

II- From development to cancer: tumour growth mechanical cues in the reactivation of mechanosensitive embryonic pathways

Mechanical induction of the tumorogenic β -catenin pathway by
tumour growth pressure
in vivo



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dépasser les frontières



Historically

- From 80's to early 2000's, Biophysicists interests in

Endothelial cell structural reactions to blood hydrodynamics stress

Ex: Martin Schwartz

Cytoskeleton reorganisation, cell division control

Tumour cell structural reactions to fibrotic stiffness:

Ex: Mina Bissel, Valérie Weaver (UCSF),

Cell culture, cytoskeleton reorganisation, cell division control

- From early 2000's to now, Biophysicists interests in

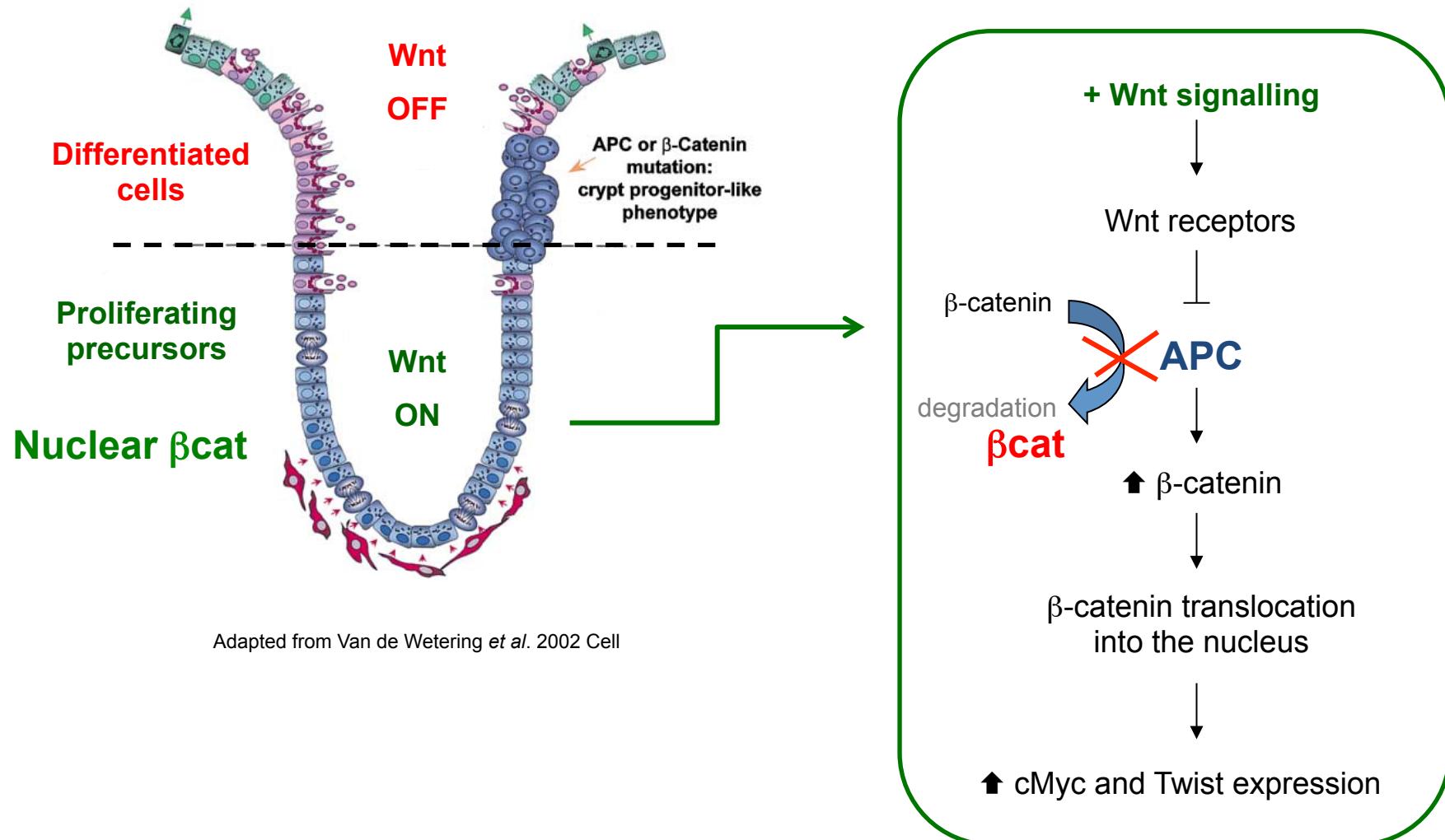
Cell differentiation in response to strain in vivo (E.

Farge (I. Curie, 2003 to now) and to stiffness in cell

culture (D. Discher, U-Penn, 2006 to now)

