Prostate Cancer Cells Alter the Nature of Their Calcium Influx to Promote Growth and Acquire Apoptotic Resistance

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In this issue of Cancer Cell, Dubois and colleagues report a remodeling of calcium influx in prostate cancer cells. Prostate cancer cells can undergo an oncogenic switch from a calcium influx pathway capable of inducing apoptosis involving ORAI1 channels to a pro-proliferative calcium influx pathway involving ORAI1/3 heteromeric channels.

The important role of calcium signaling in a variety of processes critical in cancer progression such as proliferation, apoptosis, and cellular migration (Hanahan and Weinberg, 2011) has seen increasing attention being paid to mechanisms that regulate intracellular free Ca2+ in cancer cells. A misconception is that the ubiquitous nature of the calcium signal means that Ca2+ ions are a simple on/off switch and that therapies targeting calcium transport would have major effects on all cell types and therefore could not represent an approach for molecularly targeted therapy. However, there is a suite of Ca2+ channels and pumps that enable cells to specifically regulate the multiple cellular processes controlled by Ca2+ ions. Many of these channels and pumps exhibit very specific tissue distribution, and their altered expression are a characterizing feature of some cancers (Monteith et al., 2012). The work of Dubois et al. (2014) in this issue of Cancer Cell adds further nuances and complexity in how calcium signaling may be altered in some cancers.

The field of calcium signaling was revolutionized in 2005 and 2006, when STIM1 and ORAI1 were identified as the key components of store operated entry (Feske et al., 2006; Roos et al., 2005). This calcium influx mechanism was first described by Putney in 1986, where the depletion of intracellular Ca2+ stores served as a signal for the activation of Ca2+ influx across the plasma membrane (Putney, 1986). The proteins ORAI1 and STIM1 have since been respectively characterized as the calcium influx channel and the endoplasmic reticulum Ca2+ store sensor important in the refilling of depleted Ca2+ stores in a variety of cell types. This ORAI1-mediated Ca2+ influx pathway has also been linked to various cancers, including those of the breast, where silencing of ORAI1 or STIM1 can reduce the invasion of breast cancer cells in vitro and reduce the development of metastasis in vivo (Yang et al., 2009).
In contrast to ORAI1, the roles of its related isoforms ORAI2 and ORAI3 in store operated Ca2+ entry, and, indeed calcium signaling and cellular function more generally are more opaque. In the case of ORAI3, this has led to ORAI3 being referred to as the ‘exceptional’ ORAI channel (Shuttleworth, 2012), with an identified need to better understand its activation and roles in calcium homeostasis and physiological/pathophysiological events. In the context of ORAI3 activation, ORAI1/3 complexes have been reported to be activated by arachidonic acid and have been termed the arachidonic acid-regulated calcium channel or ARC channel (Mignen et al., 2008). One of the first indications for a difference in ORAI3 in cancer emanated from studies in breast cancer. Motiani et al. (2010) demonstrated that store operated Ca2+ entry in estrogen receptor positive breast cancer cell lines were sensitive to ORAI3 silencing. In contrast, this Ca2+ influx pathway was insensitive to ORAI3 silencing in estrogen receptor negative breast cancer cell lines, where classic sensitivity to ORAI1 silencing was evident. The paper by Dubois et al. (2014) now shows that prostate cancer cells can utilize an ORAI1/3 channel to promote Ca2+ influx independently of Ca2+ store depletion and that this channel can be activated by arachidonic acid. They provide compelling evidence for the remodeling of the nature of calcium influx in prostate cancer progression, one that bestows enhanced proliferation and apoptotic resistance.

Using a variety of prostate cancer cell lines, Dubois et al. (2014) show that calcium influx activated by Ca2+ store depletion in prostate cancer cells is sensitive to ORAI1 and STIM1 but not ORAI3 silencing. Silencing of ORAI1, but not the endoplasmic reticulum Ca2+ sensor and canonical ORAI1 activator STIM1, reduces the proliferation of prostate cancer cell lines. Thus, proliferation in these prostate cancer cells must involve a STIM1-independent mechanism to activate ORAI1 and is likely to be independent of calcium store depletion. The investigators then identified that prostate cancer cells exhibit Ca2+ influx activated by arachidonic acid and that this Ca2+ influx is reduced by ORAI1 or ORAI3 silencing. Although similar to the ARC channel, the insensitivity of this channel to STIM1 silencing in prostate cancer cells suggests that some aspects of the mechanism for this Ca2+ influx may be distinct to those previously characterized for ARC channels. The importance of ORAI3 in prostate cancer growth was also demonstrated in vivo, with ORAI3 silencing reducing proliferation and ORAI3 overexpression promoting tumor growth. In support of the important role of the ORAI1/3 channel (and not just ORAI3 per se), in vivo growth of prostate cancer cells with induced overexpression of ORAI3 was reduced by ORAI1 silencing.

One of the most important implications of the results of Dubois et al. (2014) is the suggestion that elevated proliferation rates and apoptotic resistance in prostate cancer may be due to alterations in the relative contribution of calcium influx mediated by ORAI1 and ORAI1/3 channels. They propose that there is a disequilibrium in prostate cancer cells, which sees Ca2+ influx moving away from store operated calcium entry (which is important in the induction of apoptosis in prostate cancer cells) toward an arachidonic acid-activated pro-proliferative Ca2+ influx pathway. The authors also provide evidence that this shift toward ORAI1/3-mediated Ca2+ influx in prostate cancer cells can be
driven by either inherent upregulation of ORAI3 expression in some prostate cancer cells or factors in the tumor microenvironment, arachidonic acid in this case. The authors refer to such changes as an oncogenic switch. This switch and its consequences are shown in Figure 1 (based on Figure 8 in Dubois et al., 2014). Their work also highlights the need for more studies addressing the role of calcium signaling in the tumor microenvironment in cancer progression.

The work of Dubois et al. (2014) of course leads to many more questions. What other tumor environmental factors may cause such an oncogenic switch, and can other ion channels contribute to the switching from proapoptotic to pro-proliferative Ca2+ influx pathways? Are other cancer types capable of such remodeling, and what are the consequences? Are prostate cancer cells that are undergoing a shift to- ward ORAI1/3-mediated Ca2+ influx hijacking a calcium influx pathway important in a physiological or developmental pathway? If so, which ones, and what will this mean for future therapies? If selective pharmacological inhibitors of ORAI1/3-mediated Ca2+ influx can be developed, they may offer a unique therapeutic strategy to reverse the double-edge sword of enhanced proliferation and apoptotic resistance in prostate cancer cells. Such agents may offer a new kind of molecular targeted therapy for this clinically important cancer.

REFERENCES
Fig 1 - An Oncogenic Switch in Prostate Cancer Progression
Increased ORAI3 expression and/or factors in the tumor microenvironment increase heteromerization of ORAI1 and ORAI3, altering the nature of calcium influx, increasing proliferation, and promoting apoptotic resistance.