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Splicing 2021 - Caparica

Dissecting how colorectal cancer cells regulate the alternative splicing of RAC1B

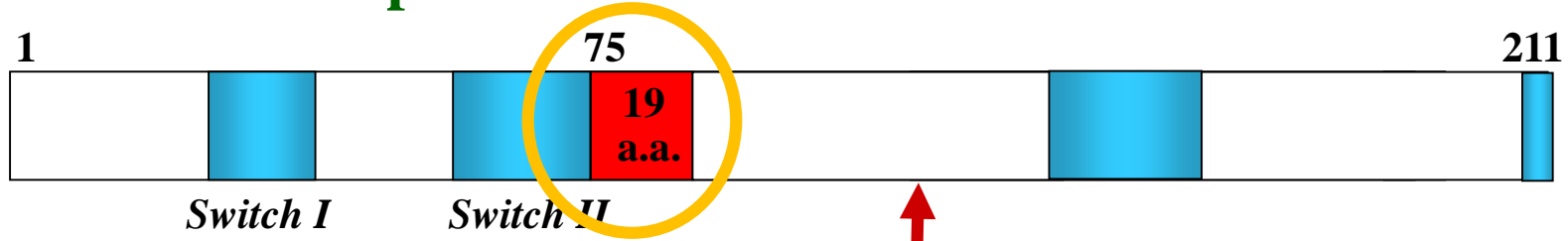
Peter Jordan

Departamento de Genética Humana,
Instituto Nacional de Saúde Doutor Ricardo Jorge,
Lisboa, Portugal

