

## Celecoxib treatment negatively influences angiogenesis and androgen receptor distribution in the prostate of TRAMP mice: effects on prostatic adenocarcinoma progression

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### Abstract

Prostate cancer is the second leading cause of deaths in western men and is associated to an imbalance in the androgen to estrogen ratio. Androgen actions occur by means of the androgen receptor (AR) and these hormones can influence angiogenic and inflammatory processes, possibly creating a permissive microenvironment for tumor development. Despite this fact, AR distribution pattern following prostatic inflammation inhibition, as well as the influence of this response on the incidence and progression of neoplastic lesions in the organ are still poorly understood. Thus, the aim herewith was to evaluate the effects of Celecoxib anti-inflammatory therapy on AR immunoreactivity and angiogenesis in the ventral prostate of the Transgenic Adenocarcinoma of the Mouse Prostate (TRAMP) model, correlating these findings with the glandular morphology and cancer progression in the organ. A total of 12 male TRAMP mice (12 week-old) were submitted to control conditions or treated with Celecoxib (15 mg/kg, orally, twice daily) for 6 weeks. Ventral prostate samples were collected for morphological analyses and immunohistochemistry for AR detection and for CD31-positive microvessel density determination. Preliminary results showed a tendency towards delayed prostate cancer progression after Celecoxib treatment, as demonstrated by the numerical decrease in the frequency of well-differentiated adenocarcinoma foci. Macroscopic tumors were also less frequent in the Celecoxib-treated group, and these showed numerically reduced tumor weight in comparison to controls. Less intense AR epithelial reactivity and significant decrease in CD31-positive vessels were also observed following the treatment. Based on these findings, we confirmed the antitumor effects of Celecoxib against prostate cancer and suggest that the decreased AR expression in the epithelium and impaired angiogenesis may play a role in delaying tumor progression after this treatment.

*Key words: Prostate, inflammation, TRAMP.*

### Introduction

Prostate is the organ most commonly affected by neoplastic diseases in men [1]. Androgens are the main male sexual hormones implicated in prostatic morphogenesis and maintenance, displaying their biological effects by means of the androgen receptor (AR) [2,3]. Different studies have pointed out inflammation as a crucial factor in prostate cancer etiology [4-6]. Considering this, non-steroidal anti-inflammatory drugs (NSAIDs) such as Celecoxib have been clinically employed to prevent cancer [5].

AR expression profile following inflammation inhibition, as well as its influence on prostatic lesion incidence and progression are still poorly understood. Thus, the aim herewith was to evaluate AR distribution and angiogenic response following anti-inflammatory therapy, correlating these findings with cancer progression in TRAMP mice ventral prostate.

### Results and Discussion

Comparing control and Celecoxib-treated groups, respectively, decreased frequency of well-differentiated adenocarcinoma foci (5.46% vs. 2.87%) and macroscopic tumor weight (4.87g vs. 3.27g) were observed following anti-inflammatory

therapy. However, these differences did not reach statistical significance. On the other hand, significant decrease of CD31-positive vessels was verified (5.16 vs. 2.21). Less intense AR reactivity was seen in the epithelium of the treated group.

### Conclusions

Celecoxib treatment showed a tendency to delay prostate cancer progression, an effect which might be due to its negative effects on AR epithelial expression and tumor angiogenesis.

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