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Microcalcifications, calcium-sensing receptor, and cancer

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ABSTRACT

Calcium stones and calculi are observed in numerous human tissues. They are the result of deposition of calcium salts and are due to high local calcium concentrations. Prostatic calculi are usually classified as endogenous or extrinsic stones. Endogenous stones are commonly caused by obstruction of the prostatic ducts around an enlarged prostate resulting from benign prostatic hyperplasia or from chronic inflammation. The latter occurs mainly around the urethra and is generally caused by reflux of urine into the prostate. Calcium concentrations higher than in the plasma at sites of infection may induce the chemotactic response that eventually leads to recruitment of inflammatory cells. The calcium sensing receptor (CaSR) may be crucial for this recruitment as its expression and activity are increased by cytokines such as IL-6 and high extracellular calcium concentrations, respectively. The links between calcium calculi, inflammation, calcium supplementation, and CaSR functions in prostate cancer patients will be discussed in this review.

1. Introduction

The effects of intracellular free calcium as a second messenger not only in cytoplasm but also in endoplasmic reticulum, Golgi apparatus, mitochondria, nuclei, and lysosomes have been extensively characterized [1–6]. The calcium-sensing receptor (CaSR) was first described more than 25 years ago [7], and this discovery lead to the finding that the calcium cation is a key regulator of the physiology and pathophysiology in many diseases and tissues [8,9]. CaSR, a G protein coupled receptor (GPCR), has been studied at the gene, transcript, and protein levels, and its functions in human tissues and its regulation have been the focus of numerous reviews by experts in the field. Due to intracellular and extracellular functions, calcium is a multipurpose messenger indispensable for life [10].

The cytosolic free calcium concentration can jump from a few tens of nM at rest to several tens of μMs when a cell is stimulated [11–13]; however, the extracellular calcium concentration is tightly controlled [14]. Extracellular calcium concentrations higher than those observed in plasma have been observed under certain conditions [15], and the presence of calcium stones or calculi within human kidney [16], breast [17], pancreas [18], and prostate [19,20] suggest that calcium concentrations in these organs can locally reach tens of mM. It remains unclear how these confined extracellular calcium hotspots influence activities of channels and GPCR activities within tissues. The relationship between the occurrence of these calculi and cancer is also interesting as calcium channel and CaSR expression are often increased as cancer progresses [21,22]. Here we will review our current understanding of the links between calcium calculi, inflammation, calcium supplementation, and CaSR functions in prostate cancer patients and will discuss the putative sources of calcium calculi and the role of inflammation as either a cause or consequence of microcalcifications.

2. Calcemia and free extracellular calcium concentration

Most cells are faced with extracellular calcium concentrations close to those measured in plasma, which is called calcemia. Normal calcemia ranges from 9 to 10.5 mg/dl (2.2 to 2.6 mM) in human with upper and lower limits depending on age as adults over 40 years old are mostly between 9 and 10 mg/dl, whereas calcemia in teenagers is slightly above 10 mg/dl [23]. Other factors can also influence calcemia including sex and the season of the year [24].

Calcemia refers to total calcium in the plasma but only the free ionized calcium is physiologically active. Calcium is present in serum in three main fractions: protein-bound (approximately 45% of the total), complexed calcium (approximately 10%) and the so-called ionized fraction (approximately 45%) [24,25]. These fractions are in

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equilibrium. Several parameters control the plasma calcium concentration including regulation by parathyroid hormone (PTH), 1,25-dihydroxy vitamin D (1,25$(OH)_2$D), and kidney and skeleton factors, pH, serum phosphate and magnesium concentrations, calcium daily intake, and intestinal calcium absorption [24,26]. It is recommended that in humans normal extracellular free calcium concentration be maintained between 1.1. and 1.3 mM [14].

3. Extracellular calcium concentration and calcium-sensing receptor

Extracellular calcium modulates cell physiology via plasma membrane calcium channels and the CaSR, which senses extracellular levels of calcium [27,28]. Opening of a plasma membrane calcium or cationic channel leads to a rapid and massive increase in cytosolic free calcium due to the large gradient for this cation [29]. The physiological functions of these large and probably localized increases in cytosolic calcium concentration have discussed in many reviews over the last twenty years [30–34]. Whereas the channels work at steady-state extracellular calcium concentration, an increase in extracellular calcium concentration is essential for CaSR activation.

