Acetylsalicylic acid and cancer: where do we stand in 2017

P. Patrignani, Neuroscience, Imaging and Clinical Sciences G. d'Annunzio University, Chieti Italy

The place of aspirin in primary prevention remains controversial. More recently, the U.S. Preventive Services Task Force recommended low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC). This recommendation reflects increasing evidence for a chemopreventive effect of low-dose aspirin against colorectal (and other) cancer (1).

Over 40 observational studies and the long-term follow-up of 51 randomized clinical trials (RCTs) for CVD prevention have shown that low-dose aspirin has a measurable impact on both the incidence and mortality of common cancers such as CRC, other gastrointestinal (GI) cancers and breast cancer (2). In the post-hoc analyses of Rothwell et al. (3) the chemopreventive effect of aspirin is apparently saturable at low-doses (75–100 mg/day), a hallmark of the antithrombotic effect of the drug (4). Importantly, one of the cardiovascular RCTs in which the chemopreventive effect of aspirin was detected on a long-term follow-up involved the administration of a controlled-release formulation of aspirin (75 mg), with negligible systemic bioavailability (5). Four consistent, placebo-controlled RCTs on the recurrence of sporadic colorectal adenomas, a precursor of CRC, reinforce the hypothesis that aspirin acts at multiple steps of cancer progression (1).

Acetylation of cyclooxygenase (COX)-1 at serine-529 is the direct mechanism of action of low-dose aspirin as an antiplatelet agent. To address whether low-dose aspirin (100 mg daily administered to individuals undergoing CRC screening) preferentially targets platelet COX-1 versus extraplatelet sources of COX-1, e.g. colorectal mucosa, we used a novel assay which quantifies the extent of acetylation of COX-1 (6,7). The results show a preferential impact of low-dose aspirin towards platelet COX-1. A lower extent of colorectal COX-1 acetylation was detected and this effect was associated with changes of rectal mucosa phenotype (6). Thus, concurrent inhibitory effect of low-dose aspirin on COX-1 in platelets and colorectal epithelium may impact the development of CRC at early stages.

Additional mechanistic studies to test the “platelet hypothesis” should be performed in animal models of intestinal cancer and, ideally, in different stages of the human disease. These studies could help address the current uncertainty concerning the optimal chemopreventive dose and dosing regimen of aspirin.

An important field of clinical research is focused on the discovery of biomarkers to identify those subjects who will respond to the antineoplastic effect of aspirin. These include plasma markers, such as soluble tumor necrosis factor receptor-2, as well as tumor expression levels of genes involved in prostanoid biosynthesis or signaling pathways activated by the aberrant expression of COX-2, such as phosphatidylinositol 3-kinase (8,9). Most of these studies suffer from the limitation of investigating large cohorts of nonrandomized participants who provided data on

aspirin use in a questionnaire. Thus, these findings should be confirmed by large RCTs. A systems biology approach to the analysis of heterogeneous datasets (genomics, epigenomics, proteomics, lipidomics, and clinical) would allow performing dynamic systems modeling of candidate pathways involved in the antineoplastic effect of aspirin. This strategy would also allow the identification of susceptibility profiles for CRC and their use to develop new biomarkers to predict its occurrence and recurrence.

References

1. Patrignani et al. JACC 2016;68:967-976

2. Thun et al. Nat. Rev.Clin. Oncol.2012; 9:259–267

3. Rothwell et al. Lancet 2011;377:31–41

4. Patrono et al. NEJM 2005:353:2373–2383

5. Charman et al. Br. J. Clin. Pharmacol. 1993:36: 470–473

6.Patrignani et al Clin Pharmacol & Ther 2017

7.Patrignani et al. JTH 2014;12:1320-1330

8. Liao et al. NEJM 2012;367:1596–606

9. Nan et al. JAMA 2015;313:1133–42