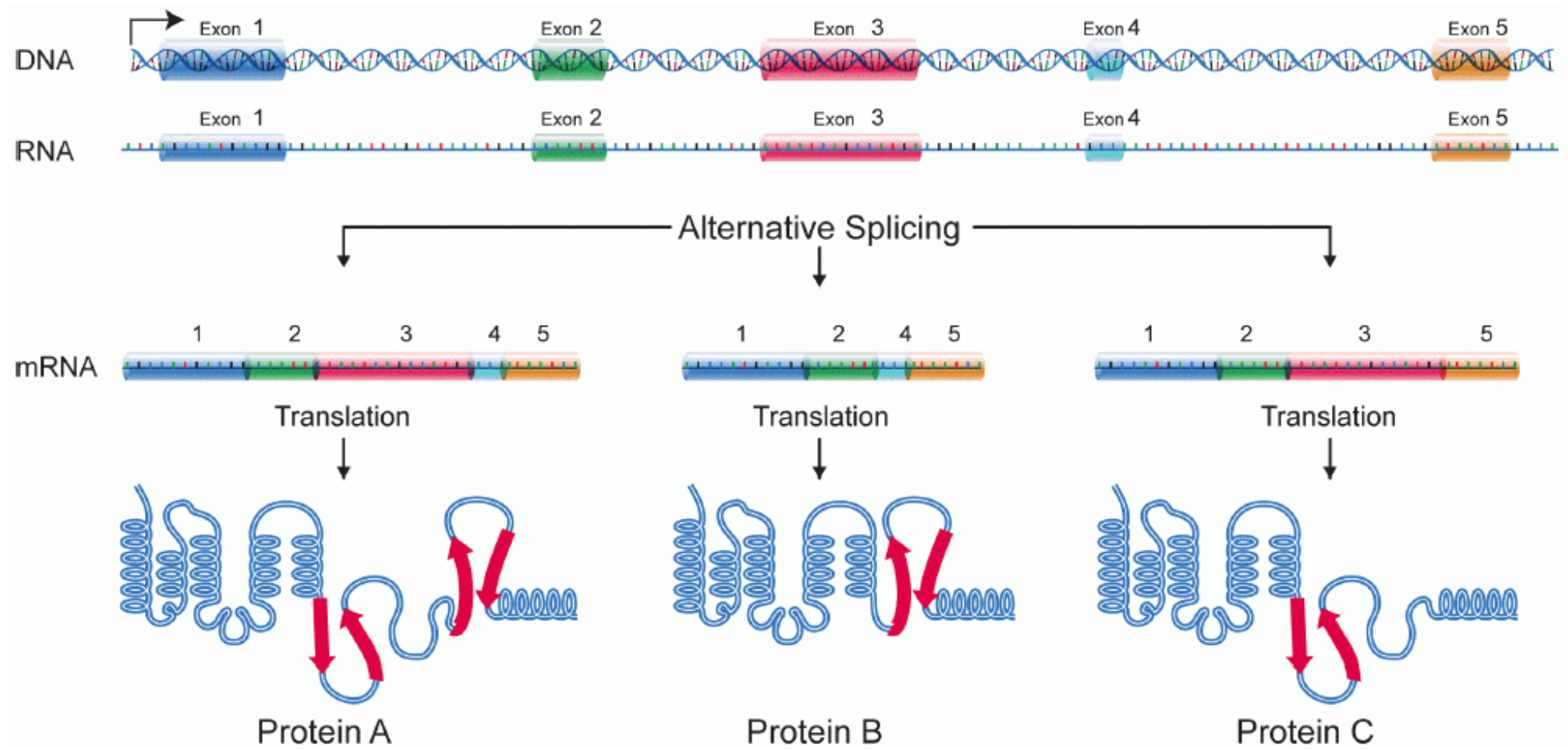


Lessons from Colon Cancer: How Signal Transduction Pathways Regulate Alternative Splicing of RAC1B

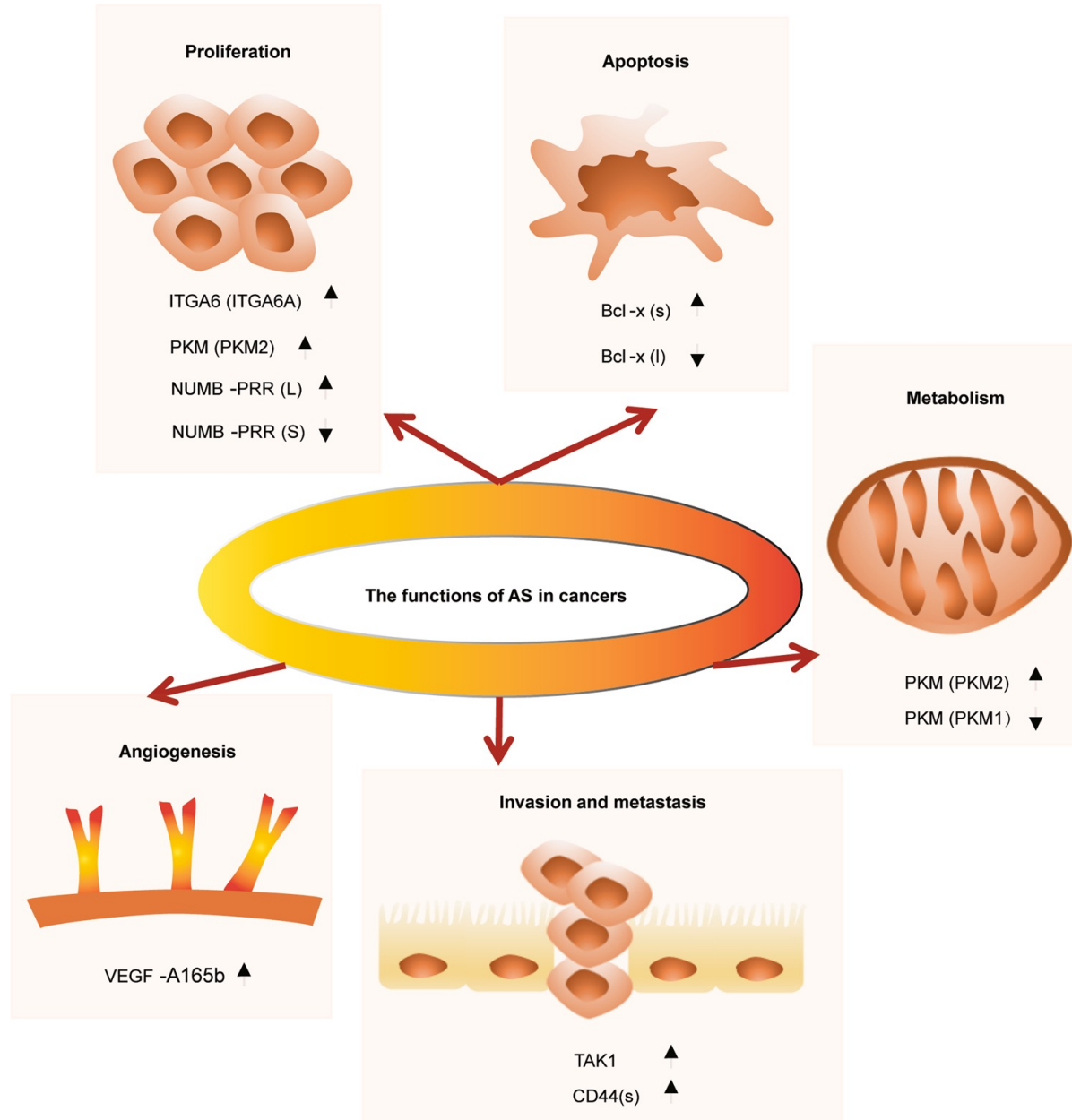
Vânia Gonçalves

Departamento de Genética Humana
Laboratório de oncobiologia e vias de sinalização
vania.goncalves@insa.min-saude.pt