Introduction : mice colon carcinogenesis

Model for the role of β -Catenin in the early stages of intestinal tumorigenesis

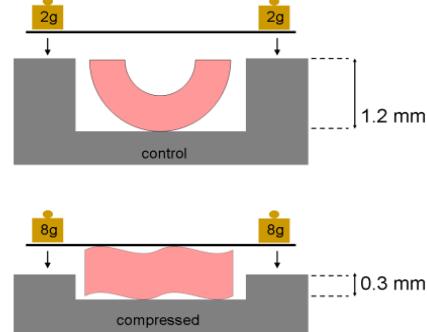


Induction of the tumour gene Myc *ex-vivo* in *Apc* heterozygous mice colon

Ex vivo mechanical compression of the distal colon,
0.8 kPa

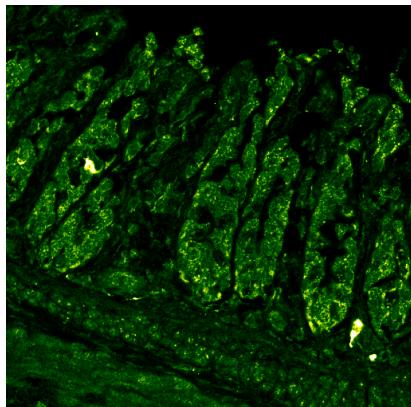


$APC^{1638N/+}$

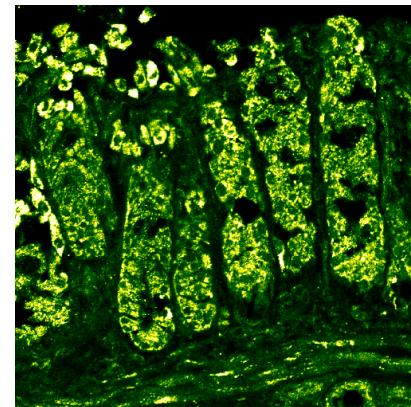


Whitehead et al. HFSPJ 2008

1 cMyc control

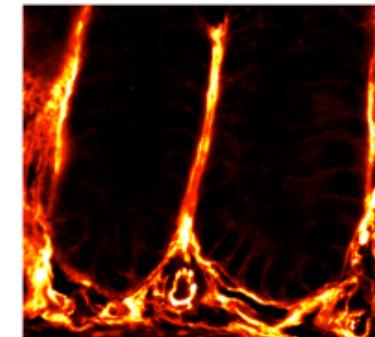


compressed

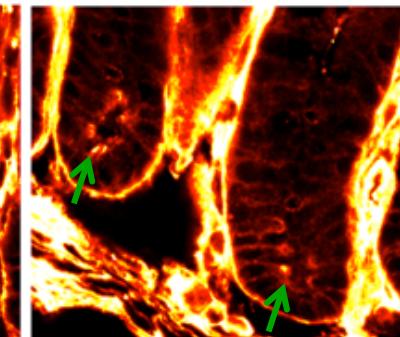


pY654 β -catenin

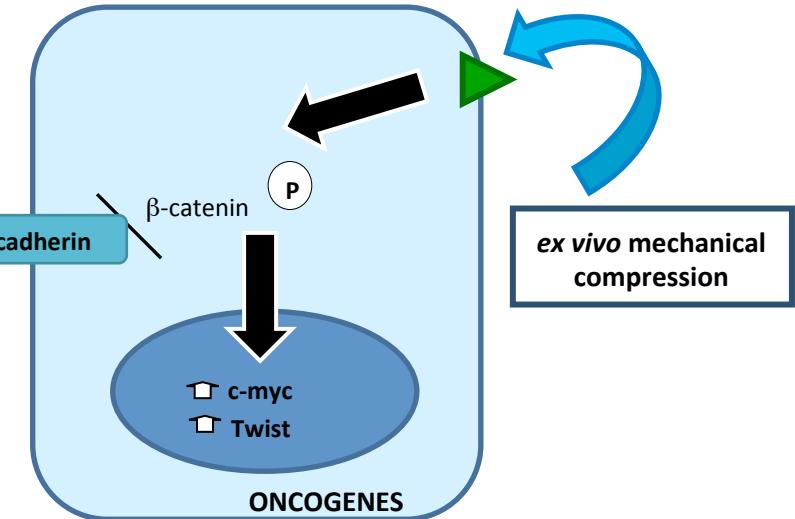
control



compressed



2



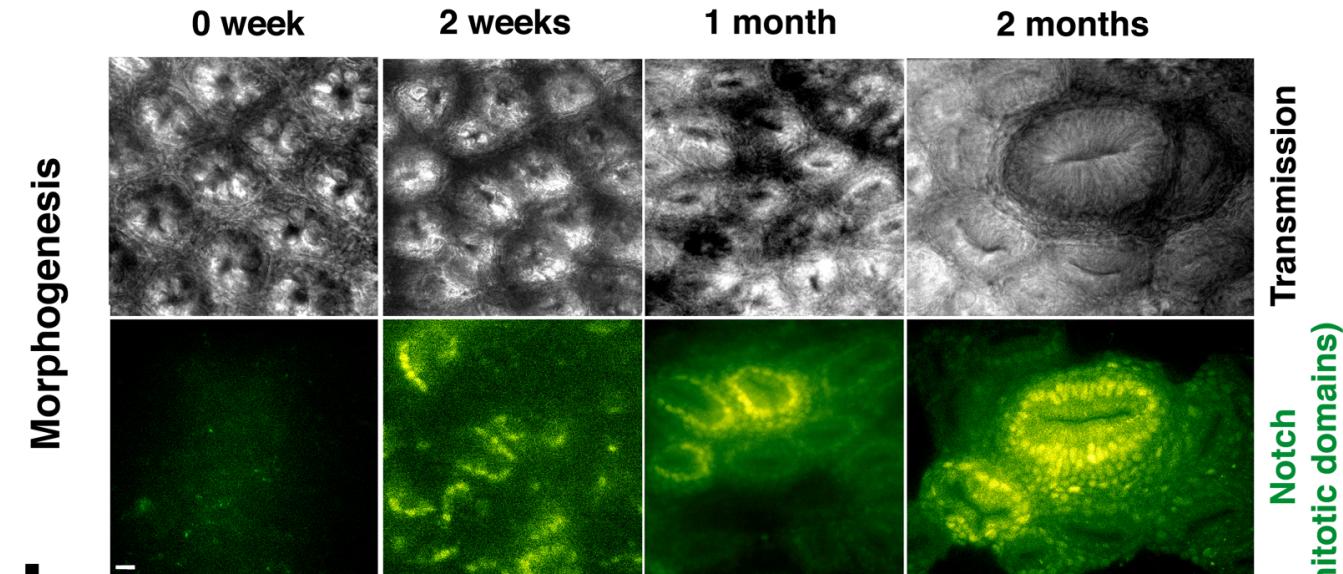
Whitehead et al, HFSPJ, 2008 (β -cat pathway activated by external pressure)

Samuel et al, Cancer Cell 2011 (β -cat pathway activated by stiffness increase)

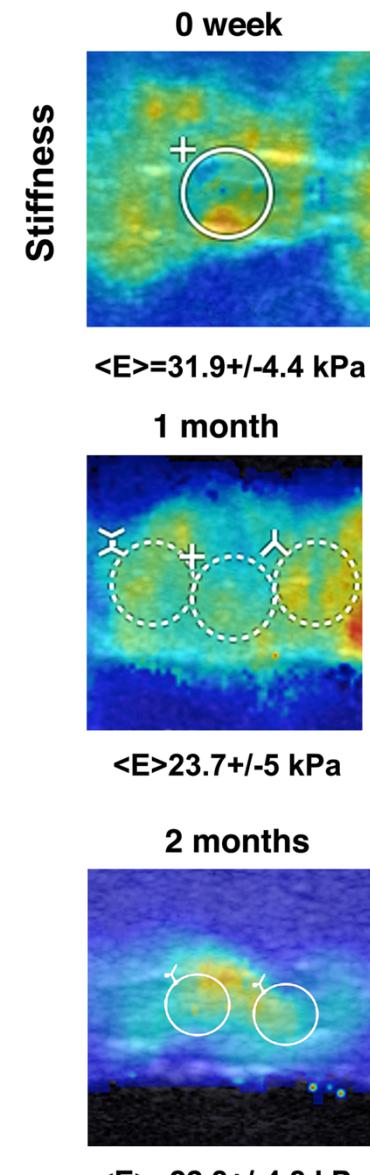
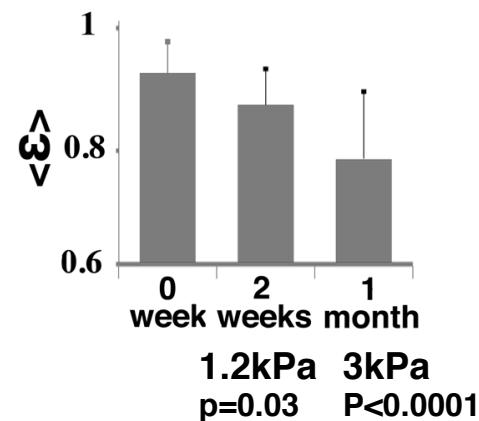
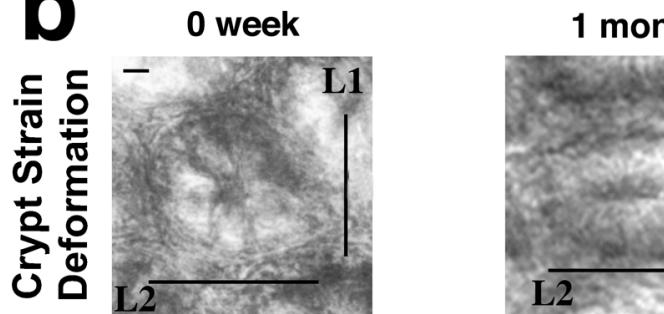
Notch hyper-proliferative domains induce crypt strain deformation without change of stiffness