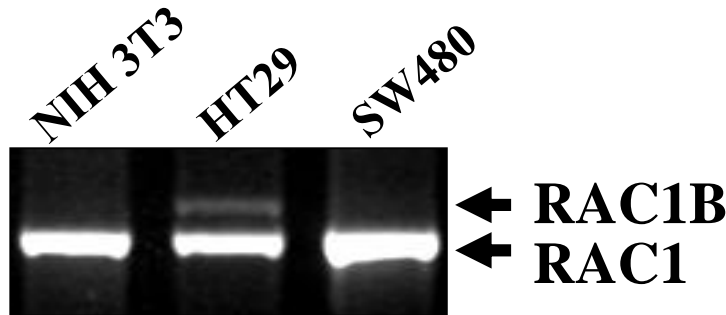
peter.jordan@insa.min-saude.pt

A RAC1 variant overexpressed in CRC

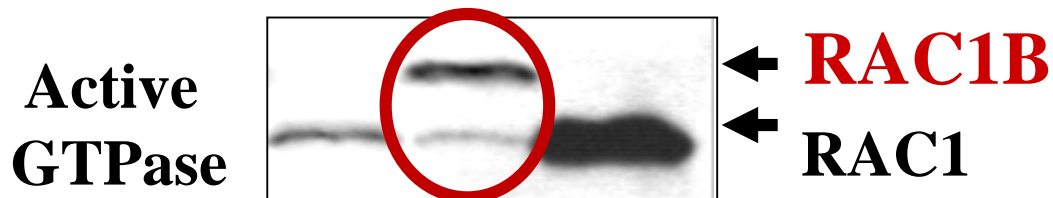
RAC1B protein



Jordan 1999, Oncogene 18: 6835-6839

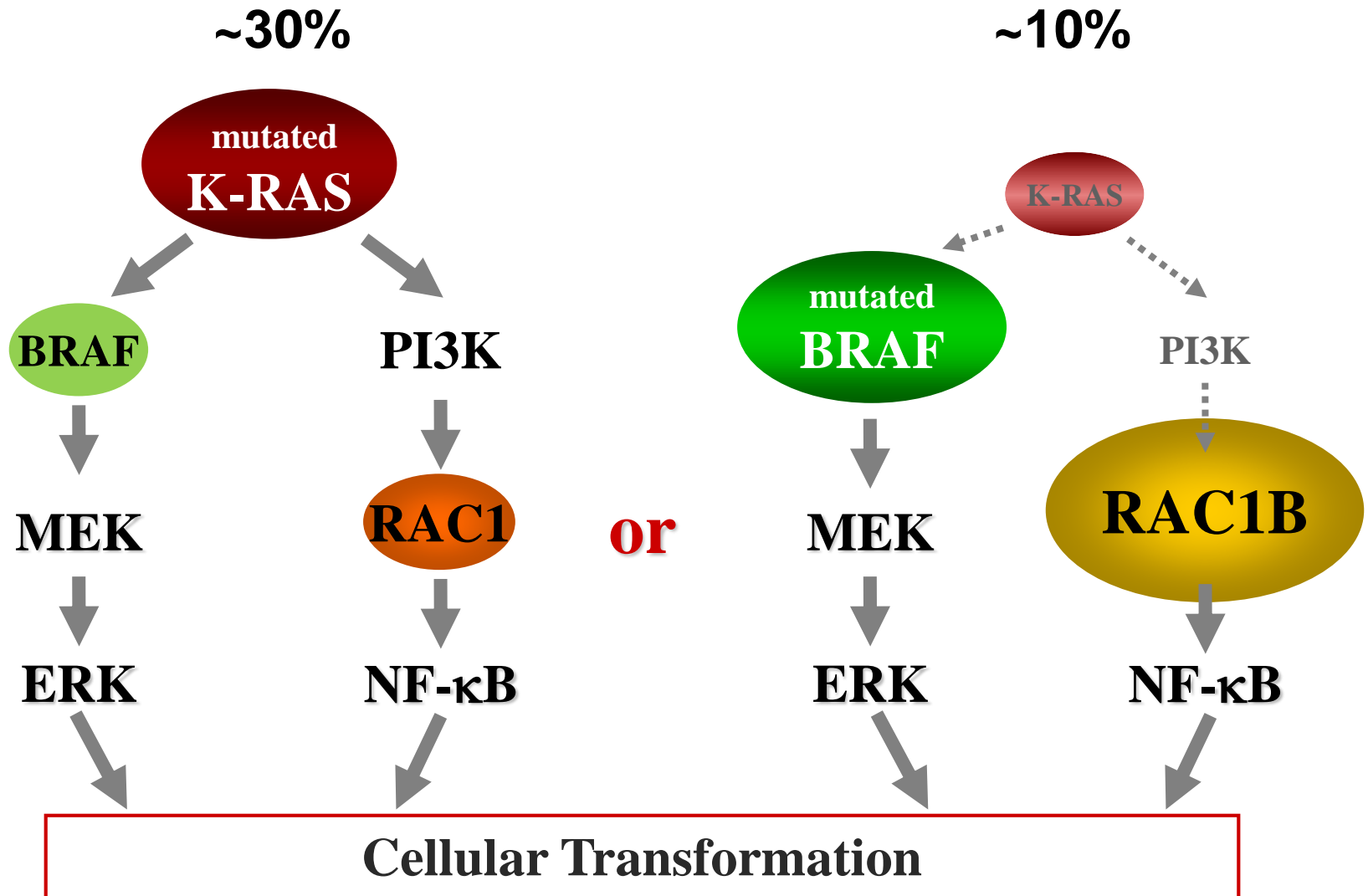


Matos 2003, J Biol Chem 278:50442-48.

