



## The overexpression of COX 2 in Wilms' tumor

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### ABSTRACT

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Cyclooxygenase 2 has become an important pharmacological target in anticancer therapy due to the over expression of COX 2 in pathological conditions.

Wilms' tumor is a common kidney cancer in children which has shown an increase in COX 2 enzyme level. Here we reviewed various articles that considered the cyclooxygenase 2 changes specifically in Wilms' tumor regarding the mechanisms of action and inhibitors of COX 2.

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## Introduction

During every malignancy there may be various changes in normal gene expression and protein synthesis which lead to functional changes of the affected limb. Cyclooxygenase 2 (COX2) is one of the major enzymes which will be overexpressed in cancers and tumors which consequently lead to the increased in the prostaglandins synthesis. Various evidence have proposed COX2 a major therapeutic target which may be suppressed by using non-steroidal anti-inflammatory drugs (NSAIDs) or

prototypic inhibitors of COX-2 such as celecoxib, rofecoxib. Wilms' tumor is the most common cancer of kidney which primarily affects children kidney (1,2). In this article we aimed to review the literature considered the expression of COX2 in Wilms' tumor.

### COX enzyme

Cyclooxygenase (COX) is the key enzyme in charge for the synthesis of prostanoids, consisting of prostaglandins, prostacyclins

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and thromboxanes, which are the biological mediators that eventually lead to the activation of anaphylactic, inflammatory and vasoconstriction reactions. Among the major physiological adjuster of kidney can be mentioned to the Prostaglandins which interfere in water and salt equilibrium, vascular resistance, renal hemodynamic and rennin release. COX1, COX2 and COX3 are the identified COX isoenzymes. COX 1 and COX 2 have almost 60% homology in their amino acids sequences (3).

Unlike COX 1 which is present in almost all tissues, COX2 is an inducible enzyme with a low possibility of being detected in normal tissues. Although COX2 expression is detected in brain and kidney of rodents, but it is actively expresses in specific unusual circumstances and disease processes such as carcinomas and tumorogenesis due to several stimuli such as growth factors, cytokines, mitogens and tumor promoters. The conditional activation of COX2 protein turned it to one of the main target for therapeutic and chemoprotective procedures, pathological situations and a noticeable indicator of abnormal of cell growth and malignancies (4,5).

Previous studies have been detected the expression of COX2 in various types of malignancies such as nervous system, gynecologic system, bone structure, breast, lung, colorectal tumors, intestinal neoplasia, gastrointestinal, pancreatic, prostate cancer, head and neck carcinoma (6-14). According to reported results, over expression of COX2 positively participates in tumorogenesis, invasion and metastasis through modulation of the mechanisms such as apoptosis, angiogenesis, inflammation and immune system function, carcinogen production and tumor cell proliferation (3).

### ***COX expression in kidney***

Expression of both isoforms of COX

has been detected in normal kidney using a variety of molecular techniques. A substantial expression of COX1 is observed in vascular smooth muscle and collecting ducts. The expression of COX2, not only is detected in pathological conditions of kidney but also a low level of its expression is identified in macula densa, interstitial cells, podocytes and arteriolar smooth muscle cells. Expression of COX2 enzymes is also observed in fetal kidneys which have shown influential role in renal development. An altered in the expression of kidney COX1 and COX2 mRNA during the senescence is observed which leads to the increases of the COX2 expression in protein level. Tissue prostanoids content which is related to the rate of COX expression, have shown some supporting action including maintenance of vessels stability, glomerular filtration, renal hemodynamic in stressful conditions such as dehydration, salt diminution and hypertension (15,16).

### ***COX2 and Wilms' tumor***

Wilms' tumor is the most prevalent kidney cancer in children. This cancer is resulted from germline mutations or deletions of Wilms' tumor gene-1 (WT1) which is located on the short arm of chromosome 11. The blastemal, epithelial and stromal parts constitute the triphasic histology of Wilms' tumor. Hematuria, fever, malaise and anorexia, are some primary indicators of this tumor (17). There are limited data regarding the overexpression of COX2 in Wilms' tumor and the mechanisms result in tumor progression and metastasis. Only four studies have specifically considered the expression of COX2 in Wilms' tumor with the aim of evaluating the prognostic value of this criterion, identifying the effectual signaling pathways in tumorogenesis and detecting the efficacy of several inhibitors of COX2 expression and eventually the

prostanoids synthesis.

The conducted studies are summarized in Table1.