a

N/Apc tumourigenesis initiation

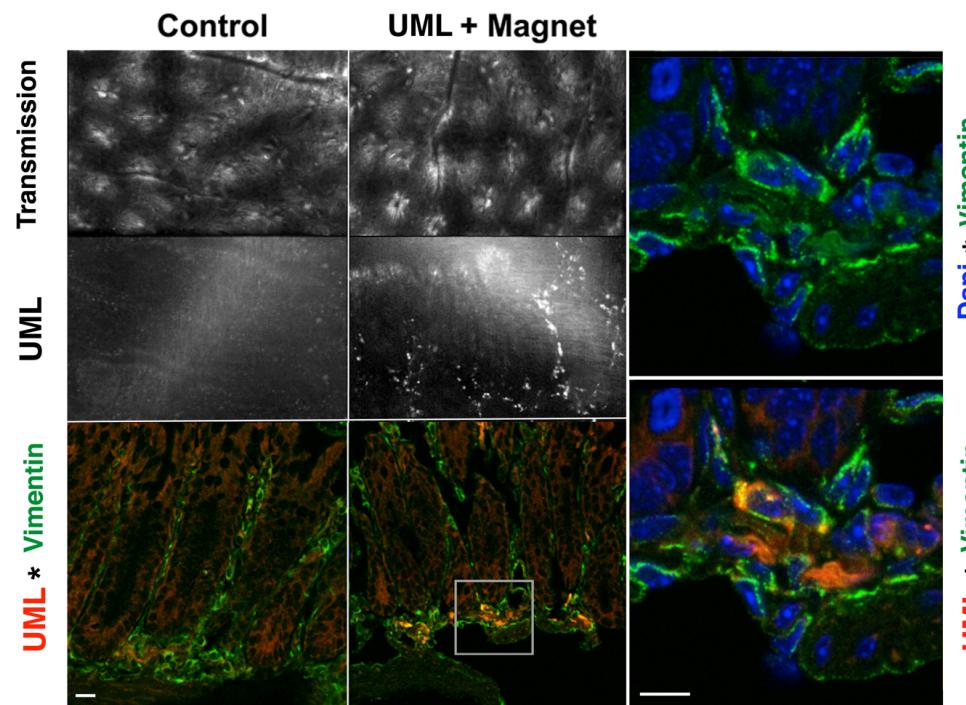
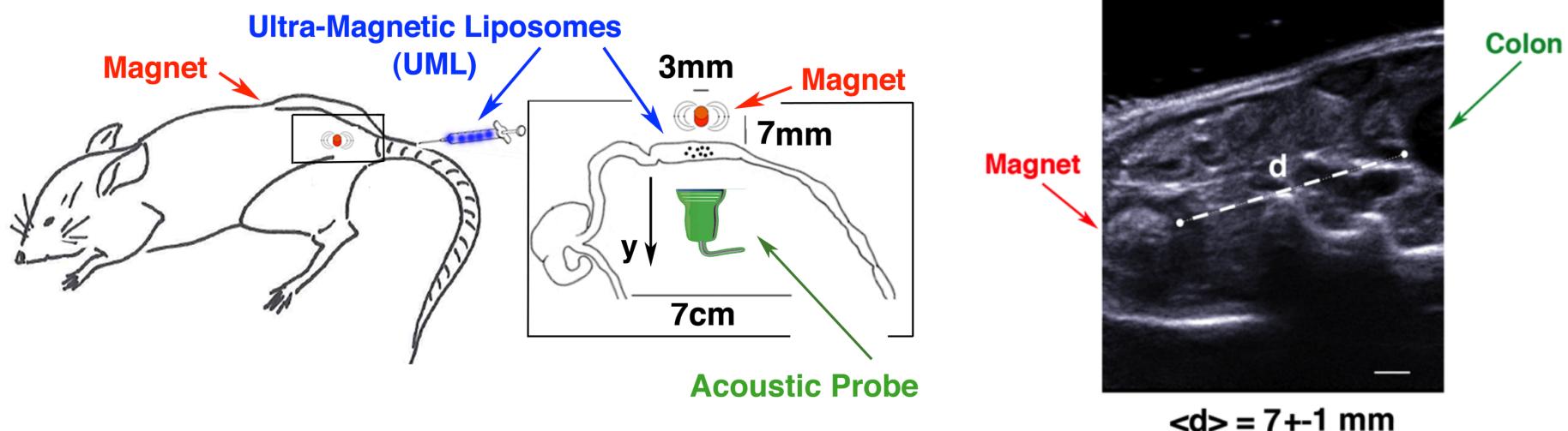


b

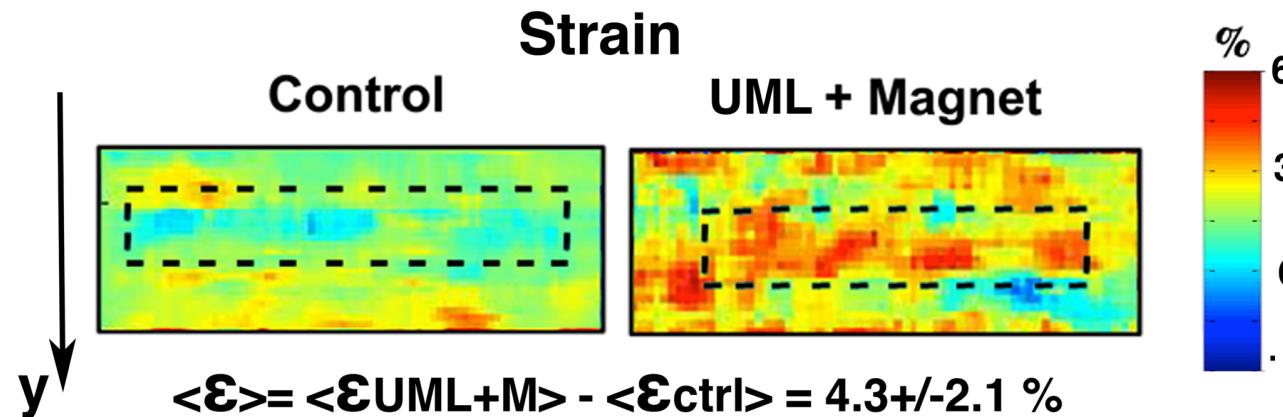


σ locally ranges from 0.4 to 5.6 kPa at one month
(3kPa mean value, 13% mean strain deformation)

Mimicking tumour growth pressure using a magnetic field gradient on magnetically loaded colon tissues, *in vivo*

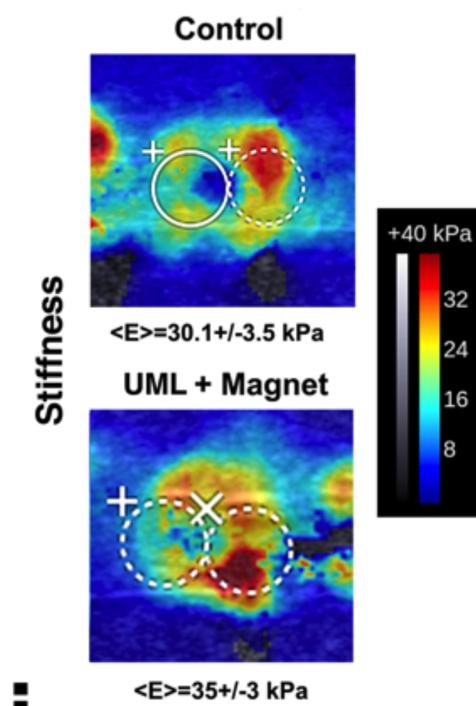


Magnetic forces induce a mean mechanical pressure on the order of 1kPa, equivalent to tumour growth pressure

