Propojení výuky oborů Molekulární a buněčné biologie a Ochrany a tvorby životního prostředí OPVK (CZ.1.07/2.2.00/28.0032)

# Will an Aspirin a Day Keep Cancer Away?

Jocelyn Kaiser

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Marie Šoborová

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# The first hint of protective factor of aspirin

- In the late 1970s by a surgeon in Melbourne
- He wanted to figure out why his country had a relatively high rate of colorectal cancer.
- He and colleagues interviewed more than 700 cancer patients and comparable number of healthy people
- Conclusion => Australians‘ penchant for beer, fatty foods and red meet all seemed to predispose them to disease
- But they also found a surprising protective factor => people who regularly used aspirin were 40% less likely to develop colorectal cancer than those didn‘t take the drug

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# Studies from UK

- Offered the first evidence from placebo-controlled clinical trials that regularly taking low doses of aspirin wards off other types of cancer as well
- The studies found that death rates from several tumor types were as much as 37% lower.
- People who developed a cancer => taking aspirin seemed to slow the spread of tumors to other parts of the body
- *„ It‘s just about the first proof of principle that a simple compound of any kind can reduce the risk of several cancers“*

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# Studies from UK

- These reports have raised attractive possibility that aspirin could serve as the first anticancer drug for general population
- Debate about the risks and benefits
- Other suggestion => medical societies and policymakers should also consider aspirin‘s general cancer-fighting effects
- The research lost momentum in the past decade when one NSAID drug, Vioxx, was pulled off the market because of safety concerns
- What is the mechanism by which aspirin and other NSAIDs protect against cancer???

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# How does taking aspirin ward off cancer?

- Researchers still don‘t understand the mechanism
- Aspirin (acetylsalicylic acid) inhibits two forms of enzymes known as cyclooxygenases (COX) that convert arachidonic acid into lipids called prostaglandins
  - COX-1 protect the stomach lining
  - COX-2 involved in inflammation
- Researchers have concluded that aspirin prevents cancer mainly by blocking the activity of COX-2 (the same inflammation-driven responses that help tissue recovery from wound injury may also help tumors grow)
- Some new clinical studies of low-dose aspirin suggest that COX-2 isn‘t directly involved at all => low doses this drug doesn‘t block COX-2 but still impairs platelets via the COX-1 pathway

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# How does taking aspirin ward off cancer?

- Studies suggest that platelets blunt immune attack on cancer cells and help them take root in a new place
- Other experiments suggest that activated platelets can also stimulate the COX-2 pathway in adjacent cells => this would explain how aspirin could block early stages of colorectal cancer
- Drugs that target only COX-2 (Vioxx, Celebrex) unacceptably raised heart attack risk => efforts to make an alternative to standard aspirin haven't yet panned out

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# Comeback

- Aspirin and some other NSAIDs first bore out their promise in trials published starting in 2000 => people who had precancerous colon polyps removed and others genetically prone to colorectal cancer
- Epidemiological evidence has suggested that aspirin could have broader anticancer effects => it‘s not conclusive
- This evidence come from studies in which people answered questions about their past use of medications
- Hopes for aspirin fell in 2005
- Vioxx, Celebrex

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# Results

- First result => aspirin was taken daily => 37% fewer deaths from cancers after 5 years
  - Found that people who taken regularly aspirin had more stomach bleeds => these incidents were not fatal => people recovered and the bleeding risk went down after several years on aspirin
- Second result => people on aspirin who developed cancer were 36% less likely to have tumors that had spread
- Third result => remarkable consistency in the drop on cancers among aspirin users in epidemiologic studies and clinical trials

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# Chan and his suggest

- Chan is part of an international panel on cancer prevention that, in response to the Rothwell studies, plans to update its stance on aspirin published 3 years ago
- The panel suggest that people take low doses of aspirin daily starting around age 50 and stopping by age 70
- Also is important when doctors should screen patients for the ulcer-causing *Helicobacter pylori* bacterium => positive test => treating this people by antibiotics before putting them on aspirin (reduce the risk of bleeds)