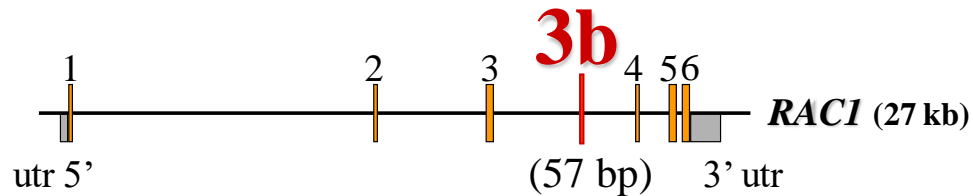


RAC1B adopts the active conformation

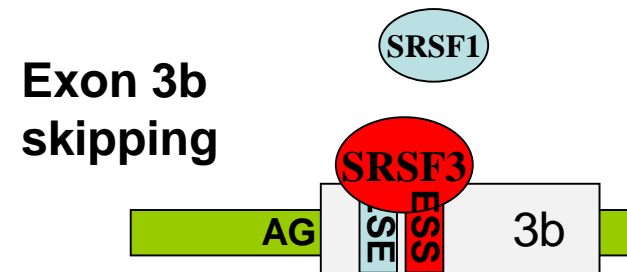
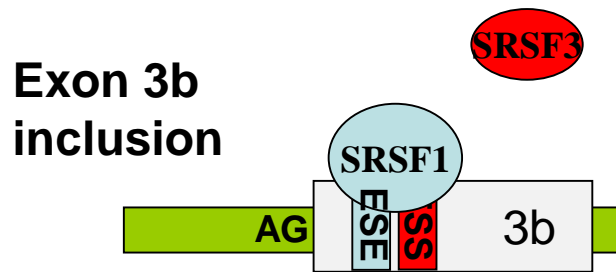
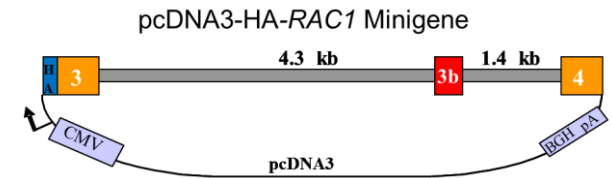
An alternative oncogenic pathway in CRC



How is alternative splicing of RAC1B regulated in colorectal cells ?



Antagonistic SFs regulate *RAC1* alternative splicing in CRC



Gonçalves 2009, Hum Mol Genet 18:3696-3707

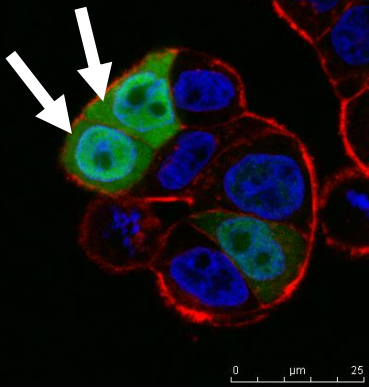
Other splicing factors involved

ESRP1 (Ishii JBC 2014, 289:27386–99) **silencer** in intron 3, HNSCC

PTBP1 (Hollander Genome Res 2016, 26:541-53) **RAC1B enhancer**, CRC

How is the binding of SRSF1 regulated?