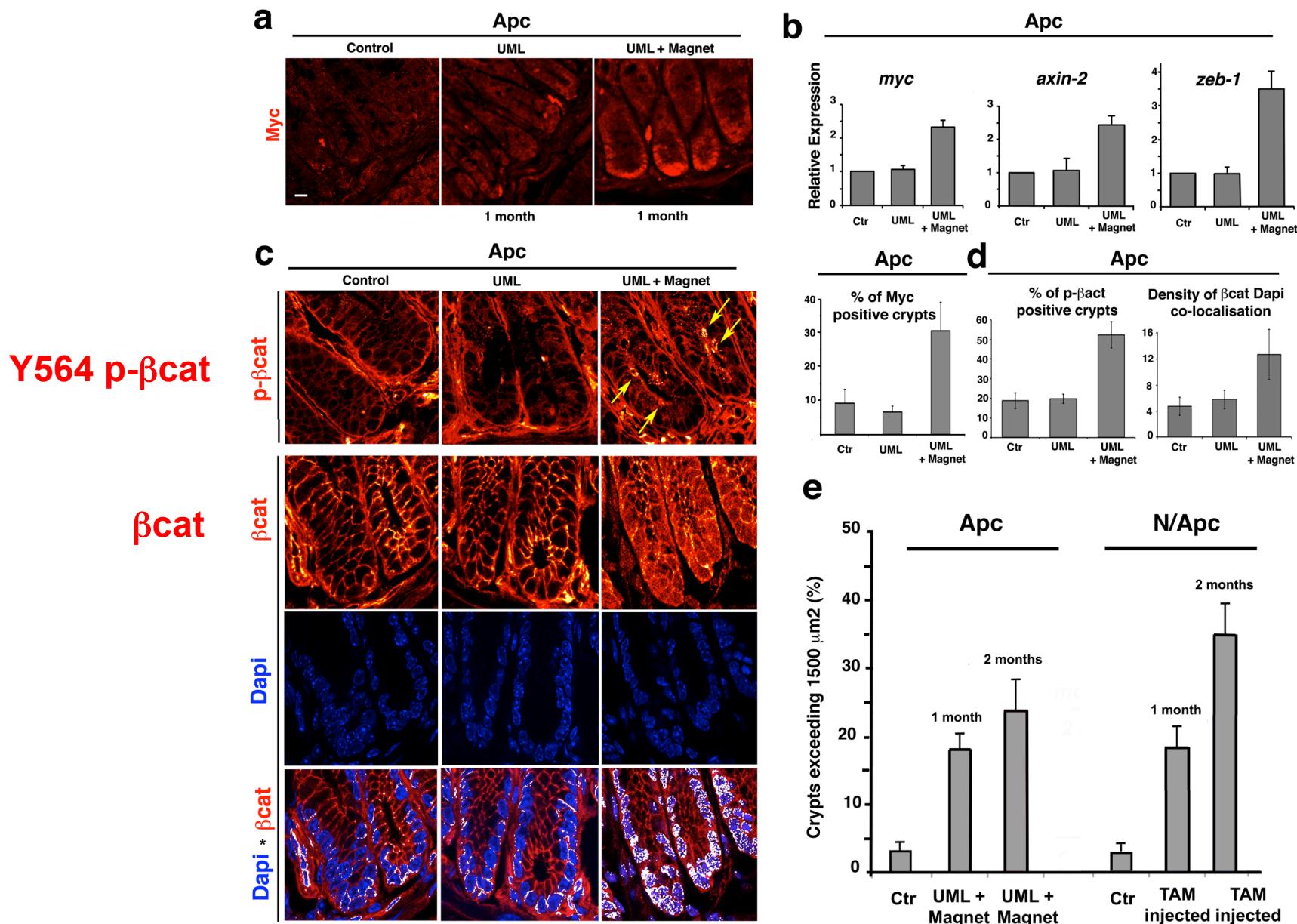


σ locally ranges from 0.6 to 1.8 kPa one week after injection
(1.2kPa mean value)

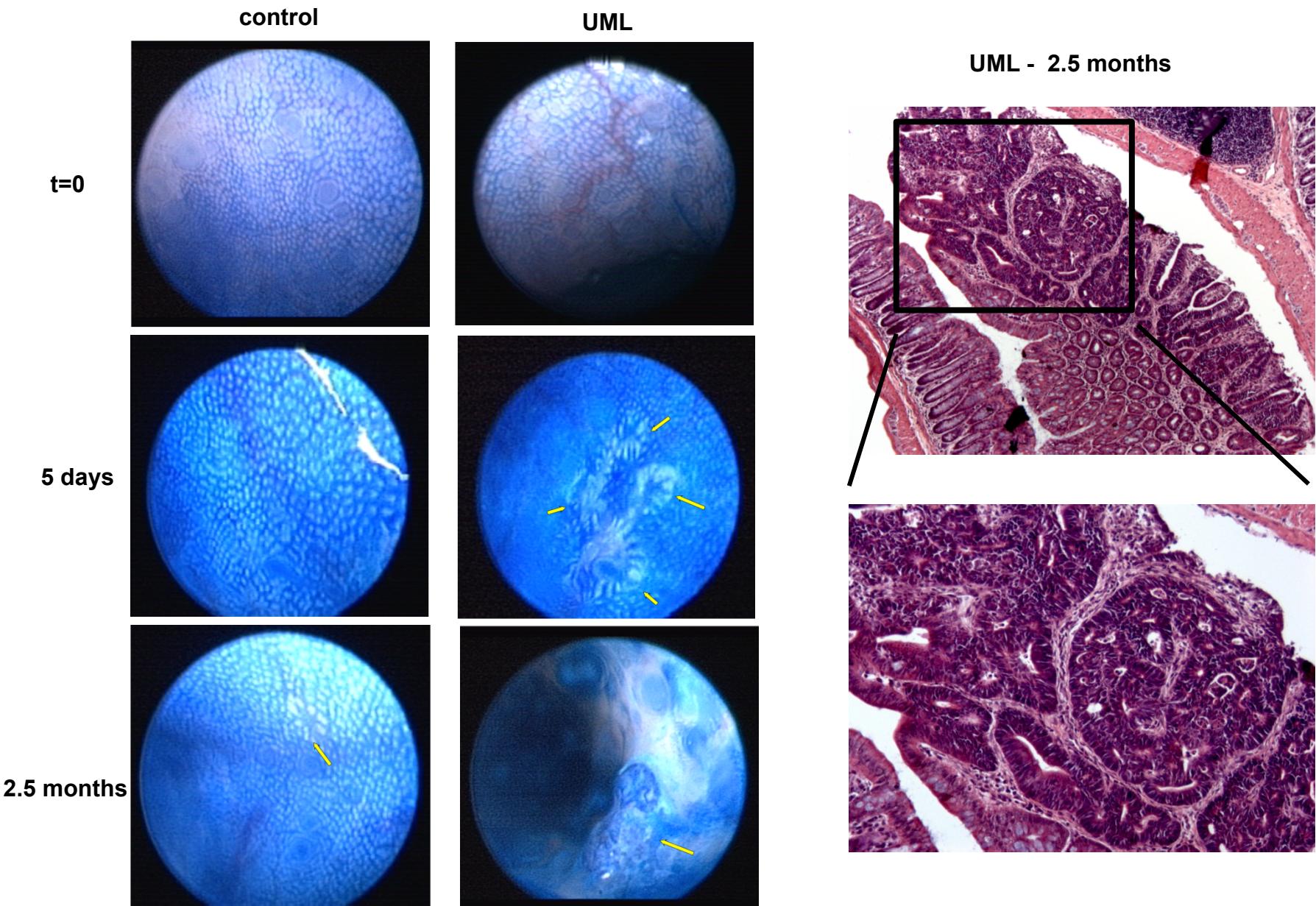
To be compared to endogenous tumour growth pressure:
1.2kPa (2 weeks of Notch activation)