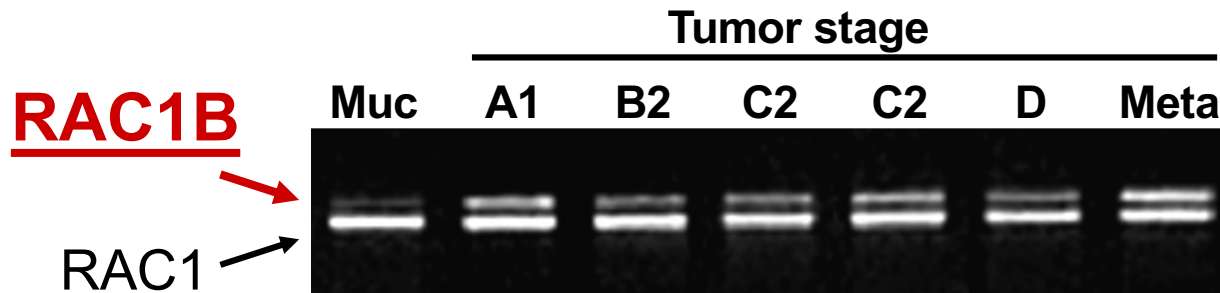
Alternative splicing and cancer



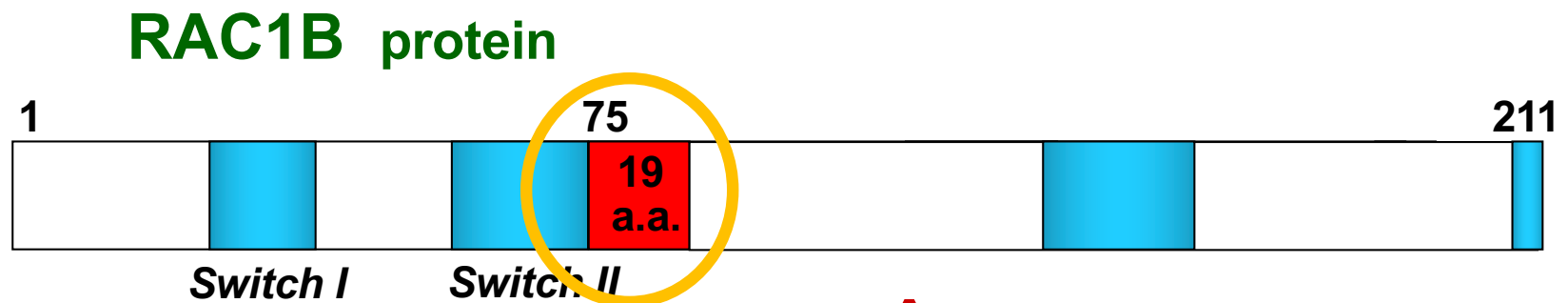
Alternative splicing and cancer



Example: *RAC1* expression in colorectal cancer



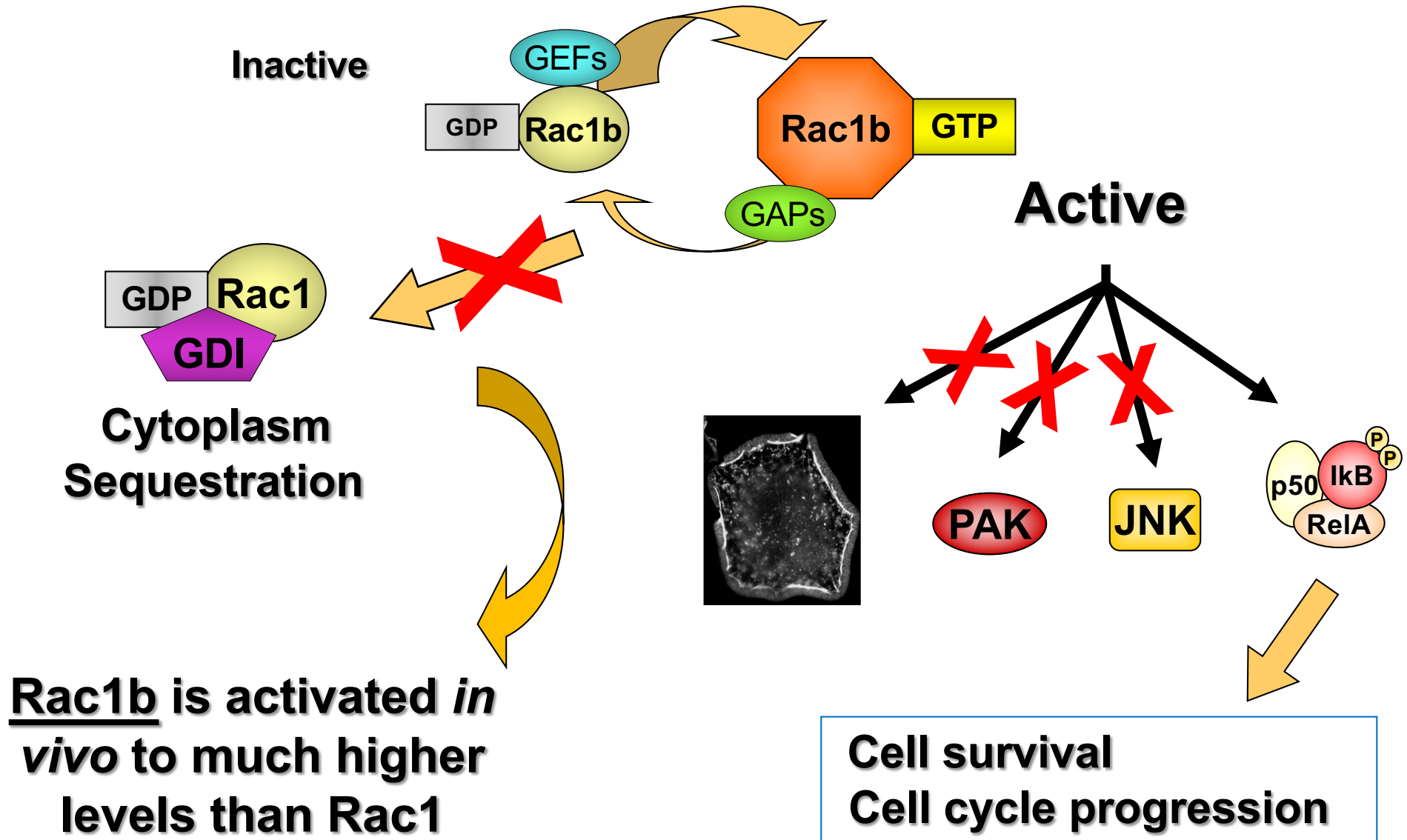
Jordan (1999) Oncogene 18:6835-39



→ **RAC1 alternative splicing**

Matos (2000) BBRC 277:741-51

Rac1b differs in regulation and signalling



Rac1b – a Rac1 splice variant

In summary...

Rac1b is a hyperactive form

Rac1b is selective in downstream signalling

Oncogene (1999) 18, 6835–6839

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Oncogene (2000) 19, 3013–3020

© 2000 Macmillan Publishers Ltd All rights reserved 0950–9232/00 \$15.00

Oncogene. 2013 February 14; 32(7): 903–909. doi:10.1038/onc.2012.99.

