

# Targeting prostatic tumor micro-environment to address therapy resistance

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Cure or control of disseminated disease remains the greatest challenge facing cancer clinicians and scientists, and is the greatest cause of patient mortality. Predominantly, the cancer related deaths stem from the growth and development of disease that is resistant to the killing effects of available oncolytic therapies. Much attention has been given to the overexpression of cellular drug transporters (e.g., MDR1) and changes associated in drug kinetics (1-6), however, over the past decade numerous reports have linked tumor heterogeneity as the root cause in the development of therapy resistant. The major contributors to intratumoural heterogeneity include: genetic variation leading to cell plasticity (i.e., the ability of a cell to reversibly and flexibly change lineage) and the microenvironment. Example of genetic variation leading to cell plasticity is seen when prostate cancer cells and human prostate tumors are exposed to sublethal doses of radiation, which will turn on key anti-apoptotic pathways leading to continued tumor growth and resistance to therapy (7). Here specific pathways may be targeted resulting in a therapeutic advantage. However these savvy cancer cells ultimately can circumvent the targeted molecule and pathway and eventually exploit another survival pathway, thus once again duping researchers and clinicians, resulting in tumor growth. Thus new approaches must be utilized to get a clear advantage over cancers and then to leverage these new approaches into carefully studying tumor biology in hopes of identifying novel targets, which in turn could radically modify current treatment paradigms. One such new approach is to identify key survival factors within the tumor microenvironment. In the article entitled 'Treatment-induced damage to the tumor microenvironment promotes prostate cancer therapy resistance through WNT16B', authors Sun *et al.* address

this critical predicament of therapy resistance in the clinical management of prostate cancer patients by assessing fibroblasts related to tumors. Specifically, WNT16B was found to be increased within fibroblasts exposed to cytotoxic agents both *in vitro*, *in vivo* and within human tumors (prostate, breast and ovarian). In human tumors, WNT16B expression was associated with higher rates of disease recurrence after conventional chemotherapy. Subsequently, engineered fibroblasts demonstrating high *vs.* low levels of WNT16B were analyzed in a panel of sophisticated experiments. Bottom line these experiments demonstrate a survival advantage when epithelial cell cultures or xenograft tumors were exposed to cytotoxic agents and WNT16B was present compared to exposure with cytotoxic agents and WNT16B was low or absent. Lastly, the authors illustrated that WNT16B expression is regulated by NF- $\kappa$ B. After DNA damage, WNT16B signals in a paracrine manner tumors cells, which then can increase their proliferation or resist apoptosis. This is not the first paper to remark how the tumor microenvironment can exert a growth advantage. Previous researchers have demonstrated that certain growth factors and immune suppressor cells within the tumor microenvironment can result in continue tumor growth despite therapy (8-10). However, the current manuscript does add substantial to the body of literature describing this phenomenon. In fact, perhaps more attention should be given to the microenvironment which acts as a scaffold and supports the growth of tumors. If key survival proteins and pathways can be identified then perhaps targeting these proteins and pathways will lead to unsuitable milieu to support the growth of the cancerous epithelial cells or perhaps such an unsuitable milieu would render epithelia cells more susceptible to the killing of effects of

conventional oncolytic therapies at lower doses and thus portraying a better therapeutic index.

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