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REVIEW

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Calcium and CaSR/IP3R in prostate cancer development

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Abstract

Prostate cancer (PrCa) progression and mortality are associated with calcium metabolism, parathyroid hormone level, and vitamin D level. However, the lack of comprehensive understanding on the molecular rationale of calcium intake, serum homeostasis, and cytoplasmic function, is critically hindering our ability to propose a mechanism based technique for targeting calcium in PrCa. Recently, studies performed on PrCa samples have shown that calcium-sensing receptor regulates cytoplasmic calcium levels in relation to extracellular calcium concentrations. Recent publications have also revealed the role of BAP1 and FBXL2 associated endoplasmic reticular IP3Rs in controlling the trafficking of calcium from cytosol into the mitochondria of PrCa cells. Competitive binding between BAP1, PTEN and FBXL2 to IP3Rs regulates the calcium flux of mitochondria and thereby controls apoptosis. Analysis of data released by Prostate Adenocarcinoma (Provisional TCGA) reveals that calcium related proteins play critical role in the development of PrCa. From this constantly expanding appreciation for the role of calcium outside the muscle, we predict that calcium-induced-calcium-release ryanodine receptors could also be involved in determining cell fate.

Keywords: Prostate cancer, CaSR, RyR, IP3R, BAP1, FBXL2, PTEN

Background

Calcium metabolism, parathyroid hormone (PTH) level, and vitamin D level have been implicated in the progression and mortality of prostate cancer (PrCa) [1–3]. A 4-year dietary assessment of 47,750 men revealed that increased calcium intake is associated with an elevated risk of advanced and poorly differentiated PrCa, indicating that high levels of dietary calcium and supplemental calcium should be avoided [4]. However, due to the disease complexity and importance of calcium for bone health in late life, these results have been disputed [5]. In fact, it has been argued that men with high calcium diet in these studies ate less red meat and consumed mainly low- or non-fat dairy products, and thereby consumed less conjugated linoleic acid (CLA), a molecule known to have antiproliferative and metabolic effects [6]. One factor contributing to these contradictory theories is the lack of comprehensive understanding of the molecular mechanisms of calcium intake, serum homeostasis, and cytoplasmic function (Fig. 1). Current known regulators of calcium homeostasis include calcium-sensing receptor (CaSR) responsible for adjusting cytoplasmic calcium level based on extracellular concentrations, and inositol 1,4,5-trisphosphate receptors (IP3Rs) responsible for balancing cytoplasmic, mitochondrial, and endoplasmic reticulum (ER) calcium storage via the ryanodine receptors (RyRs).

CaSR is responsible for cellular calcium influx

Five independent studies have demonstrated that serum calcium is regulated by the *CaSR* gene. Genetic variations [7] and amplification of this gene has been positively associated with PrCa mortality [8, 9]. An analysis of 706 African-Americans with and without PrCa showed that the *CaSR* Q1011E minor allele (rs1801726) provided a protective effect against PrCa [10]. Another study of 2437

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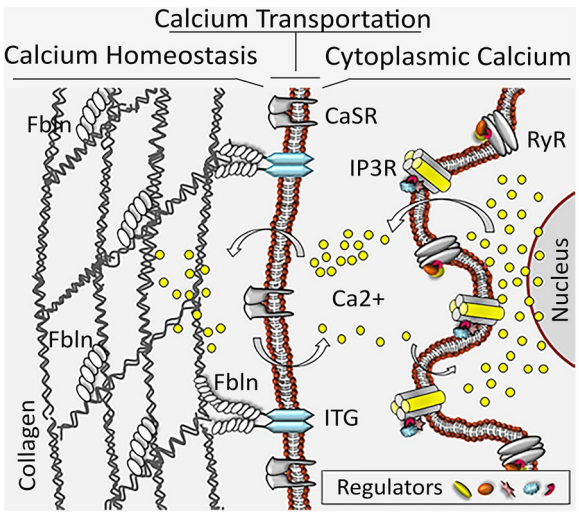

Fig. 1 Calcium homeostasis is controlled by extracellular environment and calcium transporters in cytoplasmic membrane. Extracellular calcium homeostasis, calcium transportation across cell membranes, and cytoplasmic calcium regulation are the three major components of calcium regulation in prostate cancer

patients further supported the importance of this gene in PrCa by finding an association between *CaSR* polymorphisms with lethal PrCa [11]. A genetic study of 12,865 individuals with European and Indian-Asian descent revealed that the *CaSR* gene regulates serum calcium [7]. Further research has shown that *CaSR* plays a central role in calcium regulation via extracellular serum calcium ion detection.