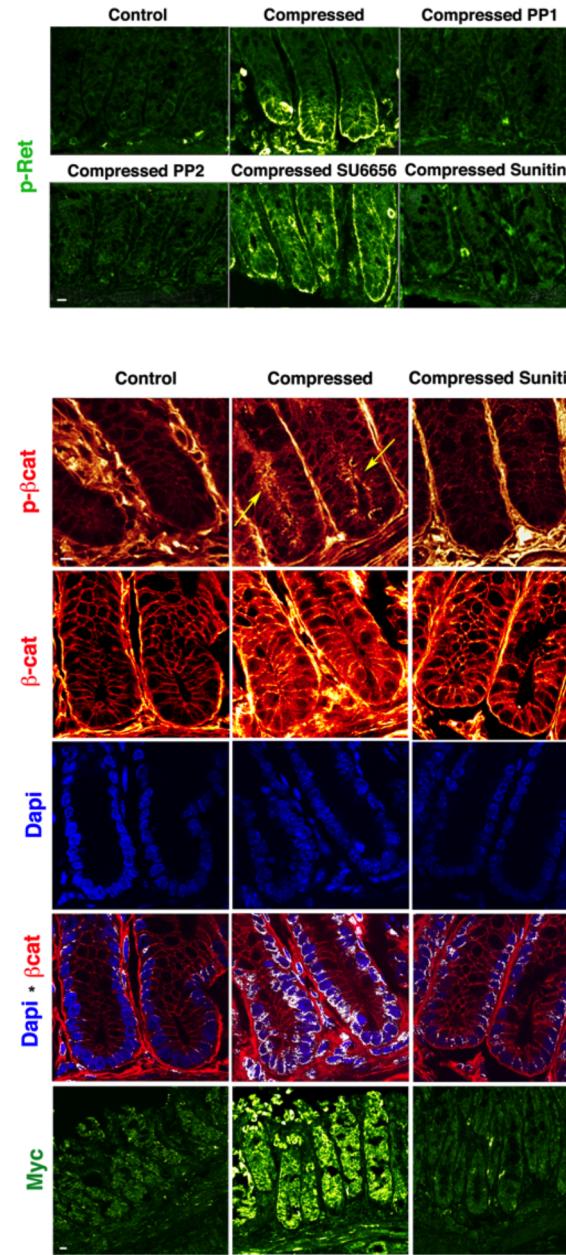
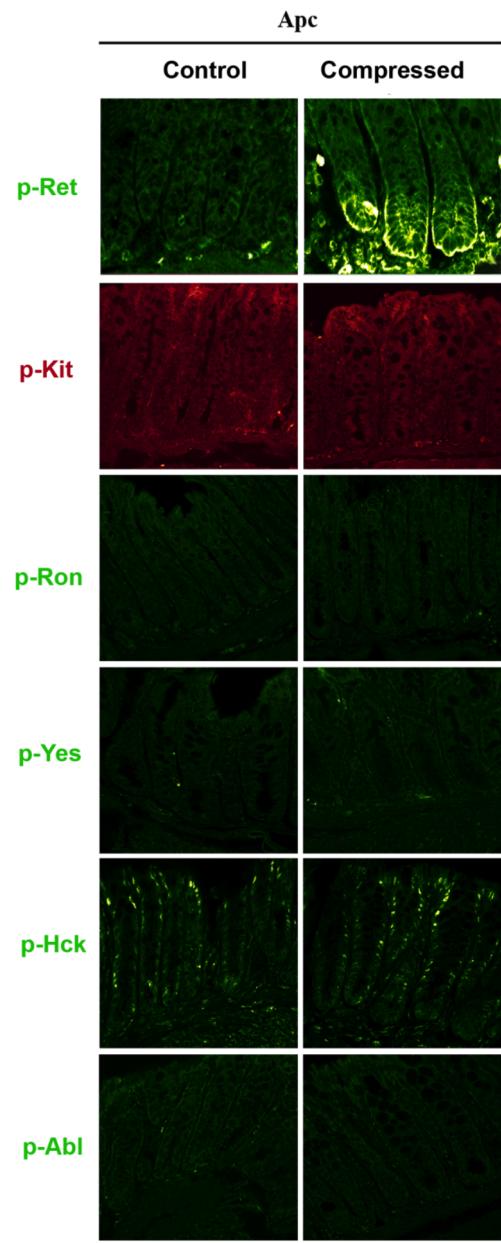
Magnetic forces mimicking tumour growth pressure activates the β -catenin tumorogenic pathway, in Apc mice colon



Magnetic forces mimicking tumour growth pressure can induce adenoma-carcinoma, in Apc heterozygous mice colon



Mechanotransductive pathway: Ret phosphorylation is upstream of β -cat tumorogenic pathway mechanical activation