European Journal of Endocrinology (2013) 168 795–804

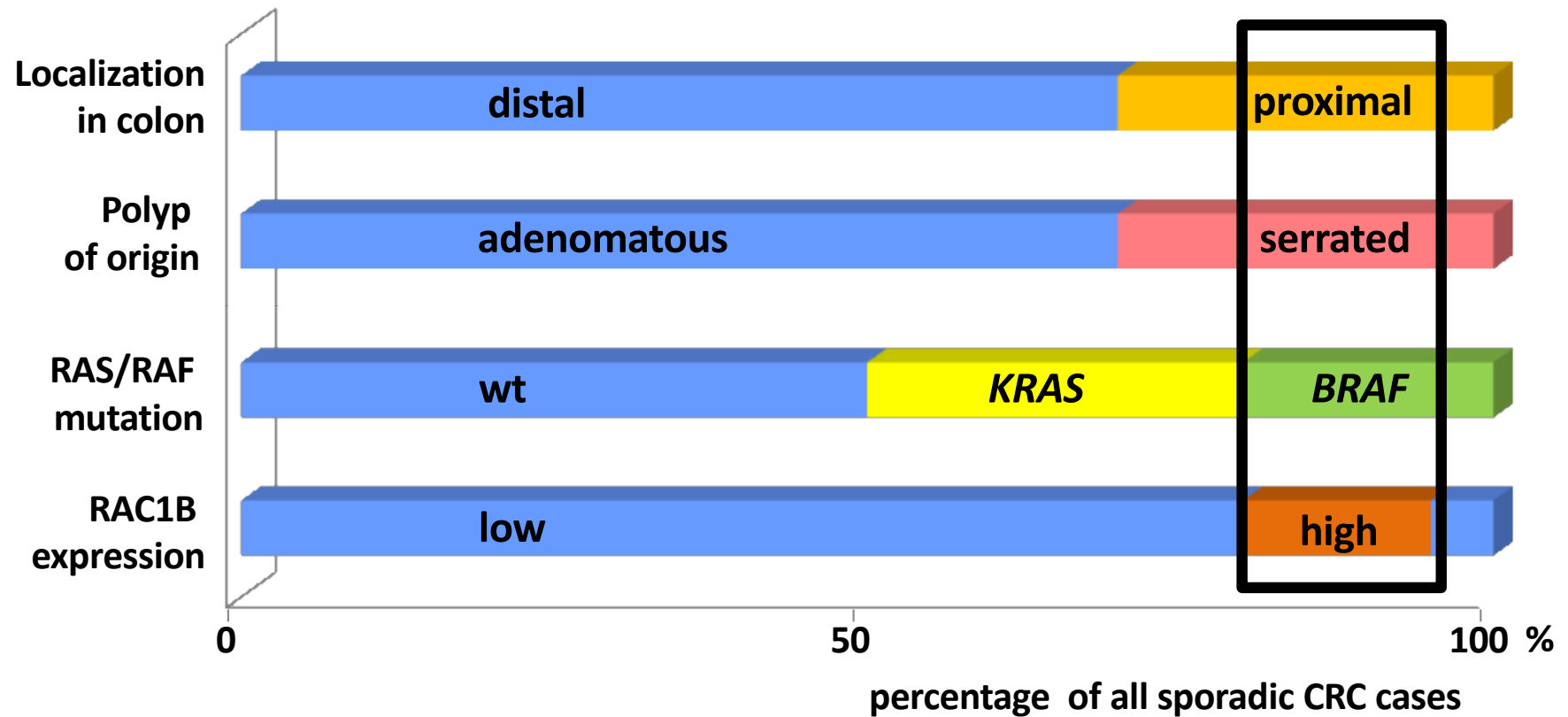
ISSN 0804-4643

Mol Cancer Res. 2014 October ; 12(10): 1430–1439. doi:10.1158/1541-7786.MCR-13-0557-T.

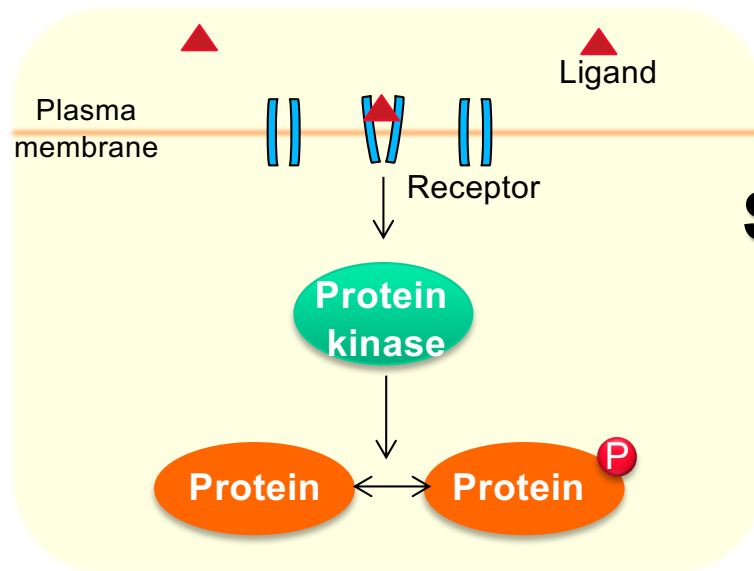
Tumor Cell-derived MMP-3 Orchestrates Rac1b and Tissue Alterations that Promote Pancreatic Adenocarcinoma

Christine Mehner¹, Erin Miller¹, Davitte Khauv¹, Aziza Nassar², Ann L. Oberg³, William R. Bamlet³, Lizhi Zhang⁴, Jens Waldmann⁵, Evette S. Radisky¹, Howard C. Crawford¹, and Derek C. Radisky^{1,*}

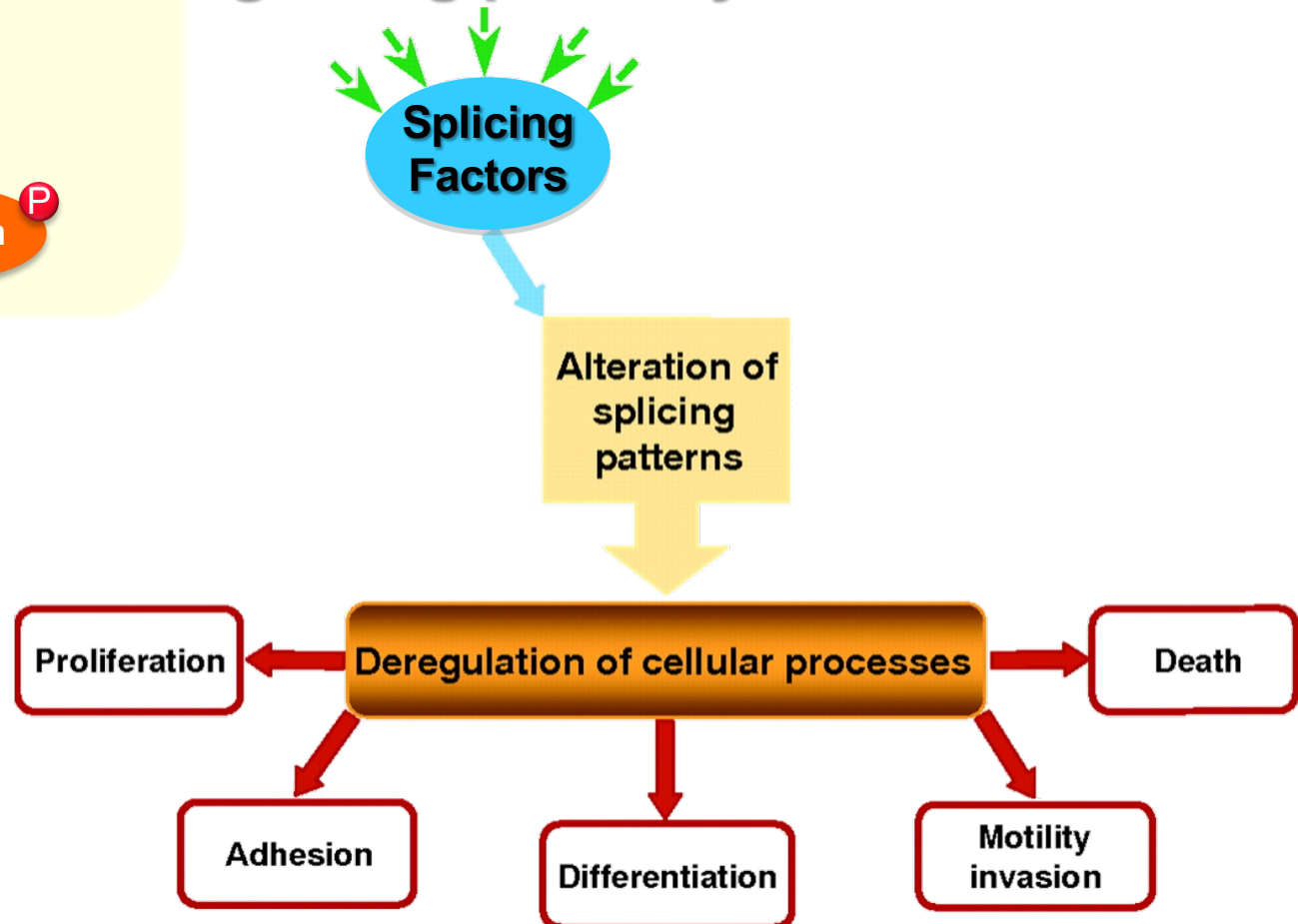
CRC classification: RAC1B overexpression characterizes a subtype



How can splicing become deregulated in tumours?

