mTORC1-mediated translational elongation limits intestinal tumour initiation and growth


Mathilde Willemin
19th of May 2015
APC inactivation is a predisposing event\textsuperscript{1} in colorectal cancer.

\textsuperscript{1}Korinek, V. et al. Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC\textsuperscript{2}/2 colon carcinoma. Science 275, 1784–1787 (1997).
Overview of mTOR pathway

To keep in mind:

→ Mammalian target of rapamycin
→ Raptor part of the complex
→ Involve in translation regulation

→ mTOR pathway involves in cell proliferation and tumour growth²

Increased phosphorylation of mTOR effectors 96h after APC deletion.

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Regeneration of crypts after a challenge as a model of early stage of intestinal cancer

→ rapamycin treatment and raptor deletion decrease intestinal regeneration…

→ …and prevent Wnt-driven Proliferation.

mTOR is required for regeneration process !

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Rapamycin treatment and raptor deletion → NO effect on normal enterocytes, only cells with high level of wnt activity = APC deleted cells = tumour cells!

Therapeutic window ?
Prophylactic treatment

Rapamycin sufficient to treat?!

Yes! Mice remain tumour free!

→ rapamycin treatment prevents tumorigenesis in APC deleted cells!
Chemiotherapeutic treatment

Mice are loosing clinical symptoms → rapamycin treatment drives the regression of established tumors!
What translational process is affected by rapamycin treatment?

→ decrease number of polysomes:

1) faster elongation
2) reduced initiation
Rate of elongation measurement

- Harringtonine run off assay

Nature Structural & Molecular Biology (2014)

→ increased rate of elongation in APC loss cells

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Which mTOR effectors are playing a role here?

→ K.O. of 4EBP : no effect (predicted = increasment of regeneration)
→ K.O of S6K : less regeneration observed

S6K is acting through Rps6 (= more established effector)
or eEF2K ?

Rps6 mutant = const. inactivatif
Expected : no regeneration

eEF2K K.O. = eEF2 const. actif
Expected : regeneration and Resistance to rapamycin
SUMMARY

- mTOR = important for Wnt signaling pathway in intestine

- mTOR is acting through the mTORC1 - S6K – eEF2K – eEF2 axis, non expected!

- mTOR as a strategy to treat early stage of colorectal cancer and to prevent tumour development
Questions ?!
Colorectal cancer

General epidemiology:
- Affects colon or rectum = part of big intestine
- Second most deadly cancer in EU
- 450 000 new cases and 232 000 deaths
- Risks: age, lifestyle and heredity

Source: OMS (http://www.euro.who.int viewed on 17th of May 2015)
Wnt/β-catenin signaling pathway upregulates c-Myc expression to promote cell proliferation of P19 teratocarcinoma cells.

Shuai Zhang, Yi Li, Yuling Wu, Kun Shi, Lujun Bing and Jing Hao* (2012)
TOR as a sensor of nutrients (aa, glutamine, etc.) or Growth factors (Insulin, IGFs)
Elongation regulation

Initiation regulation

http://www.nature.com/nrmicro/journal/v6/n4/fig_tab/nrmicro1855_F3.html