The Crosslink between COX2 and Chemoresistance

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Abstract

Background: Chemoresistance and tumour relapse remain major clinical problems. Accumulating evidence indicates that the COX2/PGE2/EP axis plays critical roles not only in tumor development including initiation and progression but also in the development of therapeutic resistance. Few studies evaluated the crosslink between COX-2, chemotherapy and chemoresistance. In this review we will give an overview about the relation of the COX-2 gene expression with chemoresistance in colon cancer patients. Also, the effects of cytotoxic chemotherapy on COX-2 expression.

Keywords: Cox2 , chemoresistance.

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Introduction

Colorectal cancer (CRC) is the third most common type of cancer and the second leading cause of cancer-related death in the world, with around 900,000 deaths per year [1]. Even in patients who have undergone tumor resection, 40–50% relapsed and died from metastases, being the overall 5-year survival less than 60% [2].

Cancer treatment includes surgery (if the tumors are resectable), chemotherapy, radiation therapy, targeted therapy, immunotherapy, and/or traditional Chinese medicine. To date, these treatment options are frequently combined—*e.g.*, a comprehensive treatment mode of surgery combined with systemic chemotherapy and local radiotherapy is the most common combined treatment. However, treatment results are often unsatisfactory and problematic, due to chemoresistance, reduced radiation sensitivity, and tumor molecular adaptions, and thus can lead to a high recurrence rate. [3].

Cell proliferation is pivotal in tumorigenesis and cyclooxygenase 2 (COX-2) is important regulatory enzyme in this process. It plays a role in various biological processes such as cell proliferation, angiogenesis, immune function and inflammation, which are all crucial in the development or progression of neoplasms [4]. The COX2/PGE2/EP axis is involved in almost all

the stages of tumor development including cancer stem cells (CSC) repopulation, epithelial–mesenchymal transition (EMT) progression, and immunosuppression, which all contribute to therapeutic resistance [5].

Overexpression of COX-2 has been associated with various premalignant and malignant lesions of epithelial origin, in particular in organs of the gastrointestinal tract. Tumors with high levels of COX-2 seem to be more aggressive and patients bearing those tumors had a significantly reduced survival [6].

Overexpression of COX-2 may reduce the response of malignant cells to chemotherapy [5]. At the same time chemotherapy may induce the expression of COX-2 [7]. Few studies evaluated the crosslink between COX2, chemotherapy and chemoresistance.

cancer cell-intrinsic activation of the cyclooxygenase (COX)-2/prostaglandin E_2 (PGE_2) pathway post-chemotherapy treatment is a prevalent phenomenon which profoundly alters the inflammatory properties of the treated cancer cells. upregulation of COX-2 expression and activity post-chemotherapy impairs the efficacy of the combination of PD-1 blockade and chemotherapy. Accordingly, pharmacological inhibition of COX-2 with celecoxib, an anti-inflammatory drug already used clinically, unleashed tumour control in preclinical models when given alongside chemoimmunotherapy combinations. [8].

Chemotherapy is mainstay of cancer treatment for both early and unresectable advanced disease. In addition to debulking the tumour mass through direct killing of proliferating tumour cells, these treatments can promote tumour control via immune-stimulating effects [8] Nonetheless, chemoresistance and tumour relapse remain huge clinical problems.

Chemoresistance causes disease relapse and metastasis, challenges the improvement of clinical outcome for the cancer patients, and remains the main obstacle to cancer therapy. The molecular mechanisms of chemoresistance include transporter pumps, oncogenes, tumor suppressor gene, mitochondrial alteration, DNA repair, autophagy, epithelial-mesenchymal transition (EMT), cancer stemness, and exosome [9]

Approximately 80–90% of mortality in cancer patients is directly or indirectly attributed to drug resistance. Resistance can be restricted to a specific drug, or different drugs with independent modes of action, named multidrug resistance (MDR) [10].

Types and Determinants of Chemoresistance

Chemoresistance (drug resistance) is classified into two categories: intrinsic and acquired resistance depending upon its time of development .Early diagnosis of the types of drug resistance helps pre-determine the sensitivity of the cancer cells to the drug, optimize therapy and reduce the toxic side effects [11].