CaSR is a member of sub-family C in the superfamily of G protein-coupled receptors (GPCRs). The *CaSR* gene is widely expressed in almost all tissues, but is primarily expressed in parathyroid and renal tubules. This gene controls calcium homeostasis by regulating the release of parathyroid hormone (PTH), whose gene is located on human chromosome 3 122.18 (NM_000388) and mouse chromosome 16 36.49 (NM_013803).

CaSR primarily consists of a dimer linked by a covalent disulfide bond between two cysteine residues (cys129 and cys131). Each monomer of the human CaSR contains 1078 amino acid residues organized into three structural domains: an extracellular domain (ECD) composed of 612 residues at the hydrophilic N-terminus, a hydrophobic transmembrane domain (TMD) composed of 250 amino acids further organized into seven TMDs, and an intracellular domain (ICD) composed of 216 residues at the hydrophilic C-terminus (Fig. 2a). The ECD contains two sites constantly bound with Ca^{2+} and multiple other Ca^{2+}–binding sites whose occupancy is dependent on extracellular calcium levels. These varying ECD calcium binding states direct the interaction of the ICD domain with intracellular Ca^{2+} [12–14].

Many intracellular signaling pathways are activated by CaSR-mediated signaling. For instance, CaSR induced activation of phospholipases (PLA2, PLC and PLD) produces IP3 which in turn activates the IP3Rs located on the endoplasmic reticulum (ER) membrane, leading to the release of ER calcium stores. CaSR has also been shown to activate PLA2 through Gαq, PLC, calmodulin, and calmodulin-dependent kinase. This complex set of signaling pathways allows CaSR to control interactions between the extracellular and intracellular environment, thereby maintaining physiological calcium homeostasis and regulating cell proliferation and apoptosis in an extracellular calcium dependent manner. This mechanism linking CaSR with cell proliferation and apoptosis may explain the association of CaSR with increased PrCa lethality, especially in tumors with increased vitamin D receptor expression [15, 16].

IP3R3 associated with BAP1 and FBXL2 determines calcium-dependent cell fate

IP3Rs are glycoproteins consisting of four subunits (313 kDa), which form a Ca^{2+} release channel activated by IP3. IP3Rs contain an N-terminal beta-trefoil domain (BTD) and a C-terminal alpha helical armadillo repeat-like domain (ARD) (Fig. 2c). Three paralogs of IP3R have been identified in mammals, including the most widely expressed IP3R1 and the most diverse IP3R3. The latter has nine different exon variants generated from four mRNA splicing sites [17, 18]. The calcium homeostasis controlled by IP3Rs oversees many physiological processes in vertebrates, including cell proliferation, apoptosis, fertilization, and development [17].

The CaSR-IP3R signaling is not the only calcium signaling mechanism at the forefront of prostate cancer pathology. In the recent June edition of *Nature*, two back-to-back papers highlighted IP3R's function in conjunction with other molecules. One paper reported that BRCA1-associated protein 1 (BAP1) mediated signaling resulted in reduced IP3R expression and Ca^{2+} flux while the other linked the PTEN-F-box protein XL2 (FBXL2) to Ca^{2+} mediated apoptosis in PrCa (Fig. 2b) [19, 20].

BAP1 is an effective tumor suppressor gene distributed in the nucleus. This gene is involved in maintaining genome integrity, thus lack of BAP1 leads to cancer development in both animal models and humans [21]. Based on new findings of BAP1 localization to the ER in proximity to IP3R3 and subsequent ER calcium release, BAP1 expression is now accepted as an effector of ER and mitochondrial calcium homeostasis. This mechanism provides a molecular rationale of IP3R3-BAP1 associated calcium regulation as a mode of treatment for PrCa [19].

