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Research Highlight

TRPM8 and prostate cancer: to overexpress or repress, that is the question—comment on "Effects of TRPM8 on proliferation and motility of prostate cancer PC-3 cells" by Yang ZH *et al*. in *Asian Journal of Andrology*

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The progression of cells from a normal differentiated state in which the rates of proliferation and apoptosis are in check, to a tumorigenic and metastatic state where these rates are imbalanced, likely involves the accumulation of mutations in multiple genes, and the evolution and clonal selection of more aggressive phenotypes. These events are associated with changes in the expression of numerous gene products including the transient receptor potential (TRP) proteins. TRP proteins are a family of Ca^{2+}- and Na^{+}-permeable channels that play a diverse and important role in cellular physiology and pathology. One member of this family, TRPM8, a receptor-activated non-selective cation channel is highly expressed in prostate cancer (PCa) cells and in recent years, has emerged as a promising prognostic marker and putative therapeutic target in PCa.

In prostate epithelial cells, expression of TRPM8 is regulated by androgen and is elevated in androgen-sensitive cancerous cells compared with normal cells. While there is some evidence that in PCa cells Ca^{2+} and Na^{+} inflow through TRPM8 is necessary for survival and function, the precise function of TRPM8 remains largely unknown. Nonetheless, in the androgen-responsive LNCaP cell line where the TRPM8 protein is expressed in the endoplasmic reticulum and plasma membrane, inhibiting its activity with an antagonist or knocking down its mRNA expression with siRNA results in cell death [1]. These results indicate that TRPM8 is an important determinator of Ca^{2+} homeostasis in prostate epithelial cells and may be a potential pharmaceutical target for androgen-sensitive PCa. In contrast to androgen sensitive PCa, expression of TRPM8 is substantially decreased in androgen-independent and metastatic prostate cancer [2]. These observations would imply that the scope of TRPM8 as a therapeutic target may be limited to androgen-sensitive PCA.

Not withstanding this apparent limitation, in this issue of the *Asian Journal of Andrology*, Yang *et al*. [3] provide exciting new evidence to support a potential therapeutic role for TRPM8 in hormone-refractory PCa (HRPC). Using the androgen-insensitive prostate cell line PC-3 as a model system, the authors demonstrate that although at an extremely low level, PC-3 cells express functional TRPM8 on both endoplasmic reticulum and plasma membrane just like PC-3 cells that overexpress TRPM8 (PC-3-TRPM8). However, overexpression of TRPM8 induced a significant cell cycle arrest in G_0/G_1 stage and facilitated the apoptosis of cells induced by starvation. Furthermore, TRPM8 significantly inhibited the migration of PC-3-TRPM8 through the inactivation of focal adhesion kinase (FAK). FAK is a non-receptor protein tyrosine kinase that localizes to cellular focal adhesions or cell contacts within the extracellular matrix and participates in growth factor receptor-mediated signaling pathways and plays essential roles in cell survival, proliferation, migration, and invasion. Considered together, Yang *et al*. [3] provide good evidence

that although, TRPM8 may not essential for the survival of androgen-independent PCa cells, overexpression of TRPM8 has negative effects on the proliferation and migration of PC-3 cells. These tantalizing data suggest that overexpressing TRPM8 or perhaps its activation via an agonist may offer novel approaches to treat HRPC.

Despite the promise offered by the work of Yang *et al*. [3], much remains to be learnt about the consequences of TRPM8 inhibition/repression and the mechanism employed to achieve this endpoint especially, with agonists of TRPM8. For example, it is well known that menthol binds and activates the TRPM8 Ca^{2+}-permeable channel that exhibits abnormal expression patterns in PCa, suggesting that TRPM8 links Ca^{2+} transport pathways to tumor biology. However, a recent study [4] has demonstrated that menthol increases Ca^{2+}(i) via Ca^{2+} influx mechanism(s) independent of TRPM8 in PC-3 cells. Indeed, menthol increased a phosphorylated form of c-jun Nterminal kinase (JNK) in PC-3 cells through TRPM8-independent mechanisms. Thus, the data indicate that there is an apparent lack of causality between TRPM8 activation and that one could inadvertently uncouple TRPM8 activation and cell death. Finally, Yang *et al*. [3] do not explain why the rat and not human TRPM8 cDNA was used in their study.

Given the high prevalence of PCa, aging of the population, and potential morbidity of treatment, there is a dire need for novel therapeutics to treat HRPC. Recently, the Getzenberg laboratory [5, 6] demonstrated that overexpression of yet another protein, the purine-rich element binding protein (PUR) alpha, is down-regulated the androgen-independent PC3 and DU145 cells. Interestingly, the authors found that like in the case of TRPM8, overexpressing PURα also negatively regulates cell proliferation, resulting in decreases in PCNA expression both *in vitro* and *in vivo*. Although it is clear that additional studies are required to assess the role of TRPM8 and PURα in HRPC and to advance them to the clinic, these novel approaches appear to have considerable promise in the near future. But unlike Prince Hamlet's dilemma in the famed play Hamlet, we may be able to answer this dilemma; overexpress TRPM8/PUR α to treat HRPC but repress them in androgen-sensitive PCa.

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