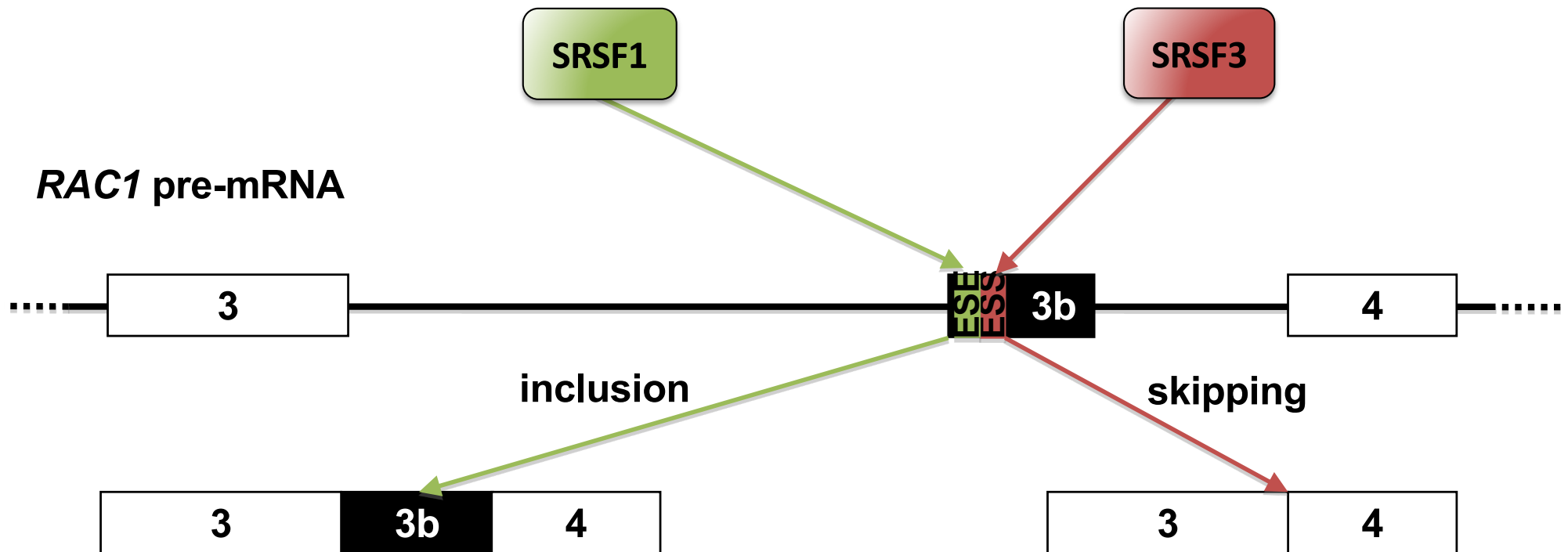


Signaling pathways



Model for regulation of *RAC1* alternative splicing in CRC

Which signaling pathways regulate binding of SRSF1 and SRSF3?

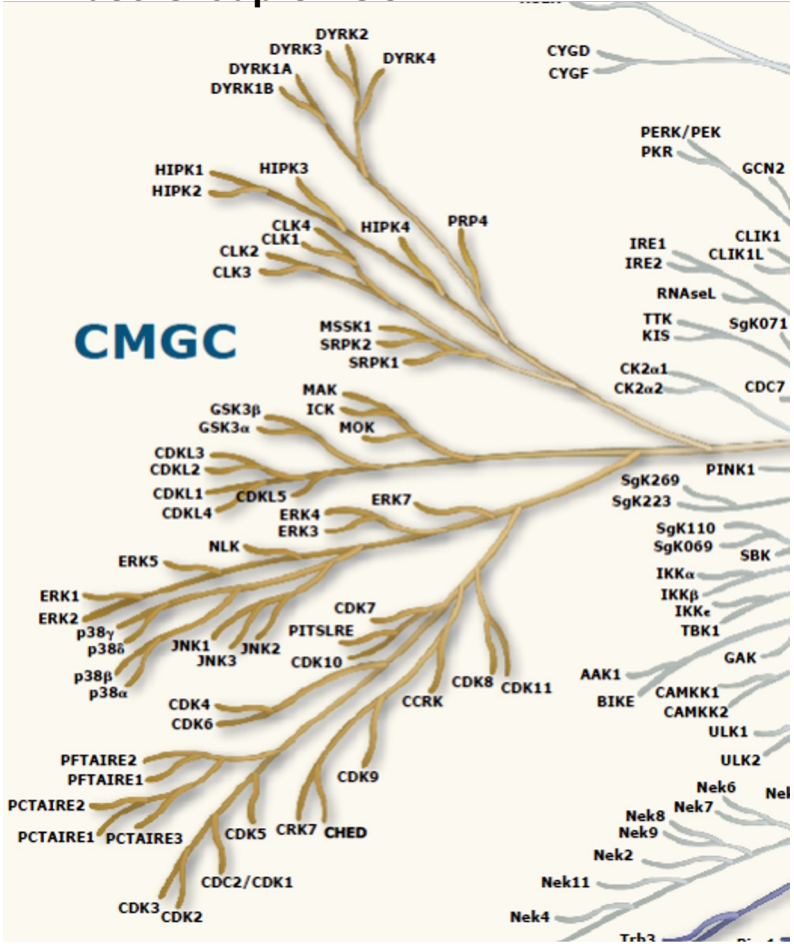


➤ **SRSF1** promote the recognition of exon-3b of the *RAC1* gene

➤ **SRSF3** inhibit the recognition of exon-3b of the *RAC1* gene

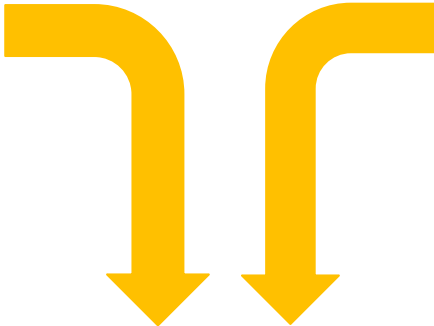
Protein kinases and phosphatases previously described to regulate alternative splicing events