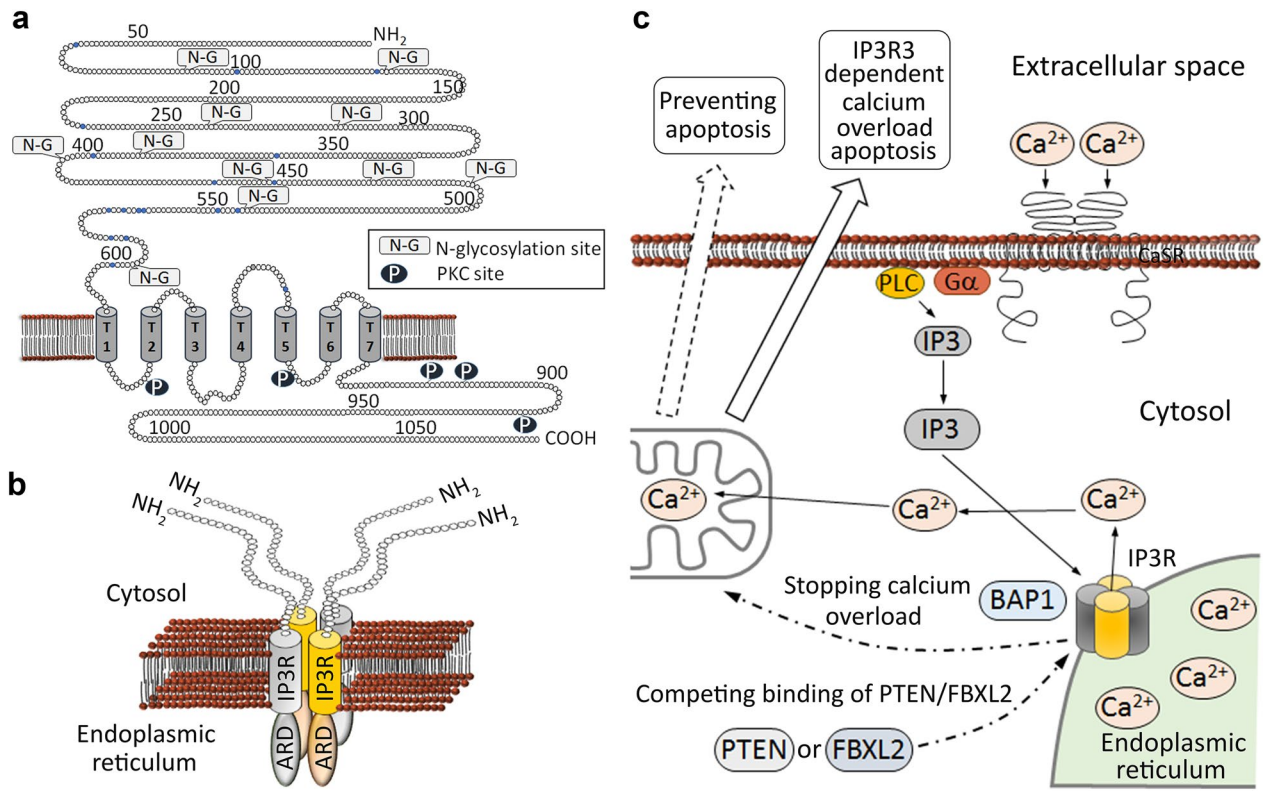

Fig. 2 Cytoplasmic calcium is controlled by IP3R and its regulators including BAP1 and PTEN in endoplasmic reticulum membrane. **a** Structure of CaSR proteins consist of an extracellular portion, seven transmembrane domains, and a cytoplasmic protrusion. **b** Endoplasmic reticulum IP3R are configured as tetramer consisting of two pairs of paired IP3R monomers. **c** Cell membrane integrated CaSR dimerizes and activates IP3 to localize to the ER, where IP3R tetramerizes and associates with BAP1, PTEN, or FBXL2, leading to the release of ER calcium which can activate apoptosis

PTEN and FBXL2 are the additional two proteins that have been recently found to correlate with IP3R3 in human PrCa. PTEN competes with FBXL2 for IP3R3 binding. Successful binding of FBXL2 to IP3R3 is known to trigger FBXL2-dependent degradation of IP3R3, which discontinues mitochondria calcium loading and prevents apoptosis due to IP3R3 dependent calcium overload. The novel binding interaction between PTEN and IP3R3 is thought to limit but not discontinue mitochondrial Ca^{2+} overload, therefore inhibiting IP3R3 degradation in PTEN-deregulated cancers [20]. It is obvious that more experiments are needed to discover the mechanism on how only FBXL2–IP3R3 interaction, but not PTEN–IP3R3, results in the IP3R3 degradation.

