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WHAT IS THE ROLE OF ADDING ASPIRIN IN PIK3CA MUTATED PATIENTS?

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ASPIRIN AND CANCER

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- Aspirin acts on cyclooxygenase (COX) enzymes that regulate the synthesis of prostaglandins (PGs) and related eicosanoids from arachidonic acid

- Aspirin prevents colorectal cancer (CRC) and it is believed to be due to inhibition of precursor lesions (adenomas), whose recurrence is inhibited by aspirin (aspirin-reduced CRC incidence)

- Aspirin intake has also been associated with a statistically significant improvement in patient survival after curative resection of CRC in large observational studies

Aspirin and colorectal cancer: back to the future. Tougeron D, et al. Clin Cancer Res. 2014 Mar 1;20(5):1087-94

ASPIRIN AND CANCER

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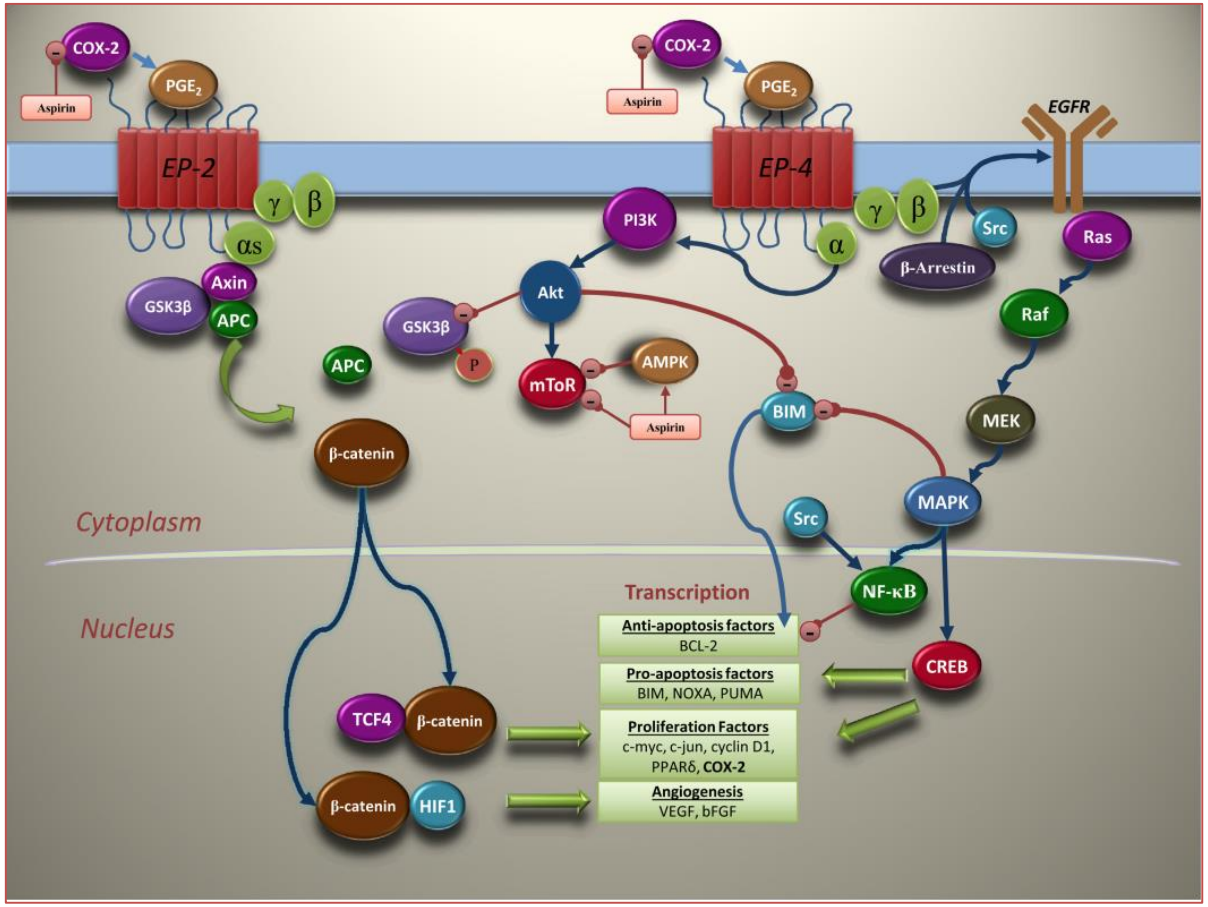