Kinase Group CMGC



CLK1
CLK2
CLK3
CLK4
DYRK1a
DYRK1b
DYRK2
DYRK3
DYRK4
CDK11
CDK12
CDK13
GSK3alpha
GSK3beta
SRPK1
SRPK2
MSSK1
PRPF4B
PRP4

TOPOI
AKT1
AKT2
AKT3
PP1alpha
PP1beta
PP1gamma



Depletion by shRNAs

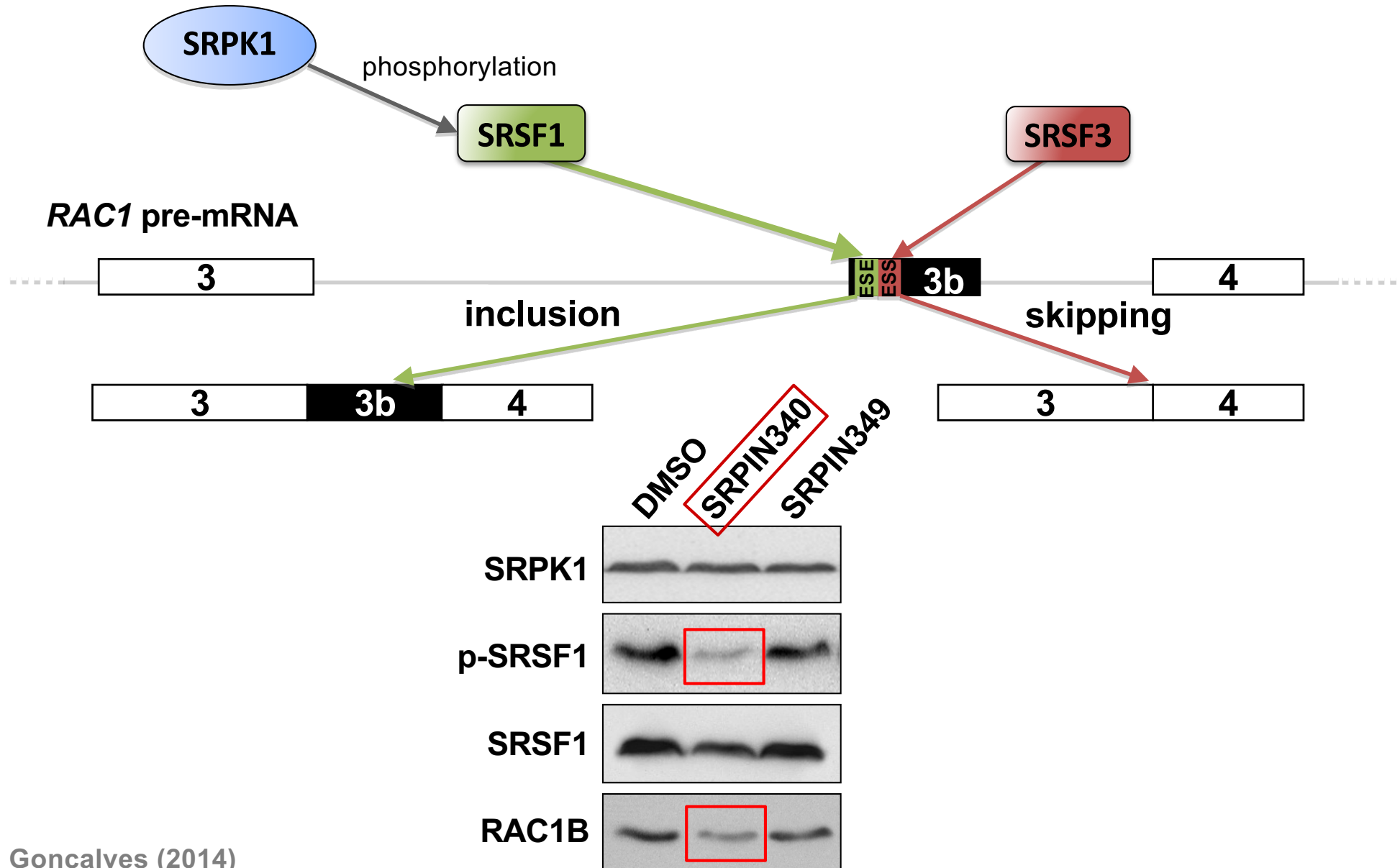


Differences in RAC1B protein levels

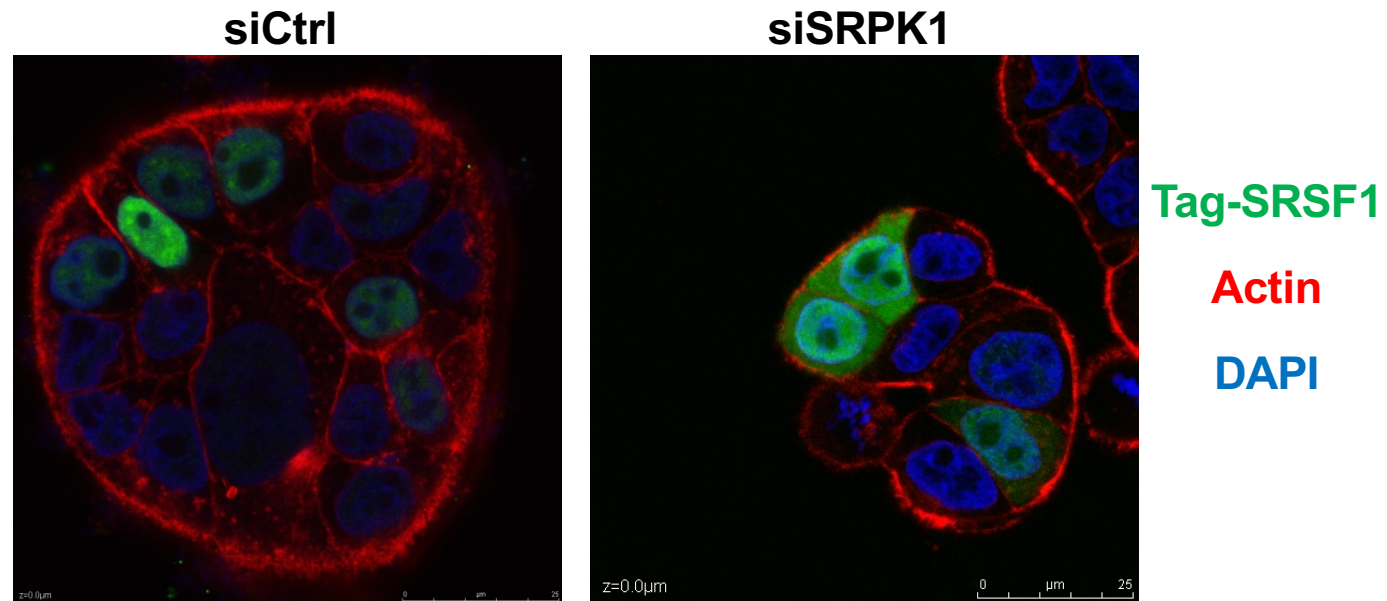
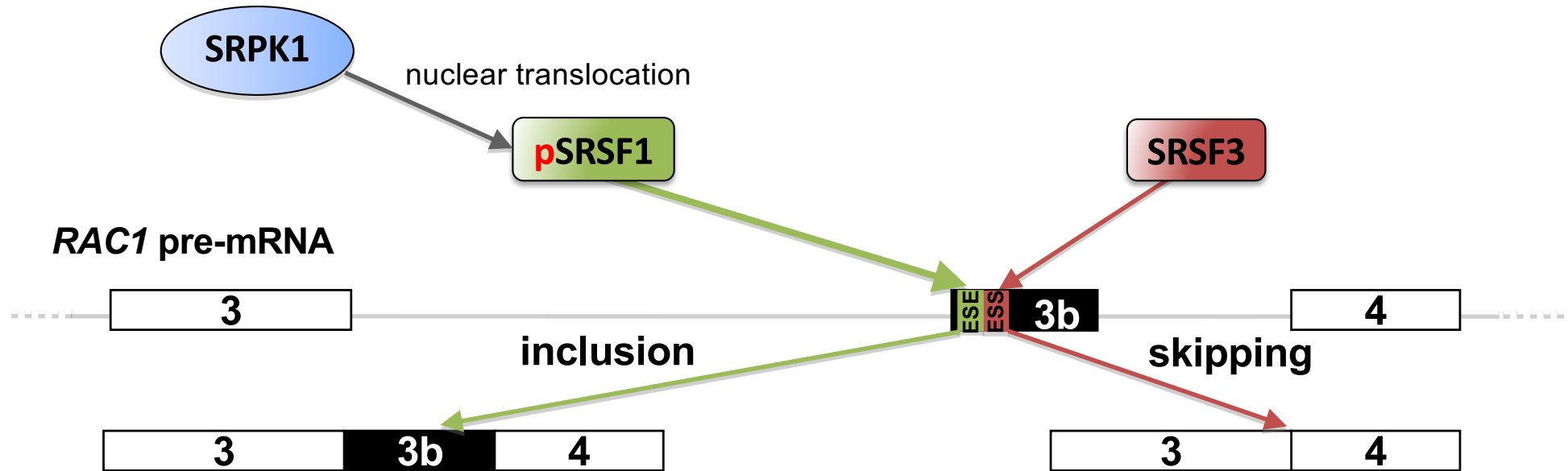


