Cell Calcium 74 (2018) 160–167

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

ORAI channels and cancer

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ARTICLE INFO

Keywords:
Cancer
Calcium
ORAI
STIM

ABSTRACT

Cancer is a major cause of death. The diversity of cancer types and the propensity of cancers to acquire resistance to therapies, including new molecularly targeted and immune-based therapies, drives the search for new ways to understand cancer progression. The remodelling of calcium (Ca^{2+}) signalling and the role of the Ca^{2+} signal in controlling key events in cancer cells such as proliferation, invasion and the acquisition of resistance to cell death pathways is well established. Most of the work defining such changes has focused on Ca^{2+} permeable Transient Receptor Potential (TRP) Channels and some voltage gated Ca^{2+} channels. However, the identification of ORAI channels, a little more than a decade ago, has added a new dimension to how a Ca^{2+} influx pathway can be remodelled in some cancers and also how calcium signalling could contribute to tumour progression. ORAI Ca^{2+} channels are now an exemplar for how changes in the expression of specific isoforms of a Ca^{2+} channel component can occur in cancer, and how such changes can vary between cancer types (e.g. breast cancer versus prostate cancer), and even subtypes (e.g. oestrogen receptor positive versus oestrogen receptor negative breast cancers). ORAI channels and store operated Ca^{2+} entry are also highlighting the diverse roles of Ca^{2+} influx pathways in events such as the growth and metastasis of cancers, the development of therapeutic resistance and the contribution of tumour microenvironmental factors in cancer progression. In this review we will highlight some of the studies that have provided evidence for the need to deepen our understanding of ORAI Ca^{2+} channels in cancer. Many of these studies have also suggested new ways on how we can exploit the role of ORAI channels in cancer relevant processes to develop or inform new therapeutic strategies.

1. Introduction

As noted throughout this special issue, the identification of the molecular components of store operated calcium (Ca^{2+}) entry (SOCE), has revolutionized not just the field of Ca^{2+}signalling but it has also provided new insights into many diseases. Studies of ORAI channels in cancer have mostly focused on ORAI1, the canonical channel component for SOCE identified in 2006 [1–3]. In this context, ORAI1 is activated by the endoplasmic Ca^{2+}sensor stromal interaction molecule 1 (STIM1) upon Ca^{2+} store depletion, promoting Ca^{2+} influx for Ca^{2+} store refilling and/or the activation of key Ca^{2+}dependent processes. ORAI1 is structurally very different to other Ca^{2+} channels except for its related isoforms ORAI2 and ORAI3 [1], the latter of which is only found in mammals [4]. The contribution of ORAI2 and ORAI3 to SOCE may be context dependent, such as the negative fine-tuning role of Orai2 through heteromeric Orai1/Orai2 channels in mouse T-cells [5]. ORAI2 and ORAI3 have also been proposed to make contributions directly to Ca^{2+} influx in response to specific factors [4]. ORAI isoforms are found ubiquitously but some cell types appear to have higher levels of specific isoforms such as ORAI1 in immune cells and ORAI2 in the brain [7–9]. ORAI isoforms may respond differently to stimuli and have distinct roles, their changes in cancer and their contribution to cancer relevant processes is likely to be similarly diverse.

The impact of the discovery of Ca^{2+} channels in oncology is evident from the approximately 200 PubMed listed publications related to channels in cancer, including specific reviews on the contribution of channels to tumour progression [10–13]. It is beyond the scope of this review to explore all of these contributions to our understanding of ORAI channels in cancer. Here, we have sought to provide a general overview of ORAI Ca^{2+} channels in cancer. We particularly focus on what we regard as three key aspects of ORAI channels in cancer; 1) the remodelling of ORAI channels in different cancers, 2) ORAI Ca^{2+} channels in the transformed cell and 3) the contribution of ORAI channels in cells relevant to the tumour microenvironment.

2. ORAI channel remodelling in cancer cells

Mutations in genes are a defining feature of cancer and many are

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https://doi.org/10.1016/j.ceca.2018.07.011
Received 27 April 2018; Received in revised form 30 July 2018; Accepted 30 July 2018
Available online 31 July 2018

drivers of the oncogenic phenotype and/or are contributors of tumour progression through promotion of cancer cell proliferation, metastasis or resistance to death signals [14]. Indeed, the diversity of gene mutations can change during cancer progression, or at metastatic sites [15]. One could imagine that mutations in some Ca^{2+} channels that increase channel activity could promote metastatic or proliferative pathways, or those that would reduce activity could potentially bestow resistance to apoptotic signals. ORAI1 mutations have been reported to occur in some cancers from the cBioPortal database and some of these mutations have been shown to confer constitutive activity to ORAI1 channels [16]. These activating mutations were found in cancers from patients with colorectal, stomach and uterine cancer. Although such changes could potentially promote tumour progression through activation of proliferative and/or metastatic signalling pathways, so far, such mutations appear to be very rare events for ORAI1 [16] compared to mutations in other genes, including those that have strong links to some cancers such as mutations in p53 or RAS [14]. However, there may be cases, as recently suggested, where mutations may remodel SOCE, e.g. oncogenic KRAS induced changes in STIM1 expression via ERK signalling [17]. However, changes in a specific Ca^{2+} influx pathway via an ORAI channel is unlikely to be a driver of transformation and ORAI channels are unlikely to ever be classified as oncogenes [10]. Nevertheless, a remodelling of Ca^{2+} influx through ORAI Ca^{2+} channels may impart features that promote disease progression, such as the promotion of growth and invasiveness or reduced sensitivity to apoptotic stimuli. Such changes have been proposed to provide opportunities for therapeutic exploitation. Indeed, Rhizen Pharmaceuticals have recently reported the commencement of a human phase 1/1B clinical trial of an ORAI1 inhibitor for the eventual treatment of relapsed or refractory Non-Hodgkin Lymphoma (ClinicalTrials.gov (NCT03119467)). In this section, we will discuss examples of the types of ORAI Ca^{2+} channel alterations that have been reported in some cancers. We will particularly highlight how such changes can be cancer type or even subtype dependent, and (in some cases), even be linked to disease outcomes and survival.

