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Dissertations-Kurzfassung

Investigations into the improvement of chemotherapeutic drug delivery methods for advanced prostate carcinoma

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Prostate cancer has to date no 100% effective treatment. In large part this lack of treatment is due to the multi-faceted cause, development and progression process of the disease. It is not known exactly what causes prostate cancer to develop and to progress, but the majority opinion is that is it not just one cause but the accumulation of many. Understanding this principle brings the theory to diagnose, prevent and treat the disease coming also from many directions.

The detection of prostate cancer has immensely improved in the last decade causing an increase in incidence. After detection of the disease, the prediction of which cases will progress and which will not is important. The new information on intrinsic poly(ADP-ribose) reactions in prostate cancer presented in this work adds to the knowledge of what goes on in progression of the disease. We have shown that in benign prostate cells this reaction is, as in other cells, only active when DNA damage is present. In prostate carcinoma cells, this reaction is always on, although to varying degrees in different carcinoma cell lines.

The precise details of how and why some tumors metastasise and others do not will keep researchers for the next decade busy. Here we have examined three varieties of treatments for advanced metastatic prostate disease. The use of acoustic energy allows direct application of cell damaging shockwaves on tumors without damaging neighboring tissues. Combination of shockwave treatment with potent chemotherapeutic agents increases tumor cell death. We also investigated incorporating the chemotherapeutic doxorubicin with a protective copolymer, Pluronic F10500. Like antibiotics targeted for bacteria, this system takes advantage of the environment of the tumor that is different from the normal, healthy tissues of the body. In vitro, we have shown that this combination treatment could hinder the growth of the rat prostate carcinoma cell, MatLu, by up to 70%. In the analysis of four other prostate carcinoma cell lines, we found that this effect was common to all. On the basis of this information, we additionally conducted in vivo studies to determine the effectiveness and toxicity in the Copenhagen rat prostate carcinoma model. These experiments showed that the combination of doxorubicin and Pluronic F10500 were more effective than doxorubicin treatments in reducing tumor growth rate. Additionally, toxic side effects were less apparent in these animals than in animals treated with doxorubicin alone. One additional beneficial result was that the use of Pluronic F10500 appears to prevent the development of metastases. After the development of advanced metastatic disease options for therapy are extremely limited. The studies conducted for this work provide not only data relating to possible methods to reduce the growth rate of primary tumors but also a possible way to prevent metastases from developing.

The understanding of the disease progression adds not only to the knowledge of prostate cancer but to other related cancers as well. Investigation such as over PARP's possible role in progression helps identify the cellular characteristics of cancer cells in comparison to normal cells – allowing for earlier determination of aggressiveness. New treatment options for treating and preventing reoccurrence of metastases will add to the arsenal of therapies for those cases of aggressive metastatic disease.