2 protein kinases affected RAC1B

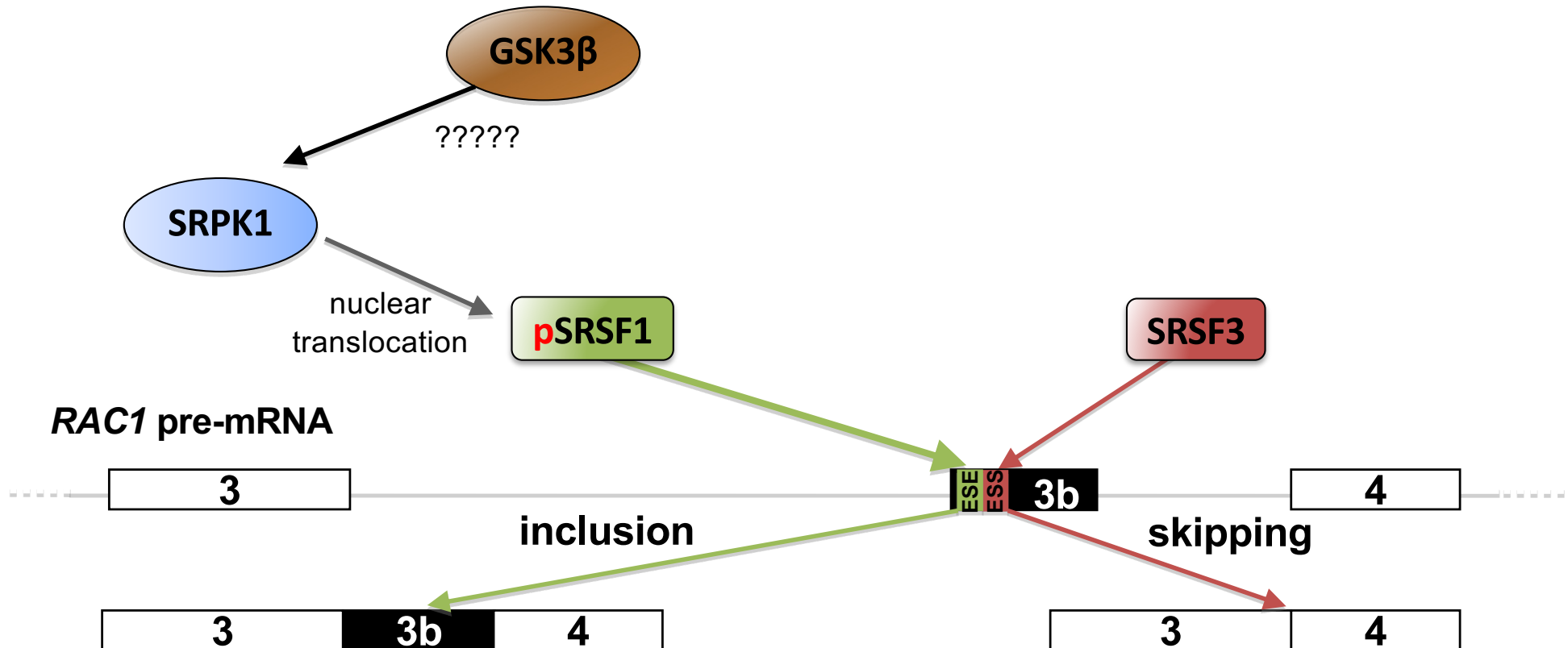
Role of protein kinase SRPK1 in RAC1B splicing



Role of protein kinase SRPK1 in RAC1B splicing



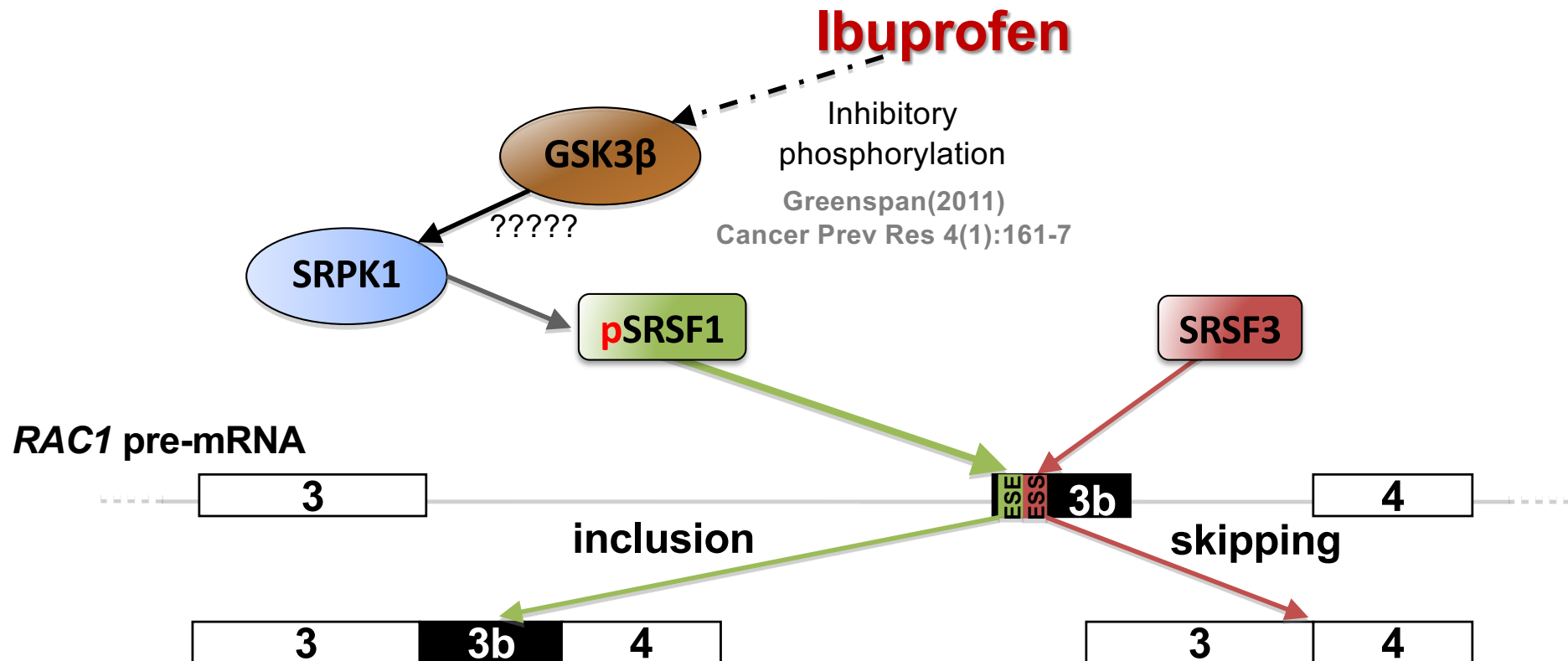
Role of protein kinase GSK3 β in RAC1B splicing