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# U.S. researchers suggest

- It‘s time to update guidelines on the risks and benefits of daily aspirin use
- The group had endorsed its preventive prowess for heart attack and stroke => discounted its anticancer effects
- The potential to protect against both cancer and heart disease could tip the balance toward recommending aspirin for many more healthy adults
- Others are more cautious about recommending aspirin => only people with a particular genetic profile will see their cancer risk go down if they take aspirin

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# U.S. researchers suggest

- Researchers from Houston in Texas are also wary => they thought they could put aspirin in the drinking water => but they admitted that everybody needed  a more personalized approach
- All may become clearer soon after reports on longer-term effects of aspirin on cancer risk => this will be crucial
- Thun says: *„We don‘t want to mess this up“*.

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# THANK YOU FOR YOUR ATTENTION ☺

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# When lymphocytes run out of steam

Emannuel Martin et al.

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MBB2

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- immune cells
- crucial part in protection against micro-organisms - viruses and bacteria
- T cells and B cells
- response is driven by antigen receptors on the cells' surface
- leads to rapid cell proliferation and immune protection
- Proliferation depends on metabolic adaptation

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- children from several unrelated families
- developed a severe immunodeficiency at birth or at a very young age
- persistent infections with viruses such as Epstein-Barr and varicella zoster
- infections from bacteria such as pneumococcus
- patients might be suffering from an inherited immunodeficiency that compromises lymphocyte function

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- Sequencing of DNA from the affected children
- all carried a mutation in *CTPS1* -> absence of this enzyme in the patients' lymphocytes
- CTPS1 is one of two forms of CTP synthase enzymes
- production of cytidine nucleotide triphosphate (CTP)
- required for cellular DNA and RNA synthesis

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- normal lymphocytes express both CTPS1 and CTPS2
- CTPS1 is present at low levels - markedly expressed in activated lymphocytes
- CTPS2 is already expressed at high levels in non-activated lymphocytes
- Analyses of T and B cells from the CTPS1-deficient patients
- cells' capacity to synthesize DNA and proliferate following stimulation of the antigen receptor was severely compromised
- Intracellular levels of CTP were also very low

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- defects were reproduced when CTPS1 expression was artificially reduced in normal lymphocytes
- when 3-deazauridine, a pharmacological inhibitor of CTPS enzymes, was used to suppress their activity

- defects were corrected when CTPS1 was introduced into cells of CTPS1-deficient patients by retrovirus-mediated gene transfer
- when CTP was added to the cells' culture medium.

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- findings show that CTPS1 and its product, CTP, are required for lymphocytes to proliferate intensely during antigen-induced activation

- In the absence of CTPS1, antigen-stimulated lymphocytes do not produce sufficient quantities of CTP, causing defects in DNA synthesis and cell proliferation

- These effects explain in large part why CTPS1-deficient children develop life-threatening viral and bacterial infections

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- even though CTPS2 is expressed in lymphocytes, it cannot replace CTPS1
- possible explanation for this is that CTPS1 is much more active than CTPS2
- possibly to modifications such as phosphorylation or co-factor binding that could influence the enzymes' aktivity
- differences between CTPS1 and CTPS2 remains to be clarified

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- The data also raise the provocative possibility that pharmacological inhibitors of CTPS1 could be useful tools for treating human diseases associated with excessive or uncontrolled lymphocyte proliferation
  - transplant rejection
  - graft-versus-host disease
  - some forms of cancers such as leukaemia and lymphoma

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- CTPS inhibitor 3-deazauridine has already been shown to display some therapeutic efficiency against leukaemic cells *in vitro*
- Although it probably also inhibited targets other than CTPS in these cells

- development of more-specific inhibitors of CTPS1 will help the further investigation of this possible therapeutic methods

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# Thank you for your attention.

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