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Visions & Reflections (Minireview)

Aspirin: recent developments

O. Yasuda*, Y. Takemura, H. Kawamoto and H. Rakugi

Department of Geriatric Medicine, Osaka University Graduate School of Medicine 2-2 Yamadaoka, Suita, Osaka 565-0871 (Japan), Fax: +81 6 6879 3859, e-mail: yasuda@geriat.med.osaka-u.ac.jp

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Abstract. Aspirin exerts anti-thrombotic action by acetylating and inactivating cyclooxygenase-1, preventing the production of thromboxane A_2 in platelets. Through this inhibition of platelet function, aspirin is considered as a preventative of ischemic diseases such as coronary and cerebral infarction. However, many studies have revealed that aspirin has other beneficial actions in addition to its anti-platelet activity. For example, aspirin may confer some benefit against colorectal cancer. Here, we discuss the involvement of inflammation in atherosclerosis and how aspirin exerts its beneficial actions in atherosclerotic diseases and cancer.

Keywords. Aspirin, atherosclerosis, cyclooxygenase, lipoxin, nuclear factor-κB, nitric oxide.

Since the days of ancient history, willow bark extract has been known to reduce pain and inflammation. Hippocrates in ancient Greece used willow bark to reduce fever and pain and used willow leaves to lessen the pain of childbirth. In Asia, people separated the fibers of willow stems and rubbed the interdentium with them to reduce dental pain. In the 19th century, salicylate was extracted and identified as the effective component in willow. In 1897, an acetylated derivative was synthesized in a pure and stable form that was not as bitter as salicylate and had an anti-inflammatory action [1]. The resulting acetyl salicylate has since been widely used as an anti-inflammatory, analgesic, or antipyretic drug, and even today we are still identifying novel therapeutic actions.

Aspirin is known not only as an anti-inflammatory agent but also as an anti-thrombotic drug. Ischemic vascular disorders, including myocardial and cerebral infarction, are less frequent in aspirin users [2–5]. Aspirin exerts this anti-platelet activity through the inhibition of cyclooxygenase (COX), which is involved in the production of a platelet activator, thromboxane A_2 (TXA_2), and a platelet inhibitor, prostaglandin I_2 (PGI_2), also known as prostacyclin. There are two COX isoforms, COX-1 and COX-2, encoded by two separate genes. COX-1 is constitutively expressed in many tissues and is relatively unresponsive to stimuli, while COX-2 is expressed in vascular endothelial cells and is induced by growth factors and inflammatory cytokines such as interleukin-1ß (IL-1ß) and tumor necrosis factor α (TNFα) [6–8]. Mature platelets possess only COX-1 [9], and aspirin acetylates a serine residue at position 530 (Ser 530) of COX-1, preventing the substrate, arachidonic acid, from contacting the enzyme's active site, located near Ser 530.

This acetylation step is irreversible, and COX-1 is inactivated permanently. Because platelets lack nuclei, their enzymes are not replaced, and the inactivation of COX-1 lasts for the lifespan of the platelets, usually more than a week. In platelets, TXA_2 is abundantly synthesized from arachidonic acid by thromboxane synthase; in endothelial cells, prostacy-

* Corresponding author.

clin synthase synthesizes PGI_2. Fortunately, COX-1, present in circulating platelets, is more sensitive to aspirin inactivation than is COX-2, which can be found in vascular endothelial cells [10, 11]. Consequently, aspirin at low concentrations preferentially inhibits synthesis of TXA_2, a platelet-activating molecule, over PGI_2, a platelet inhibitor.

The earliest stage of atherosclerotic development is the perturbation of vascular endothelial function, which can be evoked by many stimuli [12]. Endothelial dysfunction is accompanied by impaired nitric oxide (NO) production via the action of endothelial NO synthase (eNOS). The decreased level of NO promotes atherosclerosis through numerous pathways, such as increased reactive oxygen species, vascular constriction, and lymphocyte adhesion [13, 14]. Vascular smooth muscle cells (VSMCs) also play an important role in the development of atherosclerosis [15], migrating, proliferating, and producing extracellular matrix components in atherosclerotic plaques. In addition to VSMCs and extracellular matrix, inflammatory cells such as macrophages and T lymphocytes occur in these plaques. T lymphocytes are present at every stage of atherosclerotic development and are fundamental components of the pathology of both the early and late stages of atherosclerosis [12, 16]. Adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), are implicated in the adhesion of lymphocytes to VSMCs, and the expression of these molecules is increased in coronary atherosclerotic tissue [12, 17–19]. Inflammatory cytokines such as IL-1β and TNFα are reported to increase the expression of ICAM-1, VCAM-1, and E-selectin through the activation of NF-κB [20].