siSRPK1



shRNA screen:
candidate regulator kinases **SRPK1** and **GSK3 β**

Shot gun-talk today
by Vânia Gonçalves

Tag-SRSF1

GSK3 β

SRPK1

nuclear
translocation

SRSF1

P

SRSF3

cytoplasm

nucleus

RAC1 pre-mRNA

3

4

inclusion

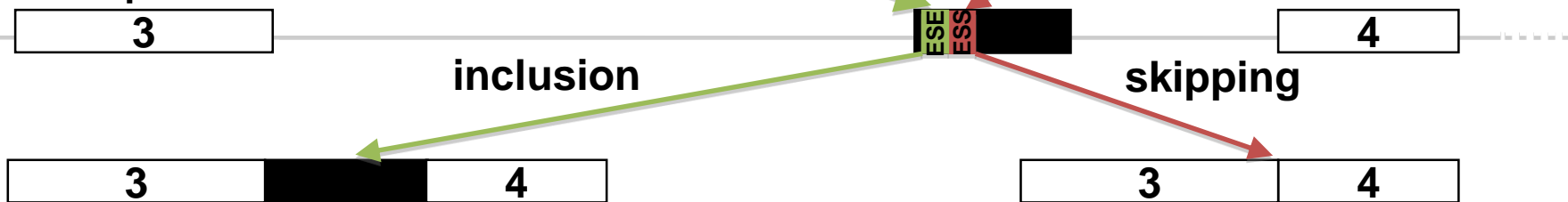
skipping

3

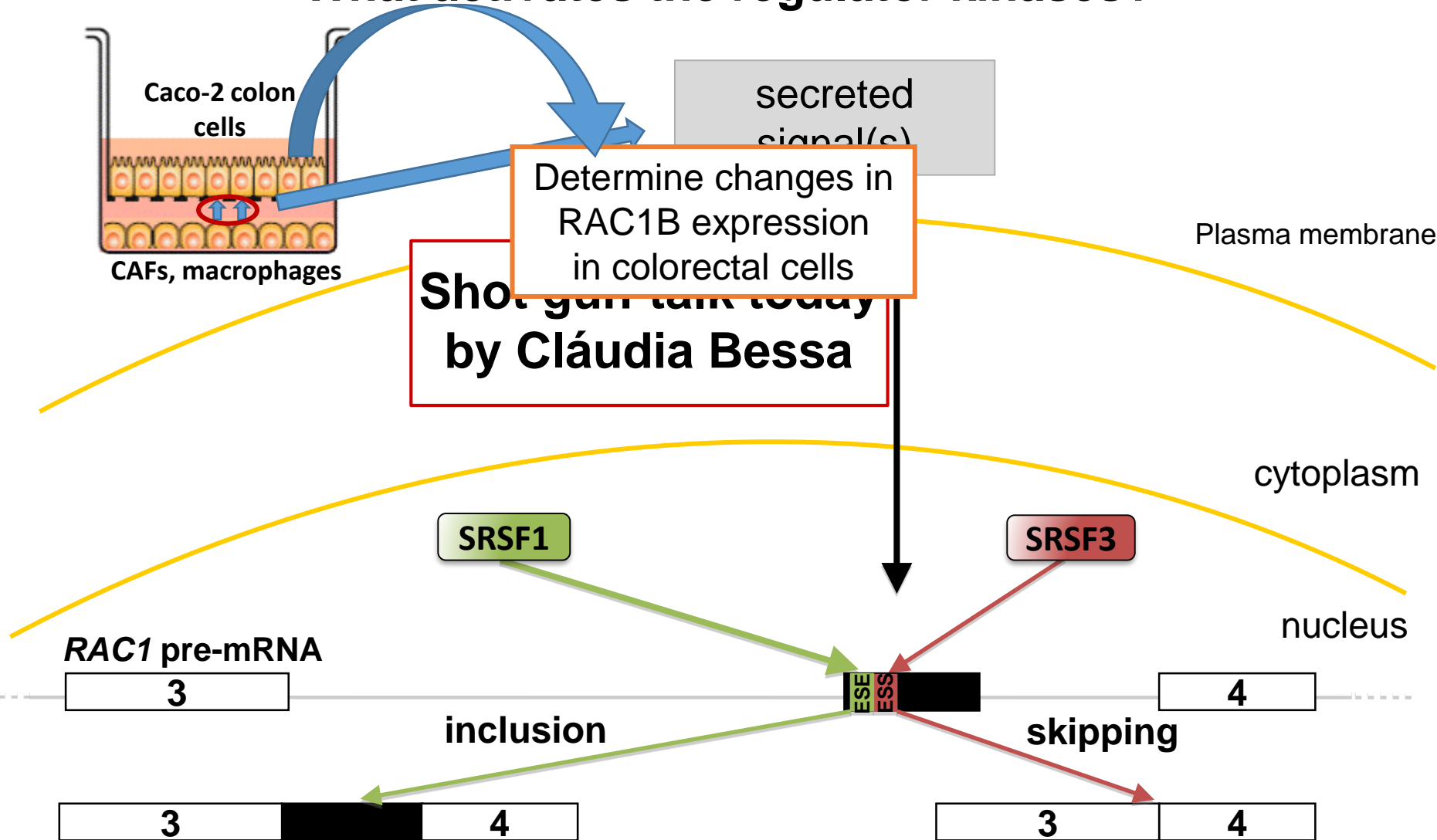
4

3

4



What activates the regulator kinases?



Summary

- **SRSF1 is a key splicing factor required in colorectal cells for inclusion of alternative exon 3b to generate RAC1B**
- **Protein kinases GSK3 β and SRPK1 are upstream regulators of SRSF1-mediated RAC1B overexpression in CRC**
- **A pro-inflammatory microenvironment induces inclusion of alternative exon 3b in colorectal cells**
- **Small-molecule protein kinase inhibitors as a therapeutic option to counteract RAC1B overexpression in tumor cells**

Acknowledgements

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