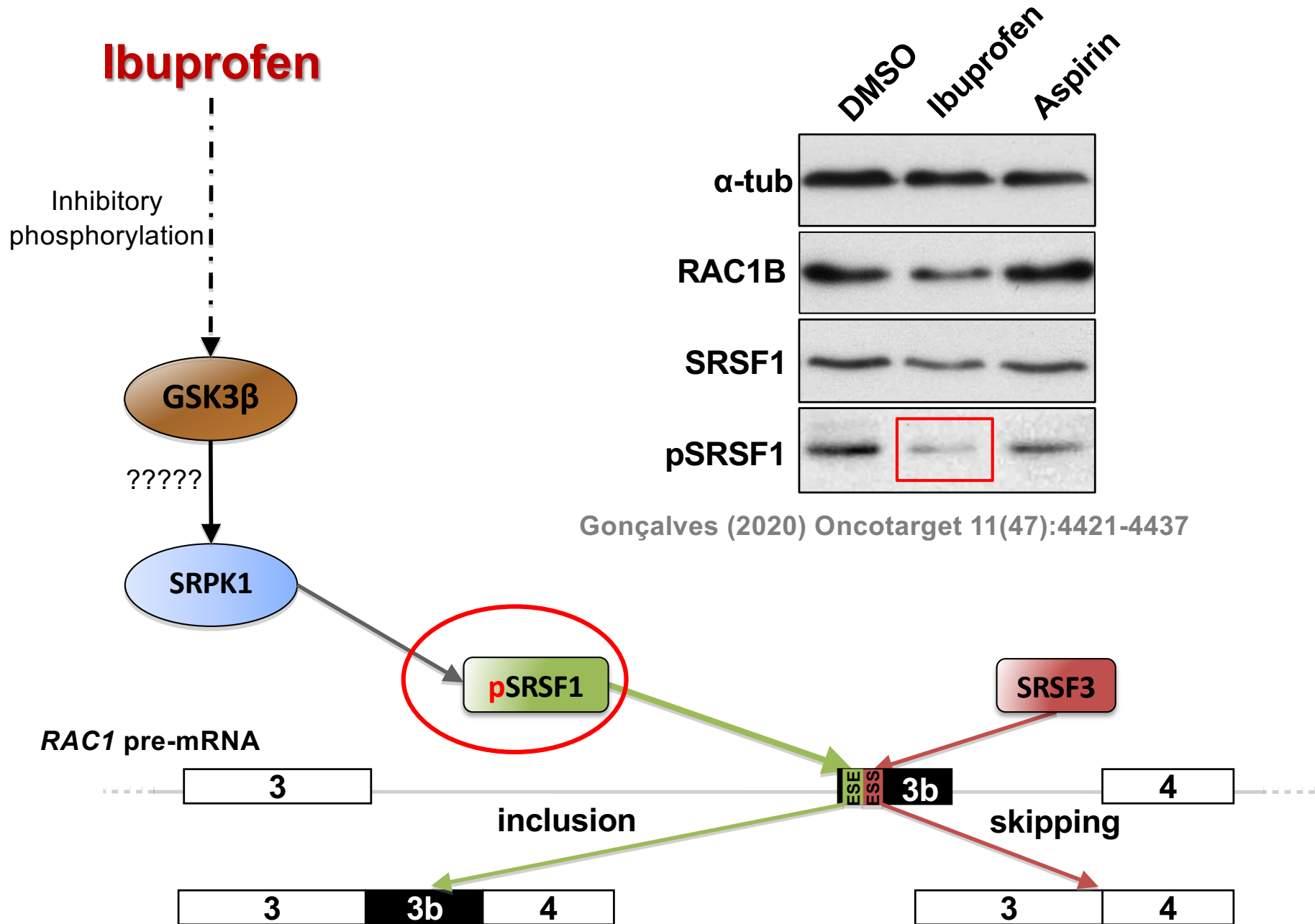
Ibuprofen inhibits RAC1B splicing

Ibuprofen Inhibits Colitis-Induced Overexpression of Tumor-Related Rac1b¹

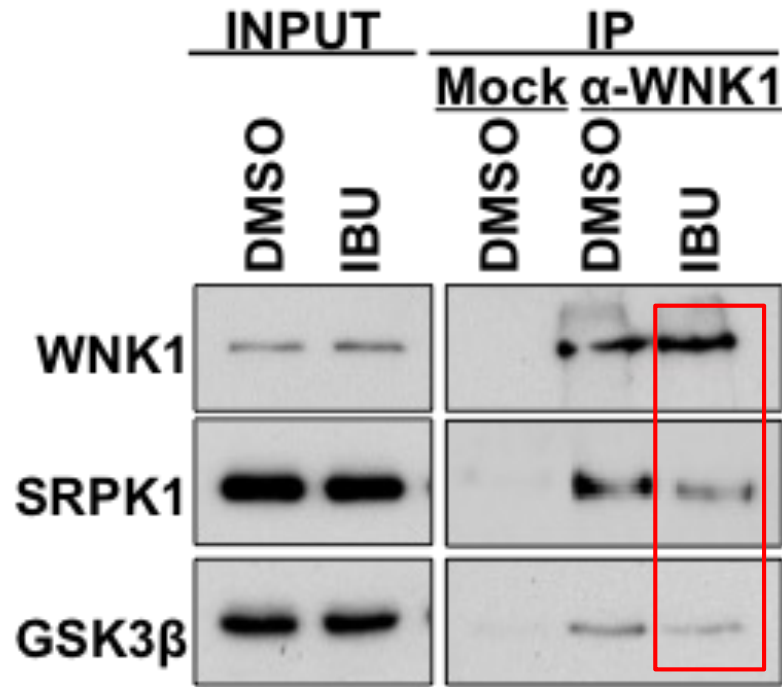
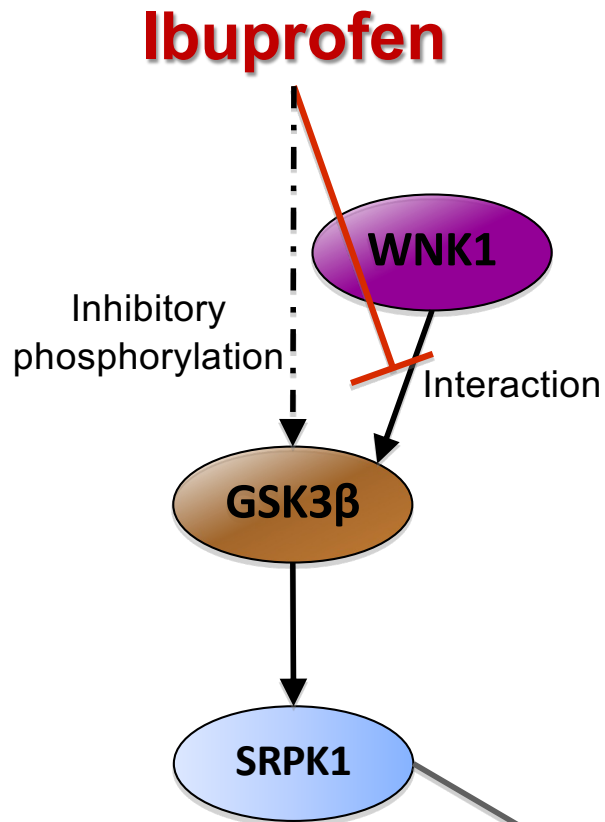
Paulo Matos^{*,2}, Larissa Kotelevets^{†,‡,2},
Vânia Gonçalves^{*}, Andreia Henriques^{*},
Philippe Zerbib[§], Mary Pat Moyer[¶], Eric Chastre^{†,‡}
and Peter Jordan^{*}



How ibuprofen interferes with RAC1B splicing ?