Complexity of calcium-induced calcium release in PrCa

It is well recognized that PTEN is a crucial factor for human prostatic tumorigenesis [22, 23]. According to the database of Prostate Adenocarcinoma (Provisional TCGA), mutation and deep deletion of the *PTEN* gene contribute to 1.2 and 4.21% of primary PrCa respectively; downregulation of PTEN at mRNA and protein levels is responsible for 6.21 and 1.8% of PrCa respectively; and multiple alterations of the *PTEN* gene is detected in 16.23% of cases. Therefore, overall alteration of the *PTEN* gene contributes to 30% of PrCa (147 out of 498 sequenced cases/patients (Table 1). Similar to these results, analysis of calcium related genes based on TCGA database indicates a similar significant effect on prostatic adenocarcinoma.

CaSR coded cytoplasmic protein is in charge of regulating serum calcium and amplification of this gene is positively associated with PrCa mortality [7–9]. However, the analysis of TCGA database reveals that the total alteration of *CaSR* gene in PrCa patients is only 4% (22 out of 498 sequenced cases/patients) (Table 1). Cytoplasmic calcium ions can induce the subsequent calcium release from ER/sarcoplasmic reticulum named as calcium induced calcium release (CICR) in myocytes as a trigger for excitation–contraction (EC)-coupling contraction. In non-muscle cells, over-expression of RyR1 resulted in irregular calcium release and induced apoptosis in culture condition [24]. In this CICR biological process,