Y1062p-Ret

Y564 p- β cat

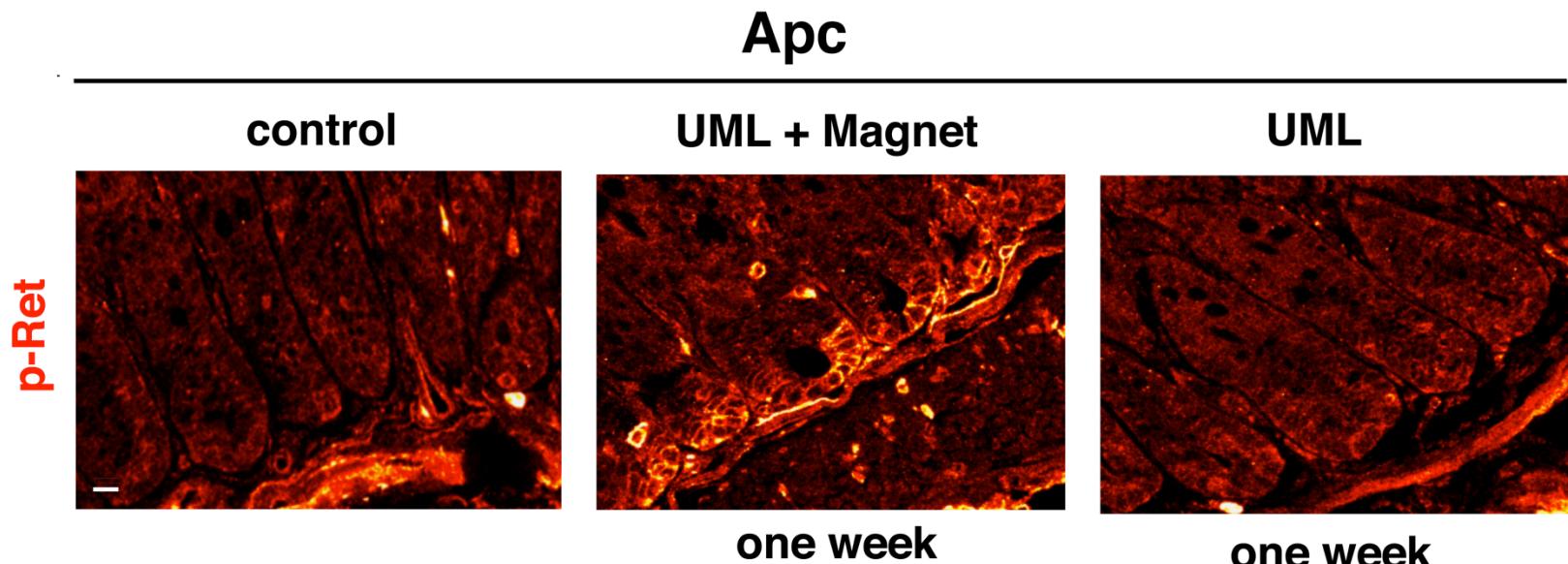
β cat

Myc

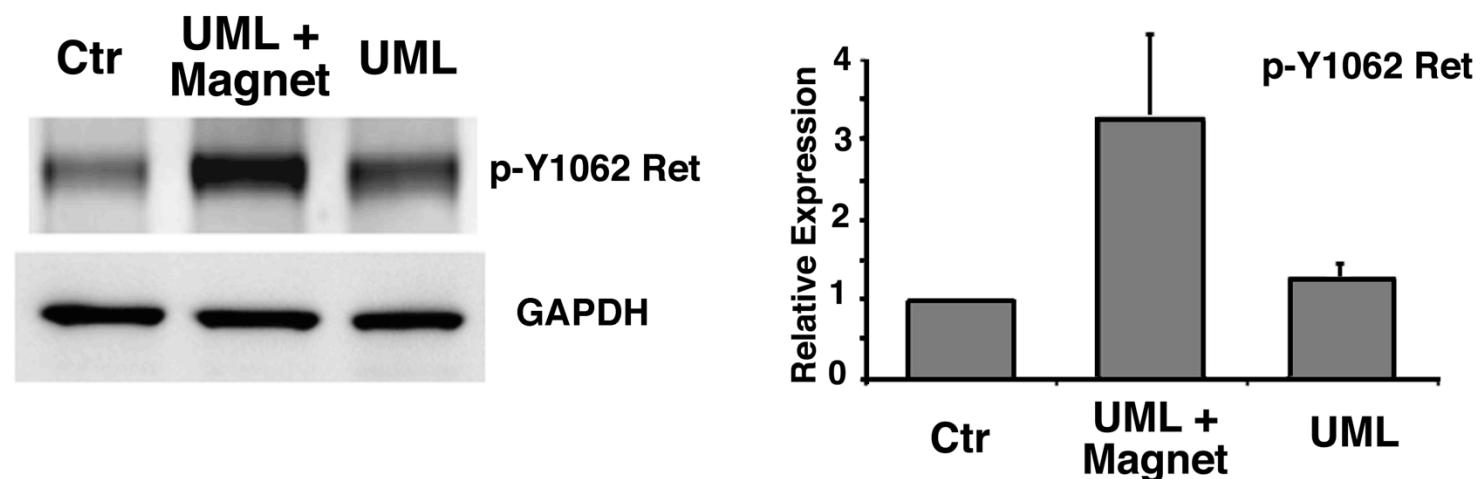
Same results
with the 2 other
Ret inhibitors
Vandetanib and
Ponatinib