Aspirin inhibits phosphorylation of IκB, an NF-κB-inhibitory protein, preventing the degradation of IκB and maintaining NF-κB in an inactive form in endothelial cells [21, 22]. Through this silencing effect on NF-κB, aspirin decreases the macrophage adhesion to endothelial cells and VSMCs [21, 23]. Recently, we reported that aspirin inhibits adhesion of T lymphoblasts to VSMCs [24]. We found that aspirin decreased the expression of the adhesion molecules ICAM-1 and VCAM-1 in VSMCs by reducing NF-κB activity. Neutralizing antibodies to ICAM-1 and VCAM-1 inhibited the adhesion of T lymphoblasts. The addition of aspirin with ICAM-1 and VCAM-1 antibodies resulted in no further decrease of Jurkat T cell adhesion, suggesting that aspirin prevents T cell adhesion by reducing NF-κB activity and decreasing ICAM-1 and VCAM-1 expression.

In addition to studies identifying the silencing effect of aspirin on NF-κB activity [25], many studies have investigated how aspirin exerts its anti-inflammatory action, including the inhibition of heat shock protein activation [26] and reduction of COX-2 expression [27]. Among these many findings, one of the most exciting reports is that the endogenous anti-inflammatory lipids, aspirin-triggered lipoxins (ATLs), are produced as mediators of the anti-inflammatory action of aspirin [28]. As mentioned above, aspirin acetylates the Ser 530 residue of COX-1, inactivating this enzyme irreversibly. Aspirin also irreversibly acetylates COX-2, another member of the COX family, at Ser 516 of the protein, but the enzyme remains active. From arachidonic acid, acetylated COX-2 produces a precursor for ATL, namely 15R-hydroxytetraenoic acid (15R-HETE); nonacetylated COX-2 generates PGH_2, an intermediate for PGI_2 in endothelial cells. 15R-HETE is rapidly converted in adjacent neutrophils to 15-epimeric-LXA_4 (15-epi-LXA_4) or 15-epimeric-LXB_4 (15-epi-LXB_4), namely ATL. 15-epi-LXA_4 and 15-epi-LXB_4 have similar activities, although distinct actions are also reported in some biologic systems [29].

ATL interacts with a cell surface receptor, ALX, a member of the G-protein-coupled receptor family, and exerts anti-inflammatory actions [30, 31]. In addition, ATL binds to the LTD_4 receptor, cysteinyl leukotriene-1 ($CysLT_1$), and is a damper of local inflammation [32, 33]. ATL is also implicated in the NO-mediated anti-inflammatory system. A therapeutically relevant dose of aspirin induces NO release from vascular endothelial cells possibly through the direct acetylation of eNOS [34], although the exact mechanism of NO release induction remains to be elucidated. Furthermore, it has been suggested that 15-epi-LXA_4 mediates the eNOS- and inducible NO synthase (iNOS)-dependent production of NO, which inhibits the interaction of leukocytes with endothelial cells and reduces inflammation in microvascular systems [35].

Given the large volume of endothelial cells and the possibility of constitutive expression of COX-2 in endothelial cells under shear stress [36], the vascular system is a major source of ATL. In fact, aspirin increases plasma ATL levels in an inverse dose-response manner: administration of aspirin once a day for 8 weeks significantly increased plasma ATL levels at a dose of 81 mg, exerted a borderline increase at 325 mg, and caused no apparent significant change at 650 mg [37]. This plateauing of ATL synthesis at a high dose of aspirin may be consistent with reports suggesting that reductions in vascular events in patients treated with high-dose aspirin (500–1500 mg/day) do not exceed that with lower doses (75–150 mg/day).