Table 1 Calcium related genes suspects to human prostatic tumorigenesis

Genes	Cases_Altered % (cases)	Sources of data bases					
		TCGA Provisional 498 patients/499 samples	TCGA cell 2015 333 patients/333 samples	NEPC 2016 81 patients/114 samples	FHCRC, 2016 63 patients/176 samples	MICH 59 patients/61 samples	SU2C 150 patients/150 samples
PTEN	Mutation	1.2% (6)	1.5% (5)	0.88% (1)	1.7% (3)	8.2% (5)	7.33% (11)
	Amplification	0	0	7.02% (8)	0	0	0
	Deep deletion	4.21% (21)	4.5% (15)	14.91% (17)	7.95% (14)	39.34% (24)	26% (39)
	mRNA/protein ↓	8.01% (40)	9.01% (30)	0	18.18% (32)	0	2% (3)
	Multiple alteration	16.23% (81)	11.41% (38)	0.88% (1)	23.3% (41)	1.64% (1)	6.66% (10)
	Patients_Altered	30% (147)	26% (88)	30% (24)	63% (40)	51% (30)	42% (63)
RYR1 RYR2 RYR3	Mutation	6.61% (33)	3.9% (13)	7.02% (8)	9.09% (16)	14.75% (9)	15.33% (23)
	Amplification	1.4% (7)	1.5% (5)	27.19% (31)	3.41% (6)	1.64% (1)	1.33% (2)
	Deep deletion	3.61% (18)	3.9% (13)	0.88% (1)	1.14% (2)	0	1.33% (2)
	mRNA/protein ↓	7.62% (38)	8.11% (27)	0	14.2% (25)	0	6% (9)
	Multiple alteration	2% (10)	0.6% (2)	3.51% (4)	1.7% (3)	3.28% (2)	0.67% (1)
	Patients_Altered	21% (106)	18% (60)	44% (36)	43% (27)	20% (12)	25% (37)
RYR1 RYR2 RYR3 FKBP1A FKBP1B	Mutation	6.01% (30)	3.6% (12)	7.02% (8)	6.82% (12)	14.75% (9)	14.67% (22)
	Amplification	1.4% (7)	1.8% (6)	28.95% (33)	3.41% (6)	1.64% (1)	1.33% (2)
	Deep deletion	4.21% (21)	4.2% (14)	0.88% (1)	1.14% (2)	1.64% (1)	1.33% (2)
	mRNA/protein ↓	14.83% (74)	13.21% (44)	0	21.02% (37)	0	8% (12)
	Multiple alteration	3.01% (15)	1.2% (4)	3.51% (4)	5.11% (9)	3.28% (2)	1.33% (2)
	Patients_Altered	30% (147)	24% (80)	47% (38)	52% (33)	22% (13)	27% (40)
IP3R1 IP3R2 IP3R3	Mutation	2.81% (14)	1.8% (6)	3.51% (4)	3.98% (7)	4.92% (3)	2.67% (4)
	Amplification	0.4% (2)	0.3% (1)	26.32% (30)	5.68% (10)	1.64% (1)	3.33% (5)
	Deep deletion	2% (10)	2.7% (9)	0.88% (1)	0	3.28% (2)	0
	mRNA/protein ↓	10.62% (53)	9.91% (33)	0	11.93% (21)	0	6.67% (10)
	Multiple alteration	1.2% (6)	0.6% (2)	0	0.57% (1)	0	2.67% (4)
	Patients_Altered	17% (85)	15% (51)	38% (31)	33% (21)	10% (6)	15% (23)
IP3R1 IP3R2 IP3R3 PP2AA PP2AB PP2AC	Mutation	1.8% (9)	2.1% (7)	4.39% (5)	2.84% (5)	8.2% (5)	2% (3)
	Amplification	0.8% (4)	0.6% (2)	34.21% (39)	5.11% (9)	4.92% (3)	2% (3)
	Deep deletion	11.82% (59)	12.31% (41)	1.75% (2)	2.27% (4)	14.75% (9)	4% (6)
	mRNA/protein ↓	22.44% (112)	20.72% (69)	0	30.68% (54)	0	15.33% (23)
	Multiple alteration	8.22% (41)	6.01% (20)	0	7.39% (13)	1.64% (1)	9.33% (14)
	Patients_Altered	45% (224)	42% (139)	47% (38)	68% (43)	31% (18)	33% (49)
CaSR	Mutation	0.6% (3)	0.6% (2)	0	0	1.64% (1)	2% (3)
	Amplification	0.8% (4)	0.6% (2)	17.54% (20)	3.41% (6)	3.28% (2)	0.67% (1)
	Deep deletion	0.8% (4)	0.6% (2)	0	0.57% (1)	0	0
	mRNA/protein ↓	2.2% (11)	1.2% (4)	0	3.41% (6)	0	2% (3)
	Multiple alteration	0	0	0.88% (1)	0	0	0.67% (1)
	Patients_Altered	4% (22)	3% (10)	25% (20)	13% (8)	5% (3)	5% (8)

↓means downregulation; all data output from prostate cancer studies at http://www.cbioportal.org/index.do

the role of RyRs and IP3Rs is well recognized. Alternation of *RyRs* and *IP3Rs* coding genes is involved in PrCa. Compared to 30% of PTEN gene alternation in PrCa patients, 21% patients (106 out of 498 sequenced cases/patients) with the alternation of *RyR* genes (RyR1, RyR2 and RyR3) has been diagnosed with PrCa. Interestingly, non-overlapping distribution of these three isoforms may implicate their compensatory function, and alteration of the three genes in one individuals may generate more severe symptom. Furthermore, alteration of the three RyR genes together with their regulator FKBP12 and FKBP12.6 genes contribute to 30% of PrCa (147 out of 498 sequenced cases/patients) (Table 1). The analysis from the other data bases including Prostate Adenocarcinoma [25–27], and Neuroendocrine Prostate Cancer [26], Metastatic Prostate Adenocarcinoma [28], and metastatic prostate cancer [29] support this prophecy as well. Therefore, the effect of CICR is worth to be considered in the investigation of molecular mechanism of PrCa development.

Calcium release through IP3Rs is another approach for cells to release calcium from the ER-storage as discussed above. Analysis of the TCGA database appears to support the possible function of calcium in PrCa development. Alternation of IP3Rs genes (IP3R1, IP3R2 and IP3R3), including mutation, amplification, deep deletion, down-regulation of mRNA and protein, and multiple alteration, occurs in 30% of PrCa patients (85 out of 498 sequenced cases/patients), while simultaneous alternation of IP3Rs plus their regulator protein phosphatase 2A (PP2A) isoforms (PPP-2R1A, -2CA, -2A and -2B) is detected in 45% of PrCa patients (224 out of 498 sequenced cases/patients), suggesting an important role of IP3R complex in the development of PrCa.

