Wnt-agonists to Prevent Intestinal Tumorigenesis

Colorectal cancer (CRC) formation is an example of stepwise cancer development where the majority of CRCs are initiated by permanent activation of the Wnt pathway, via mutations in the tumour suppressor gene APC within the stem cell pool. For the first time, researchers at AMC have identified the mechanism by which Wnt antagonist expressing cells mediate their effect against normal cells, demonstrating that replacement of intestinal stem cells (ISCs) in the crypt bottom are distorted by these mutations, leading to supercompetition between Apc-/- and Apc+/+ ISCs and ultimately replacing the population of the crypt with Apc-mutant cells, which go on to initiate tumor formation.

Key advantages

- Identified mechanism behind supercompetition between wt and mutant stemcells and therapeutic intervention to reduce/delay tumorigenesis in the gastrointestinal tract.
- Potential treatment for Familial Adenomatous Polyposis (FAP), a hereditary disease without any viable treatment options (Fig 1).
- Clinical trial at Amsterdam University Medisch Centrum (AMC) of 12 FAP patients to start in 2nd half of 2021.

Potential impact

Supercompetition

While much research is ongoing to treat CRC, knowing that supercompetition is occurring requires a new therapeutic approach. The AMC researchers have identified a known and approved drug (lithium chloride) which can be administered at concentrations lower than currently approved for other indications, which imparts a beneficial safety profile.

Application in FAP patients is potentially revolutionary, given that surgery is the only intervention for managing polyp formation before tumorigenesis occurs.
LiCl neutralizes biased drift and reduces adenoma formation in Apc-/- mice.

a, Consecutive slices of crypt bottoms of Apc mice showing recombination of the Apc-allele (ApcE14-16) and co-expression of Notum, scalebar 20 μm. b, Detection of biallelic (Notumpos;E14/16pos) and monoallelic (Notumneg;E14/16pos) Apc-mutants in the tissue. c, d, Duplex RNA-ISH of Lgr5 (magenta) and Notum (blue) in crypt bottoms, quantification of Lgr5 expression in WT (Notumneg) cells in mixed (Notumneg and Notumpos) and non-mixed (Notumneg) crypts in the absence ($P < 0.0001$) (c) or presence ($P = 0.8109$) of LiCl (d), n = 75 crypts, scalebar 10 μm. Each dot represents a crypt. e, Schematic illustration of short term in vivo treatment scheme. f, Representative crypt bottom images with Notum-ISH clones for control and LiCl treated mice, scalebar 20 μm. g, Boxplots of clone size distributions of NotumPos clones in the presence or absence of LiCl, each data point represents a crypt.
Data

**LiCl neutralizes biased drift and reduces adenoma formation in Apc-/- mice.**

h, i, Relative clone sizes (P = 0.002, Day 21) (h) and relative clone fixation (P =0.0002, Day 21) (i) in control or LiCl treated mice, n = 2 mice per condition for day 4, 7 and 10. j, Probability of fixation (Pfix) of Apc-/- mutant cells in the presence/absence of LiCl, compared to control (neutral) drift, shaded area indicates 95% CI. k, Percentage NotumPos crypts at day 21 (P = 0.0239, n > 500 crypts per mouse, 3 mice). l, Schematic illustration of long term in vivo experiment. m, Representative macroscopic images of pol-yp formation in distal small intestines 60 days after tamoxifen injection. n, Notum-ISH reveals number of adenomas in control or LiCl treated mice, scalebar 2 mm o, Boxplots showing total number of adenomas in control (n = 9) or LiCl treated (n = 12) mice (P <0.0001). Boxplot shows Min to Max, each data point is a mouse. Data are mean ± SEM, n = 3 mice unless otherwise specified.

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