The production of oxidative stress is implicated in the development of atherosclerosis. Oxidized low-density

lipoprotein is incorporated into macrophages in the vascular walls and transformed into foam cells, which produce inflammatory cytokines, such as TNFα and IL-1β. Aspirin protects endothelial cells from the deleterious effects of hydrogen peroxide. This protective action of aspirin is likely mediated through an NO-cGMP signaling system [38]. Heme oxygenase-1 may also explain this anti-oxidative action of aspirin: aspirin increases the expression and enzymatic activity of this anti-oxidant defense protein, presumably via an NO-dependent and COX-independent mechanism [39]. ATL seems also to be involved in this endothelial cell-protective action by aspirin. The aspirin-triggered lipoxin A4 analog (ATL-1) inhibits the activation of NAD(P)H oxidase, a major source of endothelial oxidative stress, by preventing phosphorylation of p47phox, a subunit of NAD(P)H, and subsequent translocation of the protein from the cytoplasm to the cell membrane [40].

The beneficial effect of aspirin on the secondary prevention of ischemic diseases such as myocardial and cerebral infarction has been established [41]. However, aspirin administration does not protect all patients at high risk for ischemic diseases from ischemic events. A meta-analysis revealed that aspirin decreased the rate of ischemic events, including myocardial and cerebral infarction and lethal arterial diseases, by 19% in high-risk patients compared to control participants [41]. This means that 81% of high-risk patients were not protected by aspirin administration. Findings such as this led to the concept of 'aspirin resistance.' 'Aspirin resistance' may arise from individual differences in the effects of aspirin, including inhibition of platelet function, or by incomplete effects of aspirin that fluctuate over time. A recent analysis shows that the reported prevalence of aspirin resistance varies because of differences in aspirin dosage and the definition of aspirin resistance, and, on average, about a quarter of patients may exhibit aspirin resistance [42].

The mechanism of aspirin resistance has not been clarified. However, a genetic polymorphism in the *COX-1* gene, the main target of aspirin in the inhibition of platelet aggregation, may explain the variation in the anti-thrombotic action of aspirin. Among the single nucleotide polymorphisms in the *COX-1* gene, A-842G and C50T are in complete linkage disequilibrium; in addition, platelets from people heterozygous for the A-842G/C50T haplotype show significantly greater inhibition of PGH_2 formation from arachidonic acid by aspirin compared with those from common allele homozygotes [43]. On the other hand, there is a dubious aspect to the existence of aspirin resistance. The term 'drug resistance' is defined and usually used when a drug, such as antibiotics or anti-cancer drugs, cannot act at its target and prevent infection or disease. Therefore, it is suggested that the phenomenon of 'aspirin resistance' should instead be termed 'treatment failure,' and the term 'aspirin resistance' should be limited to cases in which aspirin cannot inhibit COX-1 action [44].

Prostaglandin E_2 (PGE_2) is increased and is the most abundant prostaglandin in colorectal cancers. PGE_2 is generated, like other prostaglandins, by COX-1 and COX-2. While COX-1 is constitutively expressed in colon, COX-2 is an inducible COX and is increased in adenomatous polyps and many types of colon cancer [45]. Therefore, the use of nonsteroidal anti-inflammatory drugs or COX-2 inhibitors to prevent the onset or progression of colon cancers has been suggested. This notion is also supported by the observation that mice lacking PGE_2 or the PGE_2 receptor are resistant to intestinal tumorigenesis, and that oral PGE_2 treatment is associated with increased development of intestinal tumors in mice [46, 47]. Indeed, clinical trials report that the risk of colorectal cancer is reduced in aspirin users compared to nonusers [48, 49]. Recently, it was reported that aspirin use reduced the risk of colorectal cancer associated with COX-2 overexpression, although aspirin did not elicit this significant reduction in the absence of COX-2 or when COX-2 expression was weak [50]. These findings suggest benefits from the therapeutic use of aspirin and other NSAIDs for colorectal cancer; however, the optimal use, dosage, and type of disease to target are under investigation.

Investigators have demonstrated that inflammatory processes participate in every stage of atherosclerotic development from the initial stage of vascular endothelial cell perturbations to the thrombotic complications of atherosclerosis. Indeed, the plasma concentration of C-reactive protein (CRP), a marker for systemic inflammation, predicts the risk of myocardial infarction and stroke, and the reduced risk of myocardial infarction associated with aspirin administration appears to be related to CRP levels [51]. Aspirin is the most commonly administered anti-inflammatory drug, which exerts anti-atherosclerotic activity through its various anti-inflammatory actions. Furthermore, it has been suggested that aspirin has anti-cancer activity. Although aspirin has an extensive history as a widely used generalist drug, there remains much to be learned about the effects and pathways of its anti-inflammatory action.