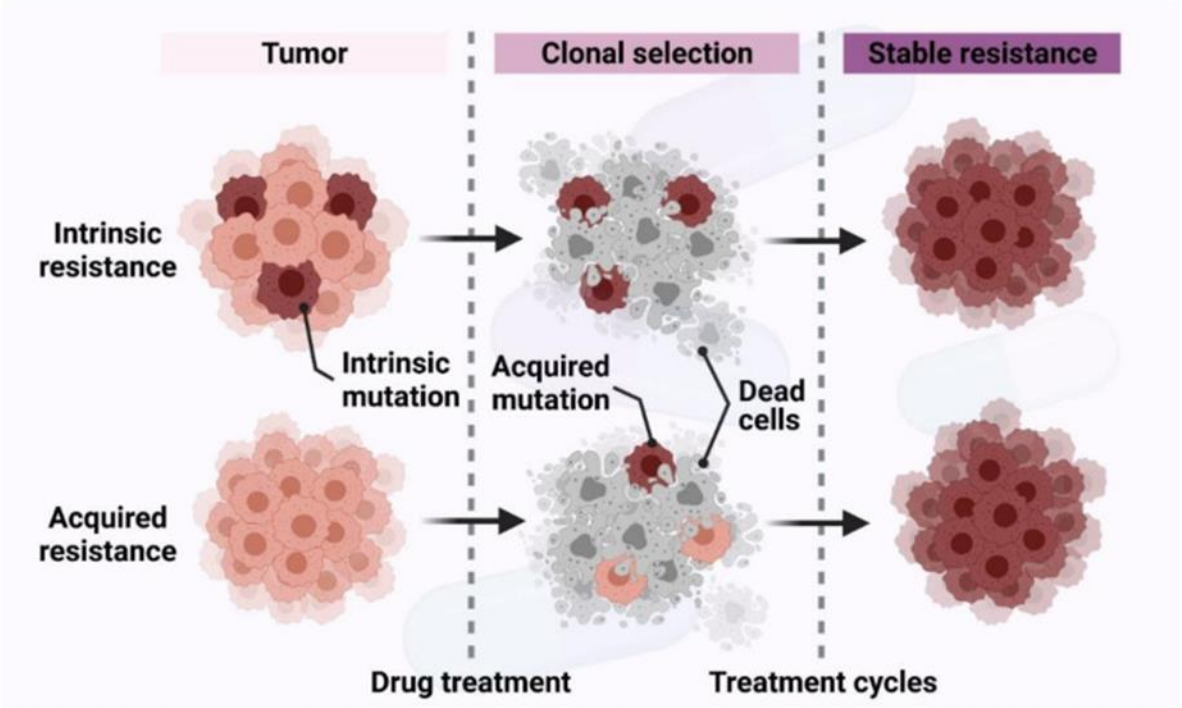

fig (1) Intrinsic and acquired chemoresistance in cancer [11].

Intrinsic Chemoresistance

Intrinsic chemoresistance exists before the drug/therapy has been administered to the patient. Tumors with intrinsic resistance show a resistant phenotype to chemotherapy before they encounter any chemotherapeutic drugs [12].

Acquired Chemoresistance

Acquired drug resistance occurs after chemotherapy treatment. It is identified by the appearance of drug-resistant cell populations and reduced efficacy of the anticancer treatment/drug. The reasons for this type of resistance are mutations of drug targets, activation of the second proto-oncogene, changes in the tumor microenvironment, epigenetic alterations by methylation, acetylation, and microRNA (miRNA) expression leading to alterations in upstream or downstream regulators, alterations in the cell cycle and its checkpoints, impairment of apoptosis, and altered DNA repair [13].

Role of Biological Factors in Cancer Chemoresistance

1. Epigenetics

The two major forms of epigenetic alterations occurring in carcinogenesis, histone modification and DNA methylation, have been successfully targeted for the restoration of chemosensitivity [14]., whereas, the demethylation of DNA promoter region induces chemoresistance through the overexpression of oncogene. Therefore, several drugs that are capable of interaction with cancer progression like DNA methyltransferase blockers and histone deacetylase antagonists can help to circumvent the drug resistance [15]

2.Cyclooxygenases

the association between COX-2 expression and chemoresistance could be a generalised phenomenon that is yet to be clarified on a biochemical level. It is conceivable that the involvement of COX-2 in the biochemical pathways influencing tumour cell susceptibility to cytotoxic agents could play a major role: in particular, COX-2 overexpression has been associated with the function of Her2/neu, which is renowned for inducing resistance to several cytotoxic agents. Moreover, COX-2 has been reported to induce the antiapoptotic bcl-2 protein and to be associated with neoangiogenesis in tumour-bearing mice .Since both inhibition of apoptosis and promotion of neoangiogenesis are strictly related to chemotherapy resistance ,it is conceivable that COX-2 expression could play a role as an indicator of chemoresistance [16]

COX-2 up-regulates the multidrug resistance gene *MDR1/pgp70* [17] suggested another mechanism by which COX-2 might promote chemoresistance.

2. EMT

EMT is a process by which epithelial cells lose cell polarity and homogenous adhesion, and gain migratory and invasive properties to become mesenchymal stem cell. It was triggered by cytokines and growth factors, non-coding RNAs or hypoxia and characterized by dissociation of cell–cell contacts, alteration of the cytoskeletal network, and increased proteolytic activity, consequently leading to cell invasiveness, anchorage-independent growth (anoikis), apoptotic and drug resistance in several types of cancer [18].

COX-2 Inhibitors as Promising Therapeutic Approach for Cancer and chemoresistance

Inhibition of COX-2 could provide a high possibility to exert therapeutic outcomes in cancer .Administration of COX-2 inhibitors for organs like lung, breast, colon, and prostate has been attested to cause a reduction of cancer risk by about 68% [19].

COX-2 inhibitors are relatively inexpensive in comparison with the standard cancer therapies, having tolerable side effects, and that they are able to sensitize cancer cells to treatments like radiotherapy and chemotherapy [19]. both of which are recognized to induce COX-2 expression in cancer cells [20].

In fact, COX-2 inhibitors are able to relieve COX-2-mediated expression of multidrug resistance proteins in cancer cells, and when they are administered in a perioperative setting, the inhibitors would reduce the risk of surgical related metastasis. COX-2 could be targeted by many types of chemotherapeutic drugs [21].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the drugs used for prevention of cancer. COX-2 inhibition by NASIDs is related to the reduction of cancer recurrence and increase of patient survival. Elevation of ROS concentration by NSAIDS is possibly accounted for inhibition of COX-2 in cancer cells [22].

COX-2 could be a target for hormonal therapy. Melatonin, a secretory product of pineal gland with diverse pharmacological effects including anticancer activity, is an example in this context showing promising results for suppression of cancer progression by inhibiting NF-κβ/COX-2 signaling in cancer cells [22].

Some chemotherapeutic agents adversely induce COX-2 expression indirectly via promotion of an inflammatory setting **[20]**. probably through developing CAFs into senescence CAFs by acquiring a proinflammatory SASP .Therefore, it would be advisable to use COX-2 inhibitors as an adjuvant with chemotherapy and/or radiotherapy.

This combination also improves the rate of tolerance to chemoradiation and overall response rate for advance stages of cancers, especially when it is administered before radiotherapy **[23]**.

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