- PGE2 promotes cancer cell growth by binding to its EP receptors and modulating signalling pathways downstream of its receptors
- EP4 receptor activates PI3K which phosphorylates GSK3β to promote β-catenin-mediated transcription

EP = Prostaglandin E2 receptor GSK3β = Glycogen synthase kinase 3 beta

BIOMARKERS OF ASPIRIN EFFICACY IN CANCER

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- Regular use of aspirin was shown to significantly reduce the incidence of CRCs overexpressing COX-2, but not those with weak or absent COX-2 expression in the primary tumor

- Regular aspirin intake was associated with a significant reduction in the incidence of CRCs with wild-type (WT), but not mutant $BRAF^{V600E}$

- Recently, aspirin intake in PIK3CA mutation carriers was associated with a statistically significant increase in survival, whereas patients whose tumors had WT alleles did not derive any benefit

Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med. 2007; 356:2131–2142.
Nishihara R, Lochhead P, Kuchiba A, Jung S, Yamauchi M, Liao X, et al. Aspirin use and risk of colorectal cancer according to BRAF mutation status. JAMA 2013; 309:2563–2571.
Liao X, Lochhead P, Nishihara R, Morikawa T, Kuchiba A, Yamauchi M, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. N Engl J Med. 2012; 367:1596–1606.

PIK3CA, ASPIRIN AND CRC

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- Mutations in the PIK3CA gene are detected in 15–20% of CRCs and lead to constitutive activation of the PI3KAkt pathway

- A mechanistic explanation is suggested by the finding that inhibition of COX-mediated prostaglandin E2 synthesis by aspirin attenuates PI3K signalling activity that is known to regulate cancer cell proliferation and survival
- In addition to inhibiting PGE2, aspirin has been shown to inhibit mTOR, a downstream effector of the PI3K pathway by activation of AMPK

Uddin S, Ahmed M, Hussain A, Assad L, Al-Dayel F, Bavi P, et al. Cyclooxygenase-2 inhibition inhibits PI3K/AKT kinase activity in epithelial ovarian cancer. Int J Cancer. 2010; 126:382–394.

AMPK = Adenosine Monophosphate-activated Protein Kinase

ASPIRIN IN PIK3CA MUTATED CRC: FOUR TRIALS

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Study group	Study population (N)	Aspirin dose used	Results [Multivariate HR (95% CI)]
Nurses' Health and Health Professional Follow-up study[1]	Stage I-IV (N=964)	325 mg	In PIK3CA mutant tumors: HR=0.18 (0.05–0.60) for CRC-specific mortality
VICTOR trial[2]	Stage II and III (N=2434)	< 100 mg	In PIK3CA mutant tumors: HR=0.11 (0.001–0.832; P=0.027) for recurrence-free survival
Dutch trial[3]	Stage II and III (N=3586)	80 mg	In PIK3CA mutant tumors: HR=0.73 (0.33-1.63; P=0.44) for overall survival
VICTOR trial[2]	Stage II-IV (N=1487)	80-100 mg	In PIK3CA mutant tumors: HR=0.96 (P=0.86) for overall survival and HR=0.60 (P=0.14) for cancer-specific survival

1. Liao X et al. N Engl J Med. 2012; 367:1596–1606. 2. Domingo E et al. J Clin Oncol. 2013;31:4297-305. 3. Reimers MS et al. JAMA Intern Med. 2014;174:732-9.

CONCLUSIONS - PERSPECTIVES

- Uncertain benefit of aspirin in PIK3CA mutated CRC due to retrospective studies with heterogeneous populations and results

- Prospective trials evaluating adding aspirin in adjuvant setting are ongoing in PIK3CA mutated CRC: ASPIK trials in England and France

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