1 Miner, J. and Hoffhines, A. (2007) The discovery of aspirin's antithrombotic effects. Tex. Heart Inst. J. 34, 179–186.
2 Diener, H. C., Cunha, L., Forbes, C., Sivenius, J., Smets, P. and Lowenthal, A. (1996) European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J. Neurol. Sci. 143, 1–13.

3 Baigent, C., Collins, R., Appleby, P., Parish, S., Sleight, P. and Peto, R. (1998) ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. BMJ 316, 1337–1343.

4 The SALT Collaborative Group (1991) Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. Lancet 338, 1345–1349.

5 Farrell, B., Godwin, J., Richards, S. and Warlow, C. (1991) The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J. Neurol. Neurosurg. Psychiatry 54, 1044–1054.

6 Breyer, R. M., Kennedy, C. R., Zhang, Y. and Breyer, M. D. (2000) Structure-function analyses of eicosanoid receptors: physiologic and therapeutic implications. Ann. NY. Acad. Sci. 905, 221–231.

7 Smith, W. L., DeWitt, D. L. and Garavito, R. M. (2000) Cyclooxygenases: structural, cellular, and molecular biology. Annu. Rev. Biochem. 69, 145–182.

8 Kuwano, T., Nakao, S., Yamamoto, H., Tsuneyoshi, M., Yamamoto, T., Kuwano, M. and Ono, M. (2004) Cyclooxygenase 2 is a key enzyme for inflammatory cytokine-induced angiogenesis. FASEB J. 18, 300–310.

9 Rocca, B., Secchiero, P., Ciabattoni, G., Ranelletti, F. O., Catani, L., Guidotti, L., Melloni, E., Maggiano, N., Zauli, G., Patrono, C. (2002) Cyclooxygenase-2 expression is induced during human megakaryopoiesis and characterizes newly formed platelets. Proc. Natl. Acad. Sci. USA 99, 7634–7639.

10 Patrignani, P., Filabozzi, P. and Patrono, C. (1982) Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects. J. Clin. Invest. 69, 1366–1372.

11 FitzGerald, G. A., Oates, J. A., Hawiger, J., Maas, R. L., Roberts, L. J., 2nd, Lawson, J. A. and Brash, A. R. (1983) Endogenous biosynthesis of prostacyclin and thromboxane and platelet function during chronic administration of aspirin in man. J. Clin. Invest. 71, 676–688.

12 Ross, R. (1999) Atherosclerosis – an inflammatory disease. N. Engl. J. Med. 340, 115–126.

13 Davignon, J. and Ganz, P. (2004) Role of endothelial dysfunction in atherosclerosis. Circulation 109, III27–III32.

14 Fuster, V., Moreno, P. R., Fayad, Z. A., Corti, R. and Badimon, J. J. (2005) Atherothrombosis and high-risk plaque. I. Evolving concepts. J. Am. Coll. Cardiol. 46, 937–954.

15 Schwartz, S. M., deBlois, D. and O'Brien, E. R. (1995) The intima: soil for atherosclerosis and restenosis. Circ. Res. 77, 445–465.

16 Hansson, G. K., Holm, J. and Jonasson, L. (1989) Detection of activated T lymphocytes in the human atherosclerotic plaque. Am. J. Pathol. 135, 169–175.

17 Sakai, A., Kume, N., Nishi, E., Tanoue, K., Miyasaka, M. and Kita, T. (1997) P-selectin and vascular cell adhesion molecule-1 are focally expressed in aortas of hypercholesterolemic rabbits before intimal accumulation of macrophages and T lymphocytes. Arterioscler. Thromb. Vasc. Biol. 17, 310–316.

18 Poston, R. N., Haskard, D. O., Coucher, J. R., Gall, N. P. and Johnson-Tidey, R. R. (1992) Expression of intercellular adhesion molecule-1 in atherosclerotic plaques. Am. J. Pathol. 140, 665–673.

19 O'Brien, K. D., McDonald, T. O., Chait, A., Allen, M. D. and Alpers, C. E. (1996) Neovascular expression of E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 in human atherosclerosis and their relation to intimal leukocyte content. Circulation 93, 672–682.

20 Montgomery, K. F., Osborn, L., Hession, C., Tizard, R., Goff, D., Vassallo, C., Tarr, P. I., Bomsztyk, K., Lobb, R., Harlan, J. M., Pohlman, T. H. (1991) Activation of endothelial-leukocyte adhesion molecule 1 (ELAM-1) gene transcription. Proc. Natl. Acad. Sci. USA 88, 6523–6527.

