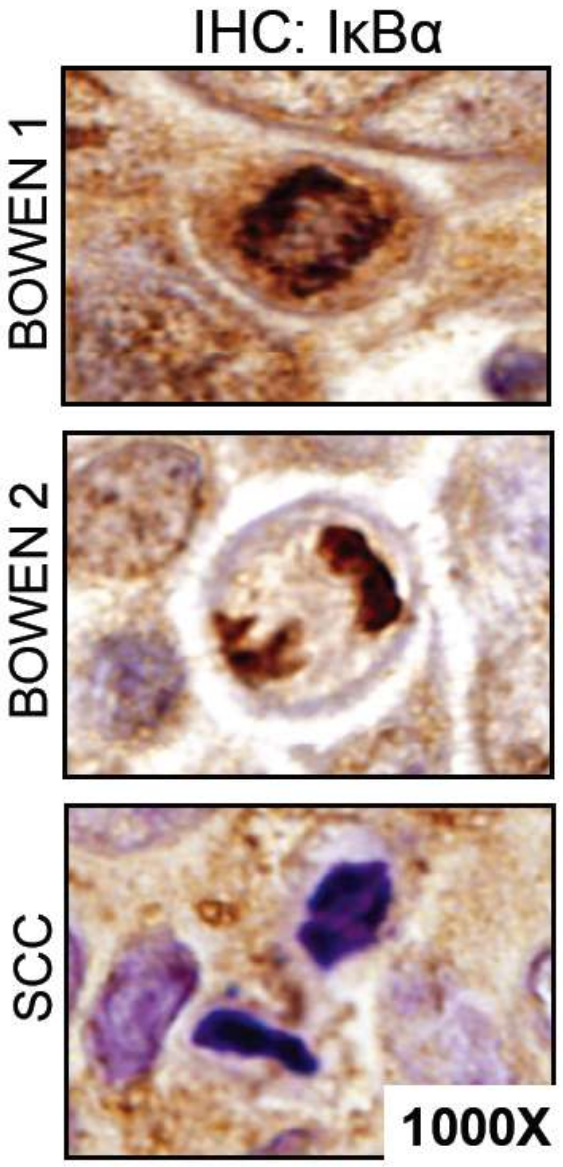
Chromatin-Bound IκBα Regulates a Subset of Polycomb Target Genes in Differentiation and Cancer

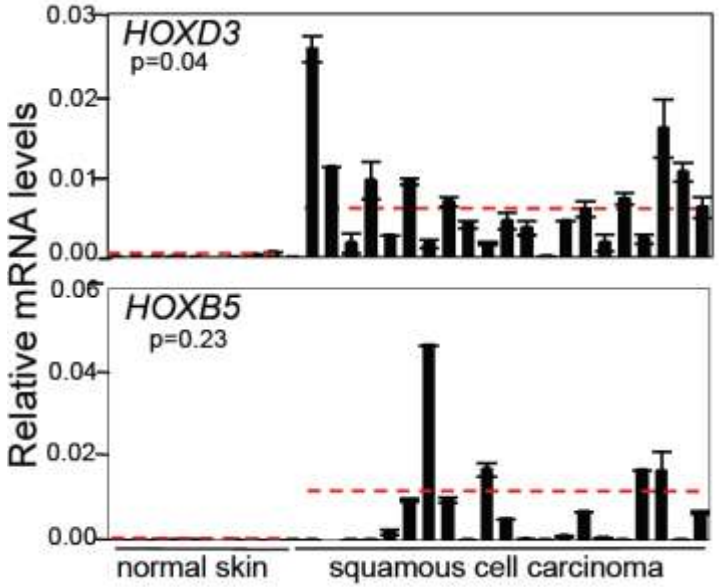
Maria Carmen Mulero,[1] Dolors Ferres-Marco,[2] Abul Islam,[3,4] Pol Margalef,[1] Matteo Pecoraro,[5] Agustí Toll,[6] Nils Drechsel,[8] Cristina Charneco,[8] Shelly Davis,[9] Nicolás Bellora,[3] Fernando Gallardo,[6] Erika López-Arribillaga,[1] Elena Asensio-Juan,[1] Verónica Rodilla,[1] Jessica González,[1] Mar Iglesias,[7] Vincent Shih,[10] M. Mar Albà,[3,11] Luciano Di Croce,[5,11] Alexander Hoffmann,[10] Shigeki Miyamoto,[9] Jordi Villà-Freixa,[8,12] Nuria López-Bigas,[3,11] William M. Keyes,[5] María Domínguez,[2] Anna Bigas,[1,13] and Lluís Espinosa[1,13,*]

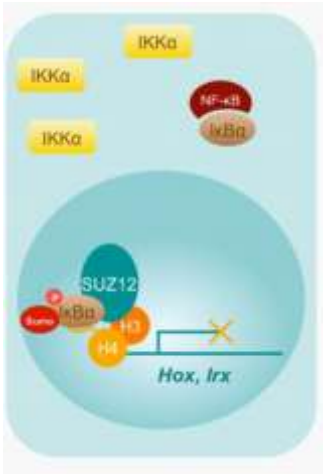



NORMAL
PSORIASIS
ACTINIC KERATOSIS
IκBα
400X
BOWEN
NON UV-EXPOSED SCC
UV-EXPOSED SCC


IκBα distribution (% of cells)
100
75
50
25
0
Control Skin
Normal adjacent
Carcinoma InSitu
Invasive Area
Metastasis
Nuclear
Nuclear/Cytoplasmic
Cytoplasmic


IHC: IκBα
BOWEN 1
BOWEN 2
SCC
1000X


HOXD3
p=0.04
HOXB5
p=0.23
Relative mRNA levels
0.03
0.02
0.01
0.00
0.06
0.04
0.02
0.00
normal skin
squamous cell carcinoma


IKKα
IKKα
IKKα
NF-κB
IκBα
SUZ12
IκBα
H3
H4
Hox, Irx

We are now studying whether nuclear IκBα can be used a a cancer biomarker

And whether we can identify any potential therapetic target in this pathway for specific tumor types

OUR LAB:

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LLUIS ESPINOSA, PhD

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RICARD GARCIA-CARBONELL
CARLOTA COLOMER
CRISTINA RIUS
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JESSICA GONZALEZ
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ERIKA LÓPEZ
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