Magnetic forces mimicking tumour growth pressure activates Ret phosphorylation

a



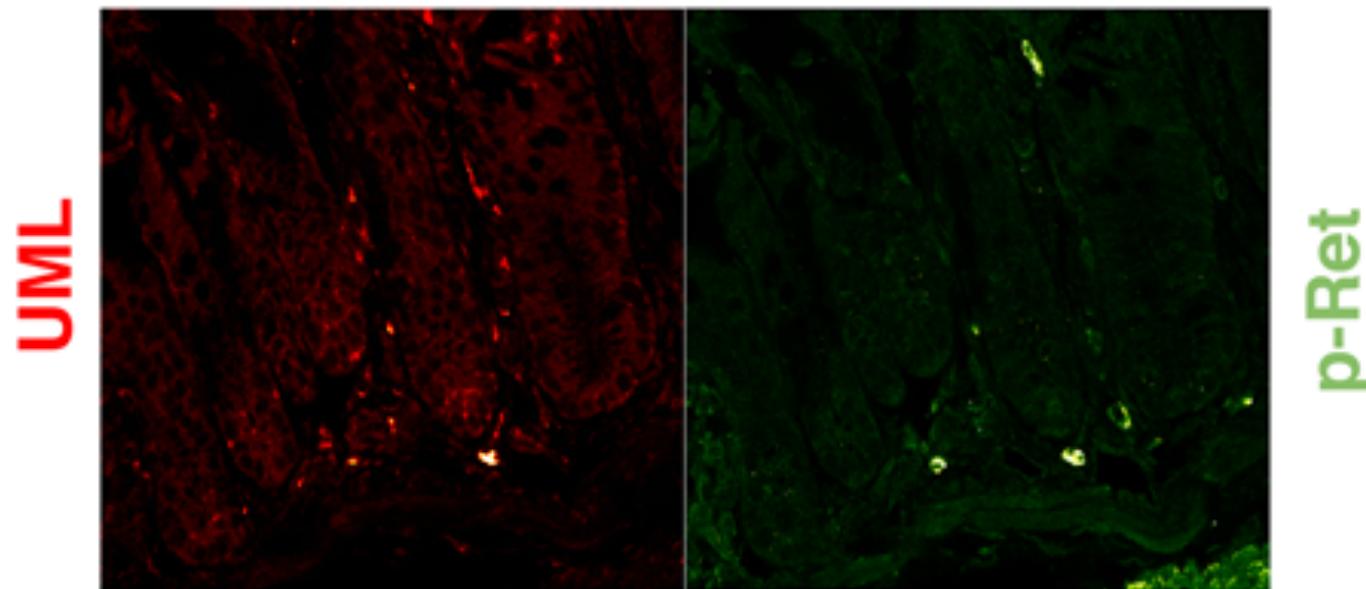
b



Ret is not phosphorylated in the presence of UMLs without magnetic field

Apc

UML without magnet

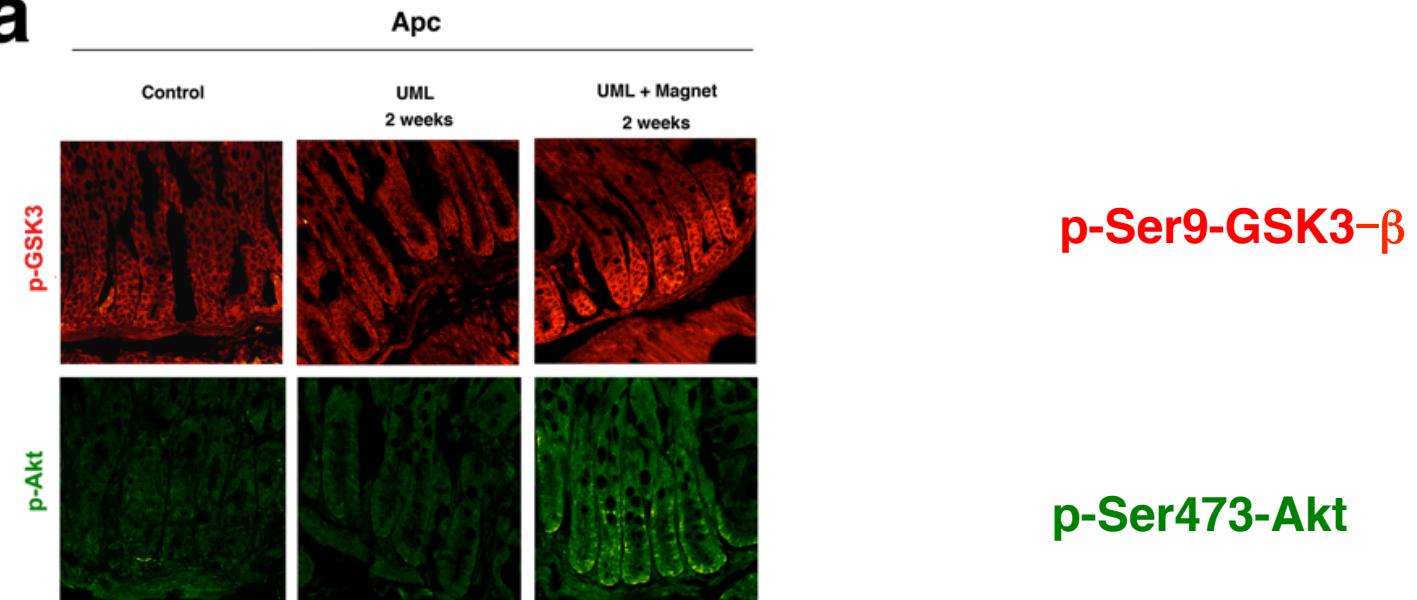


1 week

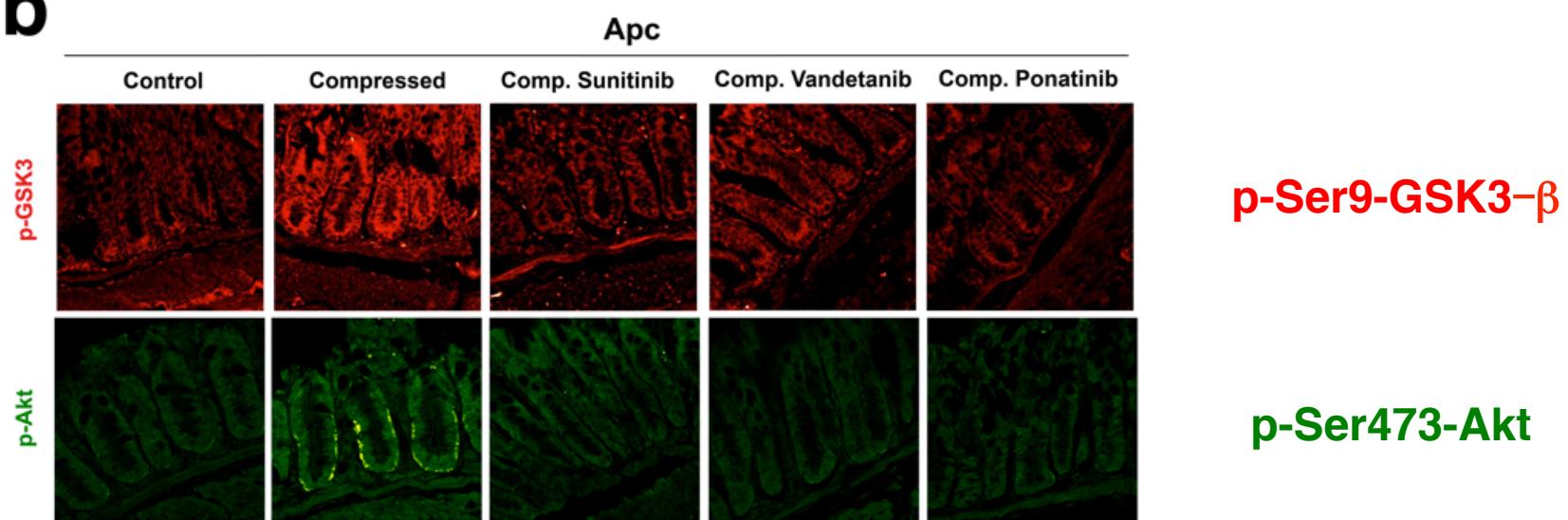
**Same for the downstream pathway: β -cat, myc, ACF, tumour formation
non activated and induced**

Ret phosphorylation is upstream of GSK3- β mechanical inactivation

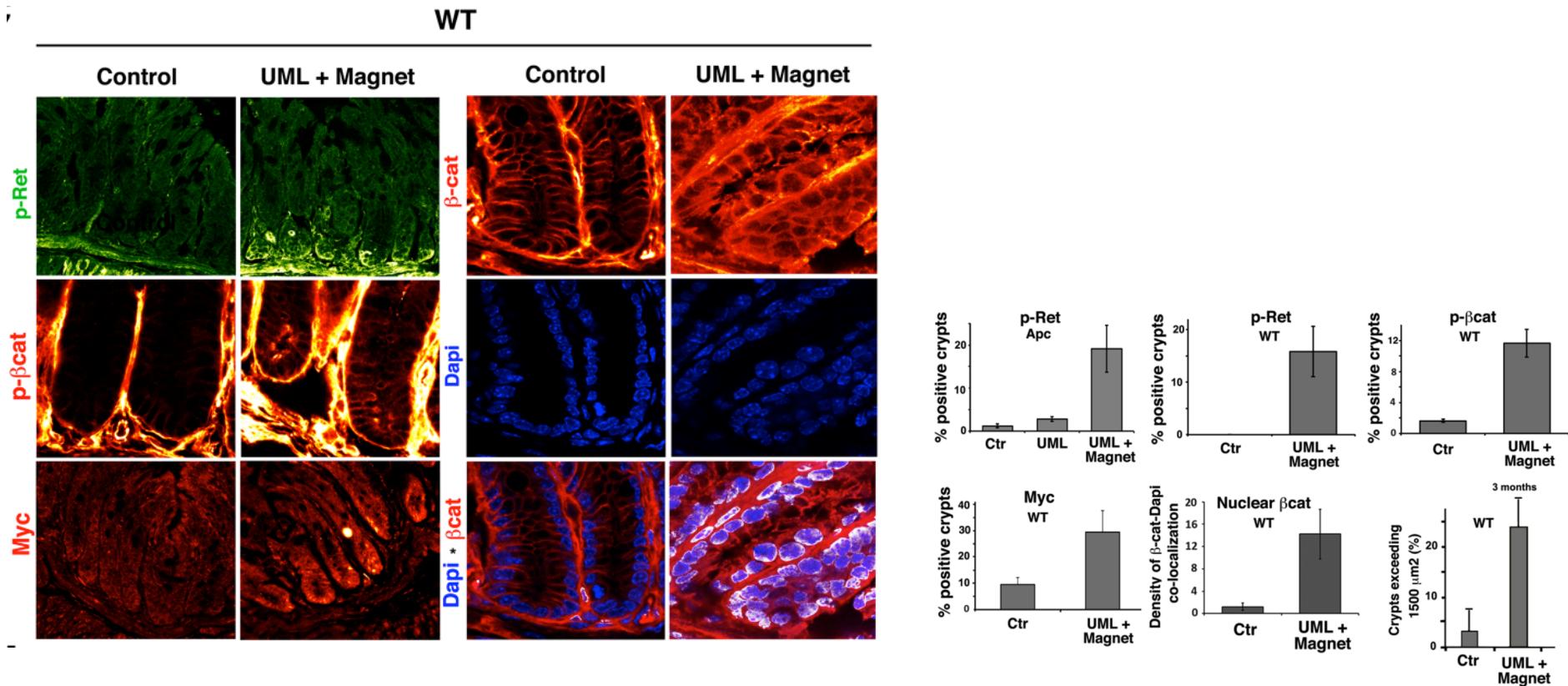
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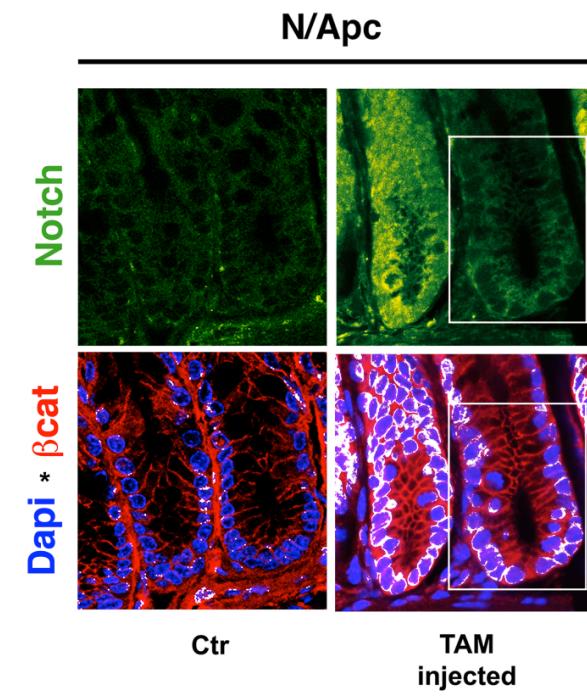
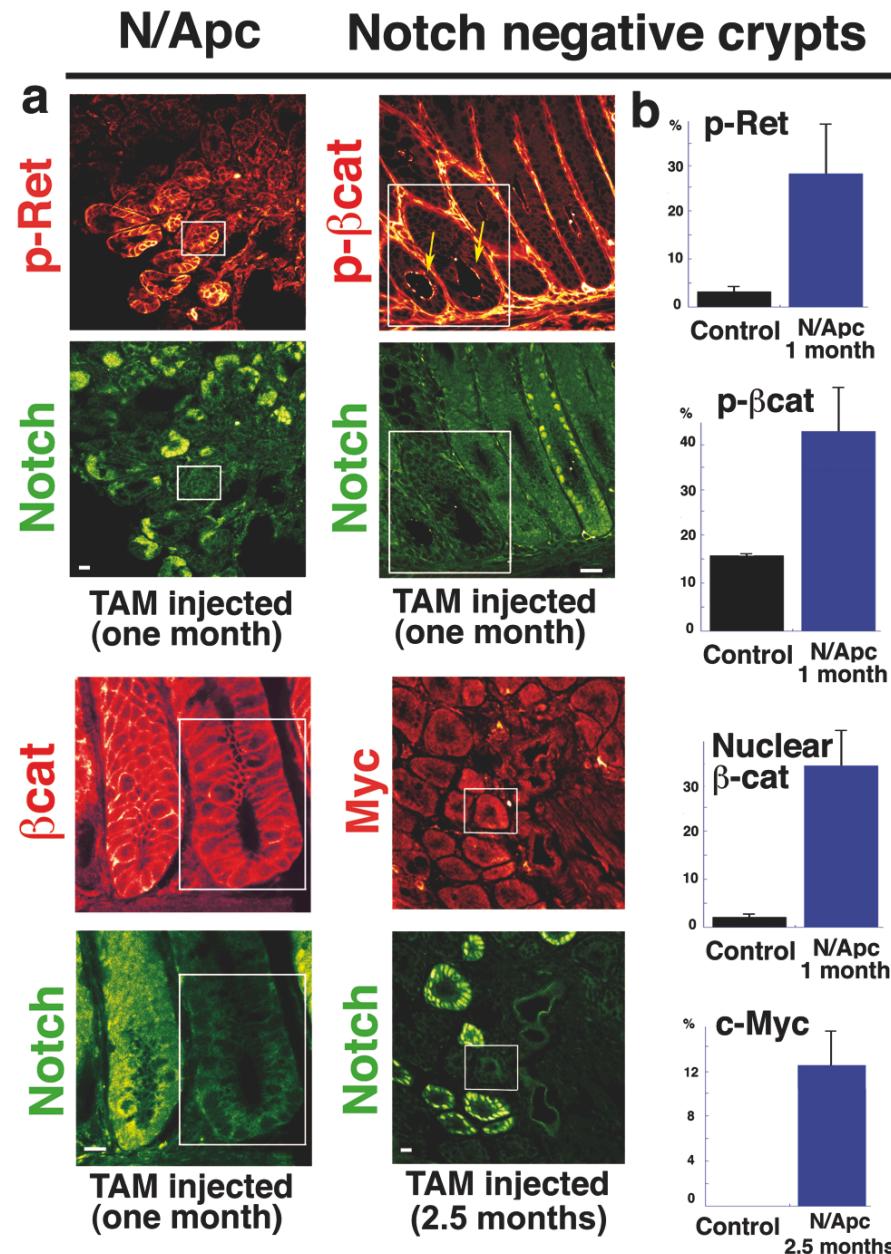
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Magnetic forces mimicking tumour growth pressure activates the β -cat tumorogenic pathway, in WT mice colon too