ORAI isoforms and STIM1 and STIM2 expression changes have been extensively evaluated in a number of cancer focused studies. Changes in ORAI channel expression could contribute to the promotion of proliferative or metastatic pathways or enhance the ability of cancer cells to avoid cell death. Although links between expression and tumour progression have not been established in every case, changes in expression of ORAI channels, STIM1, and STIM2 are evident in many studies of human clinical samples (Table 1). Indeed, recent analysis of glioblastoma RNA-sequencing data in The Cancer Genome Atlas has found higher STIM1 expression is correlated with poor survival [18].

As will be seen throughout this review, there are often examples where the contributions of ORAI Ca^{2+} channels are dependent on the type or even subtype of cancer, as well as the specific ORAI or STIM isoform. This is the case for alterations of expression in cancer and is particularly exemplified in studies assessing ORAI channel levels in breast cancer cells. Breast cancer is arguably the cancer type where diversity in gene expression and drug target expression has been the most comprehensively defined and where such differences have the greatest impact on treatment. For example, women whose breast cancers express the oestrogen receptor will often be treated with anti-oestrogen therapies such as tamoxifen and those whose cancers overexpress human epidermal growth factor receptor 2 (HER2) may receive agents such as trastuzumab [19]. Breast cancers that do not overexpress HER2 or the oestrogen and progesterone receptors are classified as triple negative breast cancer (TNBC), these cancers overlap somewhat with the molecularly defined basal molecular breast cancer subtype [19]. TNBCs lack current molecularly targeted therapies and the assessment and development of such agents is an identified priority to improve patient outcomes [19]. In the context of ORAI channels, elevated ORAI1 seems to be a feature of basal breast cancers compared to non-basal as identified in clinical samples [20]. In contrast, cell line studies strongly suggest that ORAI3 is elevated in oestrogen receptor positive breast cancer cells [6]. Indeed, ORAI3 is a regulator of SOCE in MCF-7 oestrogen receptor positive breast cancer cells, but not in the basal triple negative MDA-MB-231 breast cancer cell line [6]. This is an example where changes in ORAI channel expression appears to be directly linked to a major functional change in the nature of Ca^{2+} influx, i.e. the actual ORAI isoforms that contribute to SOCE in a breast cancer cell. The association between ORAI3 and oestrogen receptor status of breast cancer cells is also reflected by the ability of oestrogen receptor α silencing to reduce ORAI3 but not ORAI1 expression levels in MCF-7 breast cancer cells [21]. Elevation of ORAI3 has also been reported in breast cancer clinical samples [22]. Further work on clinical samples is still required to fully define the association between specific breast cancer subtypes and ORAI isoform expression levels. Another element of breast cancer subtype differences in the potential remodelling of ORAI-mediated Ca^{2+} influx is seen in the canonical ORAI1 activators STIM1 and STIM2. In breast cancer of the basal molecular subtype but not other molecular subtypes (HER2, Luminal A, Luminal B) samples are more often associated with high STIM1 and low STIM2 levels [20].

Table 1
Examples of altered expression of ORAI channels and STIM isoforms determined in human cancer clinical samples with matched non-tumourous controls ORAI.

ORAI/ STIM isoform	Cancer type	Change with cancer		Change with increasing tumour stage	Reference
		mRNA	Protein		
ORAI1	Liver cancer	↑	↑		[23]
	Oesophageal cancer	↑	↑	↑	[24]
	Renal cancer		↑		[26]
	Stomach cancer		↑		[25]
	Lung cancer	↑	↑	↑	[80]
ORAI3	Renal cancer		↔		[26]
	Breast cancer	↑	↑		[22,66]
	Lung cancer	↑	↑	↑	[27,28]
STIM1	Cervical cancer		↑		[40]
	Stomach cancer		↑	↔	[81]
	Liver cancer	↑	↑		[35,82]
	Colorectal cancer	↑	↑		[83]
STIM2	Colorectal cancer	↑			[84]

As illustrated in Table 1, there has now been a variety of studies that demonstrate the overexpression of ORAI channels in clinical samples of other cancer types. For example, ORAI1 levels are elevated in cancer of the liver [23], osesophagus [24], stomach [25] and in renal cancer [26]. ORAI3 is elevated in lung cancer [27,28]. In vitro studies have also provided clues to potential changes in expression in cancer, such as high levels of ORAI2 in an acute myeloid leukaemia cell line [29]. In some cases the changes in ORAI channel isoform expression includes a down regulation that may, as described below, contribute to resistance to apoptotic pathways. This is exemplified by the down regulation of ORAI1 in some prostate cancers that have developed castrate resistance [30]. There are also some cases where the relative levels of ORAI isoforms may be a feature of a cancer cell. A specific example is seen in the relationship between ORAI1 and ORAI3 levels; it has been reported that there is a formation of ORAI1/3 heteromeric channels in some prostate cancers proposed to be driven by an upregulation of ORAI3 [31]. However, further studies are still required to conclusively demonstrate the direct formation of ORAI heteromeric channels and to define their specific roles in prostate cancer and other diseases. The expression of ORAI channels may also be dynamic in cancer cells and influenced by tumour microenvironmental factors such as growth factors and hypoxia [32–34]. STIM1 appears important in the promotion of