



Cyclooxygenase-2 and Apoptosis Resistance in Hematological Malignancies

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Editorial

During the 80s, the interest concerned to prostaglandins and their role in the inhibition of hematopoietic progenitors proliferation. Indeed, various studies showed experimental data obtained on models of mouse reporting the relation between the inhibition of prostaglandin production and hematopoiesis. While the type E of prostaglandins acts as a negative feedback of myelopoiesis, the inhibition of the cyclooxygenase (COX), responsible for their production, leads a return in a positive control. The agents inhibiting the COX, non-steroidal anti-inflammatory drugs (NSAIDs), can activate hematopoiesis and have a protective or curative effect in myelosuppression states. The efficiency of the therapeutic use of NSAIDs in these situations is meaning in particular under the COX-2 selective inhibition, when the unwanted side effects of the COX-1 inhibition as the gastroenteritis – intestinal hurts are absent [1].

COX-2 is expressed in numerous types of hematological tumors and it's over expression is often an indicator of bad forecast. Chronic myeloid leukemia (CML), Hodgkin lymphoma and non-Hodgkin lymphoma, as well as the multiple myeloma present all an over expression of COX-2 [2].

The researchers emitted the hypothesis that COX-2 improves the tumorigenesis because its expression favorites the apoptosis resistance [3]. Secchiero et al. [4] showed that the level of the mRNA coding for the COX-2 but also the protein COX-2 were positively regulated with regard to healthy subjects (normal lymphocytes B).

The authors observed that the primary cells of CML express the protein COX-2 at levels raised compared the healthy cells, but also in bone marrow of patients affected) by CML, this expression being correlated to a decrease of the survival of patients [5]. Besides, the authors demonstrated that 70% of cells stemming from patients affected by the Hodgkin lymphoma presented an over expression of COX-2 [6].

Besides, the COX-2 favors the wickedness, angiogenesis, metastasis, the influence on the function of regulating T cells, and also affects the activity of cells having a cytotoxic function, in summary all which regulates the capacity of cancer cells to survive. The high rate of the expression of COX-2 is often correlated in a decrease of the survival of the patients affected by hematological malignancies.

The deregulations of apoptosis machinery lead the resistance of apoptosis. This resistance is characterized by an inhibition of the release of the cellular death or a delay in the progress of this one in answer to anapoptotic stimulus. Apoptosis resistance plays an important role in the tumoral development. Indeed, an uncontrolled cellular proliferation combined with apoptosis resistance are necessary and sufficient at the same time for a tumoral progress towards a malignant [7,8].

Although there are several mechanisms by which cells escape of apoptosis, the majority of these lead to an incapacity for the cell to activate the apoptosis intrinsic pathway. This pathway is regulated by the ratio between the anti- and pro-apoptotic members of the Bcl-2 family. This ratio establishes the threshold of activation of the caspases which are involved in the apoptotic process [9].

Several studies were interested in the implication of the COX-2/PGE₂ (prostaglandin E₂) pathway in the apoptosis resistance. The first indication concerning the role of COX-2 in apoptosis resistance could play come from a study to the rat [3]. A transfection of the gene of the COX-2 in intestinal epithelial cells of rat leads an over expression of the anti-apoptotic Bcl-2 protein correlated in apoptosis resistance. A later study allowed to describe a possible mechanism involved in this resistance. So, the activation of Ras-MAPK/ERK pathway by the COX-2/PGE₂ pathway could increase the expression of Bcl-2 and lead a resistance of apoptosis [10]. Furthermore, *in vitro* works

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also allowed studying the role of COX-2 in apoptosis resistance. It was shown that the COX-2 over expression in colorectal cancer cells HCT-15 decreased their sensibility in apoptosis [11]. Another study also showed that on the human cancer cell line HCT-116, initially COX-2 deficient, a transfection with the gene COX-2 made it more resistant to apoptosis [12].

It is known that the activation of PI3K/Akt pathway by PGE₂ favors the survival of mouse intestinal adenomas [13]. Recently, several works indicate that the COX-2/PGE₂ pathway can modify the thresholds of release of apoptosis by activating a number of signaling pathways. Indeed, it was described that PGE₂ was capable of activating cellular survival pathways, such as PI3K/Akt, MAPK/ERK, AMPc/PKA and EGFR pathway [14-19].

In spite of numerous studies concerning the COX-2/PGE₂ pathway in the mechanism of apoptosis resistance, the involved cellular signaling pathways are not still totally clarified and there are disparities concerning the role of the PGE₂ in this mechanism. Certain studies showed an implication of PGE₂ in the activation of anti-apoptotic pathways [14-19]. In other studies, it was noticed that only a deregulation of the expression of COX-2 protein independently of its activity (PGE₂ production) was involved in a mechanism of apoptosis resistance [11,20,21].

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