The main reported localizations of COX2 expression in Wilms' tumor components through immunohistochemistry procedures are the vascular and blastemal parts of tumor tissue which have shown the highest content of COX2 enzyme. Only in the study of Giordano et al. the relation between COX2 expression and age, sex and survival of patient was assessed which resulted in the independency of COX2 positivity with all these parameters (19).

### *S1P/COX signaling pathway in Wilms' tumor*

As mentioned, COX2 over expression is activated due to different stimuli such as hormones, carcinogens and mitogens, etc. Sphingosine-1-phosphate (S1P) is a bioactive lipid which contributes in various cellular functions including angiogenesis, carcinogenesis and also inducing COX2 expression in different cell types (22,24).

S1P exerts its inducing effect on COX2 through its different receptors (S1P1 to

S1P5) and cellular pathways which have identified as a cell specific process. In the survey of Li M-H et al. (21) using real time PCR and Western blot techniques have shown a significant inducing effect of S1P on COX2 mRNA expression in Wilms' tumor cells is considered as the possible signaling pathway of the human Wilms' tumor progression. Among the five receptors of S1P, S1P2 receptor is identified a responsible receptor for the induction of COX2 expression and prostaglandins synthesis in human Wilms' tumor cells through S1P pathway. Therefore, inhibiting the S1P/S1P2/Cox2 signaling pathway is an important therapeutic target and may eventually results in reducing the human Wilms' tumor progression.

### *COX2 inhibitors in Wilms' tumor*

Non-steroidal anti-inflammatory drugs (NSAIDs) are known the major inhibitors of COX, by suppressing the prostaglandins synthesis. They lead to limiting the biological effects of the processes modulated through prostanoids synthesis such as inflammation, fever, thrombotic, neurodegenerative and

**Table1.** Detailed data of performed studies on COX2 expression in Wilms' tumor

Author	Publication year	Technique	Number of samples	Sample	Localization of COX2 expression in WT
<b>Fridman (18)</b>	2006	Tissue micro array	14	Human	All Wilms' tumors except one anaplastic Wilms' tumor lung metastasis Tumors that overgrew chemotherapy
<b>Giordano (19)</b>	2006	Immunohistochemistry	40	Human	Blastema 45% Epithelial 7.5% Heterologous component 25%
<b>Lee (20)</b>	2006	HPLC Lectin perfusion & Fluorescent microscopy	26	Human	Blastemal 69% Vascular 92% Epithelial 73%
<b>Li (21)</b>	2008	Real time PCR & Western blot	10	WT cell line	—

oncological diseases. SC-236 and its analogue celecoxib are used as the COX2 inhibitors in considering the effect of COX2 on tumor vessel density. Almost 78% reduction in tumor growth and lung metastasis after 28 days of treating tumors using mentioned inhibitor is observed, however the declared changes are not significant statically. Using terminaldeoxynucleotidyl transferase-mediated nick-end labeling (TUNEL) procedure showed that induced limitation of the tumor growth is not the consequence of the increased apoptosis however disrupted proliferation, angiogenesis and vascular density are the responsible causes of this effect (20,25).

Angiogenesis of other tumor models are reported to be inhibited by arresting endothelial cell cycles, increasing the expression of endostatin, or inducing apoptosis by decreasing endothelial growth factor (26,27). In the considered studies, using COX2 inhibitor did not lead to decreased expression of the endothelial growth factor. Using COX2 inhibitor (SC-236), yielded some changes in gene expression of Wilms' tumor which lead to increase or decrease in the expression of genes to suppress the vascular proliferation and stability.

Data regarding altered genes expression after administrating COX2 inhibitor are summarized in Table 2.

By considering all the studies performed on evaluating the changes in expression level of COX2 protein during Wilms' tumor a considered malignancy, increase in COX2 expression was the indication of its role in pathogenesis of Wilms' tumor and immunoreactivity of COX2 protein was demonstrated in all stages of the tumor development thus Cox2 inhibitors could be considered as a therapeutic agent.

**Table 2.** Altered expression of various genes in Wilms' tumor due to inhibition effect of SC-236.

Altered genes expression	Changes after SC-236 applying
Perlecan	↑fold 1.8
Collagen IV	↑3.6fold
Tissue inhibitor of metalloproteinase-1	↑fold 1.4
Desmin	↓fold 0.62
,EDG1	↓fold 0.42
CXCR4	↓fold 0.68
Spondin-1	↓fold 0.26
CCM1	↓fold 0,77
Pleiotrophin	↓fold 0.72
CXCL14	↓fold 0.32

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## Conflict of Interest

The authors declare no conflict of interest.

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