21 Pierce, J. W., Read, M. A., Ding, H., Luscinskas, F. W. and Collins, T. (1996) Salicylates inhibit I kappa B-alpha phosphorylation, endothelial-leukocyte adhesion molecule expression, and neutrophil transmigration. J. Immunol. 156, 3961–3969.

22 Weber, C., Erl, W., Pietsch, A. and Weber, P. C. (1995) Aspirin inhibits nuclear factor-kappa B mobilization and monocyte adhesion in stimulated human endothelial cells. Circulation 91, 1914–1917.

23 Gerli, R., Gresele, P., Bistoni, O., Paolucci, C., Lanfrancone, L., Fiorucci, S., Muscat, C. and Costantini, V. (2001) Salicylates inhibit T cell adhesion on endothelium under nonstatic conditions: induction of L-selectin shedding by a tyrosine kinase-dependent mechanism. J. Immunol. 166, 832–840.

24 Yotsui, T., Yasuda, O., Kawamoto, H., Higuchi, M., Chihara, Y., Umemoto, E., Tanaka, T., Miyasaka, M., Rakugi, H., Ogihara, T. (2007) Aspirin prevents adhesion of T lymphoblasts to vascular smooth muscle cells. FEBS Lett. 581, 427–432.

25 Kopp, E. and Ghosh, S. (1994) Inhibition of NF-kappa B by sodium salicylate and aspirin. Science 265, 956–959.

26 Fawcett, T. W., Xu, Q. and Holbrook, N. J. (1997) Potentiation of heat stress-induced hsp70 expression in vivo by aspirin. Cell Stress Chaperones 2, 104–109.

27 Xu, X. M., Sansores-Garcia, L., Chen, X. M., Matijevic-Aleksic, N., Du, M. and Wu, K. K. (1999) Suppression of inducible cyclooxygenase 2 gene transcription by aspirin and sodium salicylate. Proc. Natl. Acad. Sci. U S A 96, 5292–5297.

28 Serhan, C. N. and Chiang, N. (2002) Lipid-derived mediators in endogenous anti-inflammation and resolution: lipoxins and aspirin-triggered 15-epi-lipoxins. ScientificWorldJournal 2, 169–204.

29 Claria, J., Lee, M. H. and Serhan, C. N. (1996) Aspirin-triggered lipoxins (15-epi-LX) are generated by the human lung adenocarcinoma cell line (A549)-neutrophil interactions and are potent inhibitors of cell proliferation. Mol. Med. 2, 583–596.

30 Takano, T., Fiore, S., Maddox, J. F., Brady, H. R., Petasis, N. A. and Serhan, C. N. (1997) Aspirin-triggered 15-epi-lipoxin A4 (LXA4) and LXA4 stable analogues are potent inhibitors of acute inflammation: evidence for anti-inflammatory receptors. J. Exp. Med. 185, 1693–1704.

31 Fiore, S., Maddox, J. F., Perez, H. D. and Serhan, C. N. (1994) Identification of a human cDNA encoding a functional high affinity lipoxin A4 receptor. J. Exp. Med. 180, 253–260.

32 Gronert, K., Martinsson-Niskanen, T., Ravasi, S., Chiang, N. and Serhan, C. N. (2001) Selectivity of recombinant human leukotriene D(4), leukotriene B(4), and lipoxin A(4) receptors with aspirin-triggered 15-epi-LXA(4) and regulation of vascular and inflammatory responses. Am. J. Pathol. 158, 3–9.

33 McMahon, B., Stenson, C., McPhillips, F., Fanning, A., Brady, H. R. and Godson, C. (2000) Lipoxin A4 antagonizes the mitogenic effects of leukotriene D4 in human renal mesangial cells: differential activation of MAP kinases through distinct receptors. J. Biol. Chem. 275, 27566–27575.

34 Taubert, D., Berkels, R., Grosser, N., Schroder, H., Grundemann, D. and Schomig, E. (2004) Aspirin induces nitric oxide release from vascular endothelium: a novel mechanism of action. Br. J. Pharmacol. 143, 159–165.

35 Paul-Clark, M. J., Van Cao, T., Moradi-Bidhendi, N., Cooper, D. and Gilroy, D. W. (2004) 15-epi-lipoxin A4-mediated induction of nitric oxide explains how aspirin inhibits acute inflammation. J. Exp. Med. 200, 69–78.