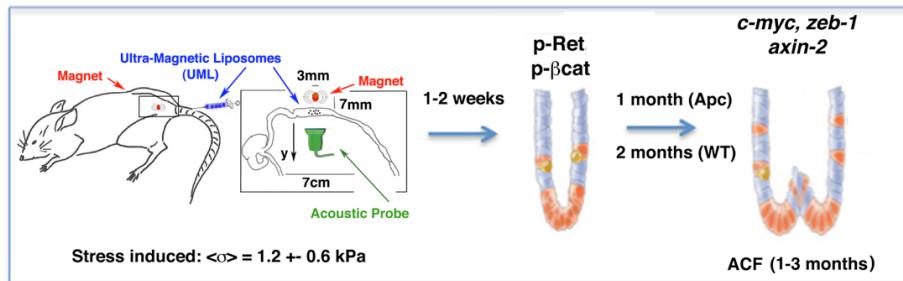
Endogenous hyperproliferative Notch tumour growth pressure activates the β -catenin tumorogenic pathway in neighbouring non tumour Notch negative crypts



Conclusion: tumour growth pressure induces tumorogenesis in healthy tissues *in vivo*

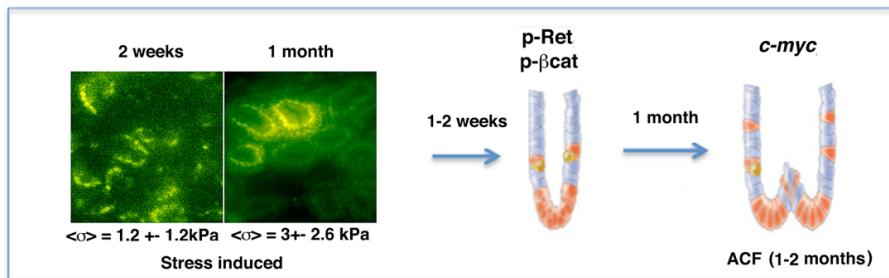
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In vivo magnetic induction of a mechanical tumour stress in Apc and WT mice is oncogenic

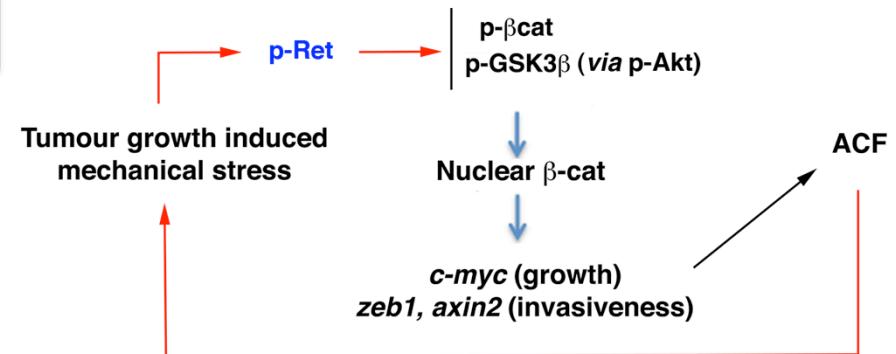


b

Notch mitotic domains induced oncogenic mechanical tumour stress in Apc



Mechano-genetic model of tumour growth instability



M-E Fernandez-Sanchez, S. Barbier et al
Nature 2015

M-E Fernandez-Sanchez, et al,
Ann Rev Cell Dev Biol 2015

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Ret phosphorylation is not locally correlated with Notch expression