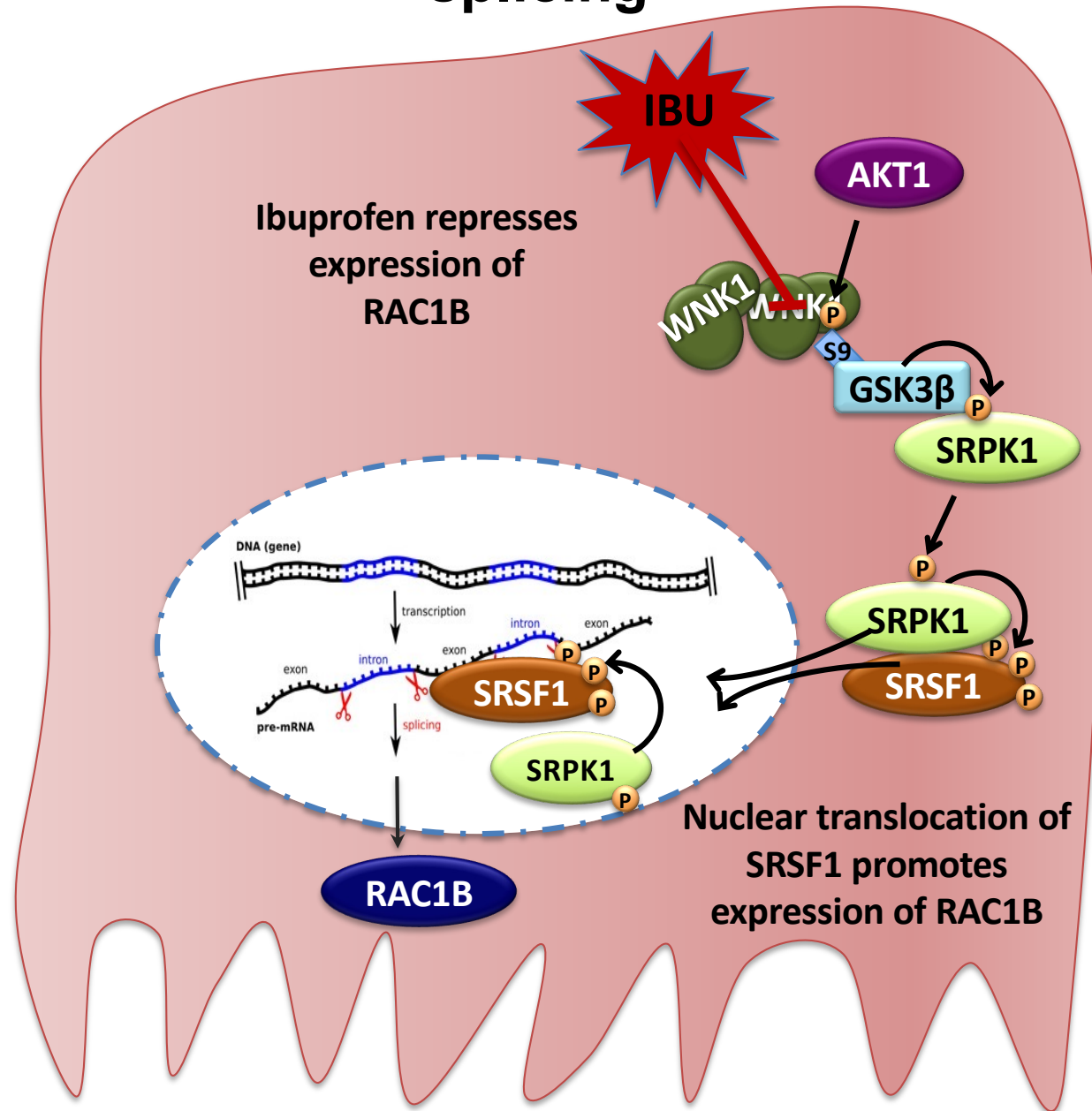
How ibuprofen interferes with RAC1B splicing ?



Gonçalves (2020) Oncotarget 11(47):4421-4437



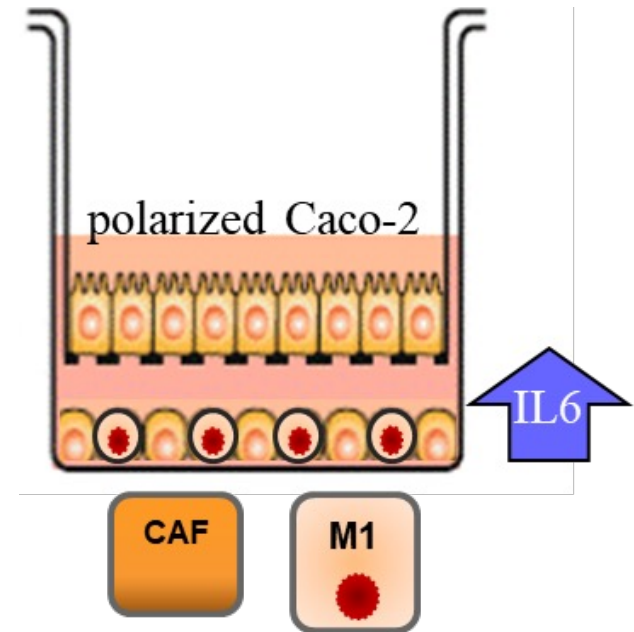
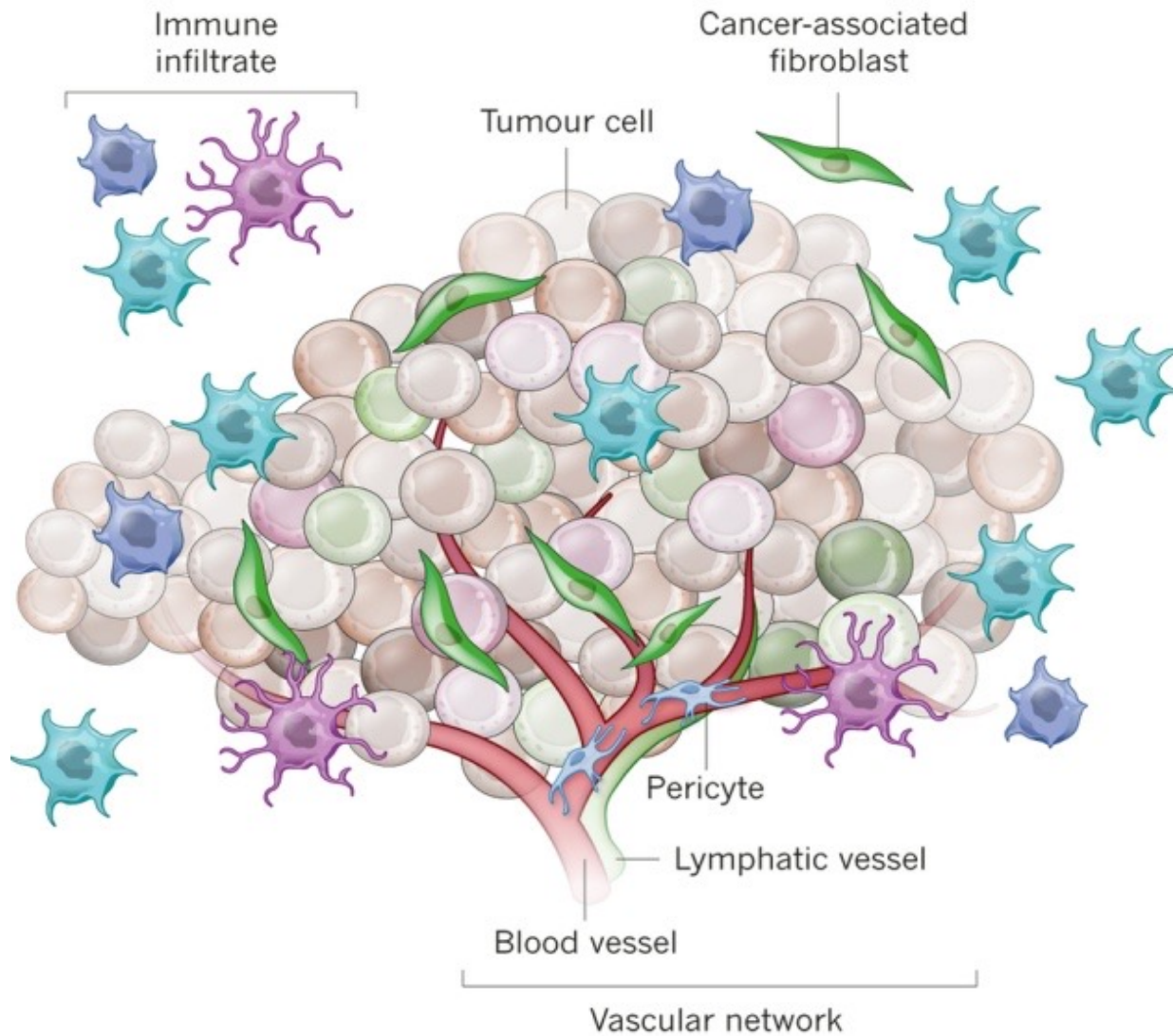
Proposed model for how ibuprofen interferes with RAC1B splicing



Main conclusions

- Rac1b is a highly active alternative splicing variant of Rac1
- Rac1b selective downstream signaling confers some advantage in tumorigenesis
- Rac1b is overexpressed in colorectal, breast, lung, thyroid and pancreatic cancer
- Rac1b alternative splicing is regulated by splicing factors SRSF1 and SRSF3, which in turn are controlled by upstream signaling pathways
- Ibuprofen is a common anti-inflammatory drug that can correct RAC1 aberrant splicing event in colorectal cancer cells

Inflammatory tumor cell microenvironment



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Vânia Gonçalves

Departamento de Genética Humana
Laboratório de oncobiologia e vias de sinalização
vania.goncalves@insa.min-saude.pt

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