36 Topper, J. N., Cai, J., Falb, D. and Gimbrone, M. A., Jr. (1996) Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. Proc. Natl. Acad. Sci. USA 93, 10417–10422.

37 Chiang, N., Bermudez, E. A., Ridker, P. M., Hurwitz, S. and Serhan, C. N. (2004) Aspirin triggers antiinflammatory 15-epi-lipoxin A4 and inhibits thromboxane in a randomized human trial. Proc. Natl. Acad. Sci. USA 101, 15178–15183.

38 Grosser, N. and Schroder, H. (2003) Aspirin protects endothelial cells from oxidant damage via the nitric oxide-cGMP pathway. Arterioscler. Thromb. Vasc. Biol. 23, 1345–1351.
39 Grosser, N., Abate, A., Oberle, S., Vreman, H. J., Dennery, P. A., Becker, J. C., Pohle, T., Seidman, D. S., Schroder, H. (2003) Heme oxygenase-1 induction may explain the antioxidant profile of aspirin. Biochem. Biophys. Res. Commun. 308, 956–960.
40 Nascimento-Silva, V., Arruda, M. A., Barja-Fidalgo, C. and Fierro, I. M. (2007) Aspirin-triggered lipoxin A4 blocks reactive oxygen species generation in endothelial cells: a novel antioxidative mechanism. Thromb. Haemost. 97, 88–98.
41 Antithrombotic Trialists' Collaboration (2002) Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 324, 71–86.
42 Hovens, M. M., Snoep, J. D., Eikenboom, J. C., van der Bom, J. G., Mertens, B. J. and Huisman, M. V. (2007) Prevalence of persistent platelet reactivity despite use of aspirin: a systematic review. Am. Heart J. 153, 175–181.
43 Halushka, M. K., Walker, L. P. and Halushka, P. V. (2003) Genetic variation in cyclooxygenase 1: effects on response to aspirin. Clin. Pharmacol. Ther. 73, 122–130.
44 Cattaneo, M. (2007) Laboratory detection of 'aspirin resistance': what test should we use (if any)? Eur. Heart J. 28, 1673–1675.
45 Yang, V. W., Shields, J. M., Hamilton, S. R., Spannhake, E. W., Hubbard, W. C., Hylind, L. M., Robinson, C. R. and Giardiello, F. M. (1998) Size-dependent increase in prostanoid levels in adenomas of patients with familial adenomatous polyposis. Cancer Res. 58, 1750–1753.
46 Oshima, M., Dinchuk, J. E., Kargman, S. L., Oshima, H., Hancock, B., Kwong, E., Trzaskos, J. M., Evans, J. F., Taketo, M. M. (1996) Suppression of intestinal polyposis in Apc delta716 knockout mice by inhibition of cyclooxygenase 2 (COX-2). Cell 87, 803–809.
47 Sonoshita, M., Takaku, K., Sasaki, N., Sugimoto, Y., Ushikubi, F., Narumiya, S., Oshima, M. and Taketo, M. M. (2001) Acceleration of intestinal polyposis through prostaglandin receptor EP2 in Apc(Delta 716) knockout mice. Nat. Med. 7, 1048–1051.
48 Baron, J. A., Cole, B. F., Sandler, R. S., Haile, R. W., Ahnen, D., Bresalier, R., McKeown-Eyssen, G., Summers, R. W., Rothstein, R., Burke, C. A., Snover, D. C., Church, T. R., Allen, J. I., Beach, M., Beck, G. J., Bond, J. H., Byers, T., Greenberg, E. R., Mandel, J. S., Marcon, N., Mott, L. A., Pearson, L., Saibil, F., van Stolk, R. U. (2003) A randomized trial of aspirin to prevent colorectal adenomas. N. Engl. J. Med. 348, 891–899.
49 Benamouzig, R., Deyra, J., Martin, A., Girard, B., Jullian, E., Piednoir, B., Couturier, D., Coste, T., Little, J., Chaussade, S. (2003) Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. Gastroenterology 125, 328–336.
50 Benelli, R. (2007) Aspirin, COX-2, and the risk of colorectal cancer. N. Engl. J. Med. 357, 824–825; author reply 824–825.
51 Ridker, P. M., Cushman, M., Stampfer, M. J., Tracy, R. P. and Hennekens, C. H. (1997) Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N. Engl. J. Med. 336, 973–979.