Angiogenesis and prostate cancer progression: Effects of the Tempol treatment on glandular microenvironment response in the TRAMP mice

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Prostate cancer (PCa) is the second cause of death related to cancer among men in worldwide. Genetic, aging and unhealthy lifestyle are some factors, which are associated with PCa incidence increase. These same factors are involved in prostatic microenvironment changes, leading to inflammatory process and free-radical increase and therefore PCa onset or progression. Tempol is an antioxidant drug that catalyzes the metabolism of cellular reactive oxygen species (ROS) and has been indicated as a coadjuvant in the different types of cancer therapy, showing an effect direct on processes such as inflammation and oxidative stress. However, Tempol effects are still poorly understood in PCa, particularly, considering the tumor stages, proliferative and angiogenesis mechanisms. Thus, the aim of this study was to evaluate the Tempol treatment effects on the proliferative and angiogenic markers in TRAMP (transgenic adenocarcinoma of the mouse prostate) mice. The prostate dorsolateral lobe from the TRAMP mice was analyzed in two different PCa stages and divided in two experimental groups; early and late groups. The Tempol early group (T8-12), the 8-week-old mice received, orally, 50 mg/kg Tempol dose during 4 weeks, 5 days per week. The Tempol late group (T16-20), the 16-week-old mice received 50 mg/kg Tempol dose during 4 weeks, 5 days per week. All animals in the different experimental groups received the same solid diet and water ad libitum and control groups (C8-12), (C16-20)

received water as vehicle. The prostate dorsolateral lobe was collected and submitted to the histopathological, immunohistochemical and Western blotting analyses. The results demonstrated a significant high-grade prostatic intraepithelial neoplasia (HGPIN) decrease and a health glandular epithelium increase, particularly, in the late group (T16-20). The PCNA proliferating cell marker confirmed the histopathological evaluation. A significant decrease of VEGFR2 immunolabeling was verified in the prostatic tissue in both experimental groups, Tempol early (T8-12) and Tempol late (T16-20), after Tempol treatment. Also, a significant decrease of VEGF and HIF-1α protein levels were verified in the dorsolateral lobe in both experimental groups (T8-12 and T16-20). Finally, we concluded that Tempol was effective to mitigate the PCa severity and exhibited a differential effect on prostate, according to cancer stage, with a better response in late-stage disease, interfering in the proliferative and angiogenic pathways, which are crucial to prostate cancer progression. CEUA: 5503-1/2020.