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Mini-review

Targeting apoptosis pathways by Celecoxib in cancer

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ABSTRACT

Celecoxib is a paradigmatic selective inhibitor of cyclooxygenase-2 (COX-2). This anti-inflammatory drug has potent anti-tumor activity in a wide variety of human epithelial tumor types, such as colorectal, breast, non-small cell lung, and prostate cancers. Up to now, the drug found application in cancer prevention in patients with familial adenomatous polyposis. Moreover, the use of Celecoxib is currently tested in the prevention and treatment of pancreatic, breast, ovarian, non-small cell lung cancer and other advanced human epithelial cancers.

Induction of apoptosis contributes to the anti-neoplastic activity of Celecoxib. In most cellular systems Celecoxib induces apoptosis independently from its COX-2 inhibitory action via a mitochondrial apoptosis pathway which is however, not inhibited by overexpression of Bcl-2. In addition, Celecoxib exerts antagonistic effects on the anti-apoptotic proteins Mcl-1 and survivin. Consequently, the use of Celecoxib may be of specific value for the treatment of apoptosis-resistant tumors with overexpression of Bcl-2, Mcl-1, or survivin as single drug or in combination with radiotherapy, chemotherapy, or targeted pro-apoptotic drugs that are inhibited by survivin, Bcl-2 or Mcl-1. As COX-2 inhibition has been associated with cardiovascular toxicity, the value of drug derivatives without COX-2 inhibitory action should be validated for prevention and treatment of human epithelial tumors to reduce the risk for heart attack or stroke. However, its additional COX-2 inhibitory action may qualify Celecoxib for a cautious use in COX-2-dependent epithelial tumors, where the drug could additionally suppress COX-2-mediated growth and survival promoting signals from the tumor and the stromal cells.

1. Celecoxib is a selective COX-2 inhibitor with anti-neoplastic activity

The non-steroidal anti-inflammatory drug (NSAID) Celecoxib (Celebrex®, Onsenal®, Pfizer, New York, USA) belongs to the drug family of COXIBs and constitutes a potent and specific inhibitor of the human cyclooxygenase-2 (COX-2). COX-2 is constitutively overexpressed in many human premalignant, malignant and metastatic epithelial tumors, e.g. colorectal, lung, breast, prostate, and head/neck cancer [1–4]. Upregulated expression of COX-2 is an early event during carcinogenesis, and is mostly associated with poor prognosis as it promotes tumor cell proliferation, angiogenesis, invasion and metastasis [1,5–7]. Similar

Abbreviations: Akt, protein kinase B; ATF-4, activating transcription factor 4; CHOP/GADD153, c/EBP homologous transcription factor/growth arrest and DNA-damage associated protein 153; COXIB, COX-2-inhibitor; COX-2, Cyclooxygenase-2; DISC, death inducing signaling complex; DMC, 2,5-Dimethylcelecoxib; EGR1, Early growth response factor 1; eIF2α, eukaryotic initiation factor 2 alpha; ER, endoplasmic reticulum; FADD, fas associated protein with death domain; FAP, familiary adenomatous polyposis; GRP78, glucose regulated protein of 78 kDa; GSK-3, glycogen synthase kinase-3; IAP, inhibitor of apoptosis protein; Mcl-1, myeloid cell leukemia sequence 1; Mito, mitochondrium; NSAID, non-steroidal anti-inflammatory drug; PDK-1, 3-phosphoinositide dependent kinase-1; PERK, eukaryotic initiation factor 2 kinase; PGE (2), prostaglandin E(2); SERCA, sarcoplasmic/endoplasmic reticulum calcium ATPase; Smac/DIABLO, second mitochondria-derived activator of caspases/direct IAP binding Protein with Low PI; TNF, tumor necrosis factor.

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to other NSAIDs, Celecoxib interferes with tumor initiation and tumor cell growth *in vitro* and *in vivo*. Epidemiological studies suggest a lower incidence of colonic polyps in patients with the hereditary familiary adenomatous polyposis (FAP) syndrome and a decreased risk for cancers of the colon, breast, esophagus, and stomach upon continuous uptake of Celecoxib and related compounds [8–10]. Moreover, preclinical investigations demonstrate promising anti-tumor activity of Celecoxib in a variety of human tumors [11–16]. In addition, Celecoxib was found to increase the sensitivity of tumor cells to chemotherapy, radiotherapy, or chemoradiotherapy in preclinical investigations [17–22]. These findings make Celecoxib an attractive compound for anticancer treatment. It has been approved for oral use in the prevention of colon cancer development in patients with FAP and clinical studies evaluate the therapeutic potential of Celecoxib in the treatment of advanced human tumors.