For normal physiological processes, many regulators such as calcineurin for RyR complex, and BAP1 for IP3Rs are required at molecular and cellular level. More and more regulators for calcium release form ER have been identified recently [30–32]. Considering PTEN's interacting with BAP1, which is a recently discovered regulator of IP3R [20], it is reasonable to speculate that intracellular calcium should play a critical role in PrCa development.

Lack of the animal models postpones the discovery of the PrCa mechanism related to calcium associated proteins

The generation of the genetically engineered mouse has produced the murine models that allow for the investigation of tumorigenic and metastatic processes of prostate cancer. Beside Xenograft mouse models with LNCaP, LNCaP-LN3, PC-3, PC-3M, TRAMP-C1/2/3, PTEN-CaP8 cell lines as high take rate and low cost approach, the engineered model animals termed as C3(1)-Tag, TRAMP, LPB-Tag (LADY), LPB-Tag/ARR2PB hepsin, Mt-PRL, PB-mAR, ARR2PB-Myc and PB-Neu are widely used to study BPH, all stages of PrCa, micro-invasive HGPIN androgenic PrCA, lymphatic metastatic PrCa and neuroendocrine originated tumors [see review 33, 34]. Up to date, no any genetically engineered murine models with modifications on the genes of calcium associated proteins are produced for PrCa study although the criticality of micro-environmental and cytoplasmic calcium has been recognized for more than 30 years.

As the discussion presented above, three families of the genes including CaSR, IP3R3 and RyRs are in charge of the calcium within macro-environments and intracellular cytoplasm directly. However, the early lethality of these genes explained the limitation that we can use for prostate tumorigenesis. The deletions of RyRs, CaSR and IP3R3 lead to sever cardiac, smooth and skeletal muscle dysfunctions in embryonic development, and results in early death of the genetically engineered model mice shortly after or even before birth [35–39]. Therefore there are no chances to use these model to examine their function in PrCa development. Another reason of their less consideration for prostate cancer study is that these calcium associated proteins play critical role on cardiac function in cardiomyocytes as calcium channels involved excitation–contraction coupling with calcium induced calcium release channels. Massive studies have been focused on their role in heart, the number one life-threatening cause for human health in western world. Therefore, producing murine models with the prostate specific over-expression and/or conditional deletion of the genes encoding CaSR, IP3Rs and RyRs would be the effective approach to comprehend the function of calcium signaling pathway in PrCa development.

Conclusion and future prospects

Functional investigation of the role of calcium in PrCa development can be categorized into three distinct components: (I) the nutritional effect of calcium, vitamin D, PTH and CLA intact on PrCa development, (II) CaSR maintenance of extracellular-intracellular calcium homeostasis, and (III) IP3R regulation of intracellular calcium in association with BAP1, FBXL2 and PTEN. To comprehensively understand the cellular and molecular mechanism of all three components in PrCa development, RyRs also need to be studied. Similar to IP3Rs, RyRs are primarily found in muscle cells and recognized for its function in the CICR during EC-coupling. A similar calcium flux triggered in non-muscle cells may also affect cytosolic calcium concentration and have the potential to induce mitochondria calcium overload apoptosis. Thus, further investigation of the function of RyRs in conjunction with CaSR and IP3Rs would provide better

understanding of the role of calcium in the development and progression of PrCa.

Abbreviations
PrCa: prostate cancer; CaSR: calcium-sensing receptor; PTH: parathyroid hormone; CLA: conjugated linoleic acid; IP3Rs: inositol 1,4,5-trisphosphate receptors; ER: endoplasmic reticulum; RyRs: ryanodine receptors; GPCRs: G protein-coupled receptors; ECD: extracellular domain; TMD: transmembrane domain; ARM: armadillo repeat-like domain; BAP1: BRCA1-associated protein 1; FBXL2: PTEN-F-box protein XL2.

Authors' contributions
XHX conceived of the study. LW, MMX, ZL, MS, and XZ developed protocols to analyze the data. XHX, LW, MMX, XJ, JB, SB, JM and WI prepared the manuscript and all authors edited the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
Not applicable.

Consent for publication
Not applicable.

Ethics approval and consent to participate
All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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