During the last decade, numerous groups studied the mechanisms of the anti-cancer action of Celecoxib. However, the underlying mechanisms are not yet completely understood. It has been demonstrated that Celecoxib and related compounds induce cell cycle arrest, inhibit tumor growth, and suppress tumor neo-angiogenesis (for a review see [23]). Moreover, Celecoxib potently induces apoptotic cell death in tumor cells and endothelial cells [24–28]. Importantly, among the drugs of the COXIB drug family the potent pro-apoptotic activity seems to be restricted to Celecoxib and 2,5-dimethylcelecoxib (DMC), a derivative without COX-2 inhibitory action [29].

Apoptosis is an evolutionary conserved programmed mode of cell death and is critical for the maintenance of tissue homeostasis. Apoptosis also contributes to the cytotoxic effects of standard genotoxic chemotherapy and radiotherapy. Apoptosis signaling is tightly regulated by two main apoptosis pathways, termed ''extrinsic pathway'' and ''intrinsic pathway''. They involve cell surface death receptors or the mitochondria and the endoplasmic reticulum, respectively (Fig. 1) [30,31]. Both pathways lead to the activation of specialized proteases, the caspases that cleave diverse cellular substrates thereby fostering death execution. However, apoptosis signaling pathways are disrupted or impaired in tumor cells, resulting in apoptosis resistance which is one of the common traits that tumor cells acquire during malignant transformation [32]. Unfortunately, the same cellular changes that allow the tumor cells to survive microenvironmental stress during tumorigenesis can cause cross-resistance to apoptosis induction by genotoxic therapies [33–35]. Therefore, current research efforts aim at the identification of novel agents that induce cell death in tumor cells with resistance to apoptosis induced by chemotherapy and radiotherapy, or that enhance the efficacy of genotoxic therapies in tumor cells with apoptosis resistance to improve treatment outcome [30,31,36].

Interestingly, numerous laboratories demonstrated that Celecoxib is able to suppress tumor growth without an apparent involvement of its target protein COX-2 [23,37]. Important molecular targets of the COX-2-independent actions of Celecoxib include protein kinase B (Akt) and its upstream kinase 3-phosphoinositide-dependent kinase-1 (PDK-1) [28,38–40], cyclin-dependent kinase inhibitors and cyclins [23,28], the anti-apoptotic proteins survivin, Bcl-2 and Mcl-1 [41,42], as well as the sacroplasmic/endoplasmic reticulum calcium ATPase SERCA [43] (for a detailed review see [23]). Some concern had been raised about the relevance of these COX-2-independent drug targets for the anti-cancer actions of Celecoxib as many observations had been made *in vitro* using drug concentrations (40–100 μM) that largely exceeded plasma concentrations achievable by a daily intake of 200–400 mg Celecoxib. However, these *in vitro* studies had mostly been performed upon short-term treatment and effective drug concentrations were found to be reduced when the *in vitro* treatment period was extended [44]. Thus, the plasma concentrations obtained *in vivo* may be sufficient to induce a substantial anti-neoplastic effect because the treatment is usually performed over a longer time period. In line with that assumption, the pro-apoptotic Celecoxib-effects were not only observed at high drug concentrations *in vitro* but also in the *in vivo*-situation (chemoprevention or treatment) at clinically relevant plasma concentrations [16,45–48]. These findings strongly suggest that the molecular targets of Celecoxib and derivatives discovered *in vitro* are also relevant for drug-efficacy *in vivo*. In this regard, some *in vivo* studies have revealed that Celecoxib-treatment affects the levels of several molecular targets with relevance for apoptosis regulation [16,41,49,50] and that these effects are associated with decreased tumor growth, increased apoptosis, or both. Accumulation of Celecoxib in cellular membranes may provide a molecular basis for its ability to exert its anti-neoplastic effects at low plasma concentrations *in vivo* [51].

2. Mechanisms of Celecoxib-induced apoptosis

2.1. Role of COX-2

The pro-apoptotic effects of Celecoxib had first been attributed to its inhibitory action on COX-2. It had been suggested that by inhibiting COX-2 Celecoxib would interfere with prostaglandin (PG)-mediated upregulation of anti-apoptotic proteins [52,53] (Fig. 2). However, later it became increasingly clear that the pro-apoptotic effects of Celecoxib do not critically rely on COX-2 inhibition. This assumption was supported by the following findings: (i) numerous reports demonstrated that Celecoxib effectively induces apoptosis in COX-2-negative cells [14,15,26]; (ii) using anti-sense constructs or RNAi to alter COX-2 expression, it was shown that COX-2 is not required for the effects of Celecoxib on apoptosis induction [25]; (iii) structural derivatives of Celecoxib not inhibiting COX-2 induced apoptosis with similar or higher potency compared to Celecoxib [15,23,29,37,38,54]. Even more important, potent induction of apoptosis is not a characteristic of all COXIBs, but seems to be restricted to Celecoxib and DMC, one of the Celecoxib-derivatives that has been reported to lack COX-2 inhibitory action [29,38,46,54,55]. However, despite lacking direct COX-2-inhibitory activity, DMC efficiently suppresses production of prostaglandins, particularly prostaglandin E(2) (PGE(2)), *in vitro* in the low μM range [56]. The analysis