CaSR is almost ubiquitously expressed in human tissues with a clear predominance in parathyroid, gut, bone, and kidney [9,10,35]. The structure of CaSR, the normally observed and alternatively spliced transcripts, and transcriptional control of CaSR gene expression have all been extensively discussed recently [36]. CaSR is a GPCR that influences calcium homeostasis by detecting variations in extracellular calcium [7,10,26,37], and it induces various intracellular signaling pathways depending on the coupling to a specific G protein subunit, $G_{q/11}$, $G_{i/o}$, $G_{12/13}$, or G_s [22,38,39]. Expression of these subunits also depends on the physiological state of the cells resulting in flexibility of the responses triggered by CaSR activation [40,41]. CaSR is involved in several calcitropic and non-calcitropic diseases [9], and CaSR expression levels are increased in several cancers including that of the prostate [22,42,43]. It is worth mentioning that several other GPCRs and multiple channels are able to sense variations in extracellular calcium concentrations [15,44]. Structural homologies, conservation of specific domains, and a common functional role as nutrient/salinity sensor clearly indicate that CaSR is part of a family that includes metabotropic glutamate and GABA receptors, taste receptors, GPRC6a, and seven orphan receptors [15,45].

Acute increases in serum calcium into the borderline hypercalcemic range were observed about 4 h following ingestion of 500–1000 mg of calcium citrate or calcium carbonate as supplements [46]. However, the change in calcium concentration, which is likely detected by the parathyroid gland [47–49], was not more than 100 μM but was larger than that recorded after ingestion of calcium-rich food [50]. This is a lower concentration than the reported extracellular calcium-evoked activation range for CaSR. When increases in cytosolic calcium concentration were monitored in fura2-loaded HEK293 cells expressing CaSR, increasing extracellular calcium concentration from an initial value of 0.5 mM showed a clear threshold effect at about 2 mM with an EC_{50} of about 3.5 mM [10,51–53]. However, CaSR activity *per se* can be modulated by numerous allosteric factors in the absence of increased calcium levels [10,54]. These include aromatic L-amino acids such as Trp or Phe, which sensitize CaSR to calcium. The L-amino acid binding site recently identified [55] also involves magnesium ions and a tryptophan-derivative ligand [56]. Both Trp and Phe concentrations are dramatically impacted by dietary amino acid and protein ingestion [57,58], and the postprandial elevation peak brings their plasma concentration up to levels of about 100 μM, a concentration at which they likely increase CaSR affinity for extracellular calcium [58]. Moreover, high levels of CaSR lower the threshold for calcium activation [52]. Therefore, in humans, CaSR is likely to detect variations in extracellular calcium concentration in the range of 100 μM allowing parathyroid and parathyroid hormone to compensate for changes in plasma calcium concentration.

4. High local extracellular calcium concentrations

In certain tissues and in the luminal contents of glands, calcium concentrations can be much higher than that observed in plasma. An obvious tissue where high local calcium concentrations are found is the bone [59]. Osteoclasts that sense extracellular calcium may be exposed to calcium concentrations of up to 40 mM in erosion sites [60]. Hence, elevated calcium released during bone resorption may activate CaSR in these cells, which in turn will allow completion of bone remodeling. Another important point related to extracellular calcium concentrations and CaSR activation is the volume of interstitial fluid surrounding cells within an organized tissue [15,61]. This remarkably small volume probably contributes to the local fluctuations in extracellular calcium concentrations [62,63]. Several factors underlie these fluctuations. Calcium export from the cells via plasma membrane calcium ATPase (PMCA) and sodium-calcium exchangers, secretory vesicles, and calcium influx can generate fluctuations in these thin interspaces between cells. Localization and kinetics of activation of these different actors are probably another source of changes that are much larger than those recorded in the plasma where calcemia is tightly controlled.

Although calcium inflow and outflow are ultimately balanced as cellular calcium concentrations return to resting levels upon signal termination, transient gradients of extracellular calcium can be generated wherever there is temporal and/or spatial segregation of calcium influx and efflux [64–66]. In another example, direct measurement of extracellular calcium concentration using calcium-sensitive microelectrodes impaled into the interstitial spaces between gastric epithelial cells and in the lumen of the gastric gland in an intact stomach revealed transient increases in extracellular calcium of up to 500 μM [67]. Large reductions in extracellular calcium concentration of the same magnitude were observed in the intercellular spaces of pancreatic islets following stimulation of islet cells with glucose [63]. Last but not least, calcium contents of secretory vesicles can be very high [68–70] ranging from 40 to 120 mM in insulin granules of rat insulinoma [71] and in chromaffin vesicles [72].

Investigation of the co-localization of these actors with CaSR could provide important information on how CaSR modulates cell signaling even when calcemia remains unchanged. For instance, PMCA and CaSR are co-localized on the apical membrane of polarized gastric acid-secreting cells [62]. CaSR (through $G_{q/11}$) is also able to modulate the expression and activity of transient receptor potential channels TRPC1 [73,74], TRPC3 [75], and TRPC6 [42]. The signal transduction of CaSR is also involved in the regulation of PMCA and SERCA calcium pumps expression and activity [76]. Moreover, CaSR is likely to change the driving force for calcium ions through the activation of plasma membrane potassium channels [77]. Regulation via plasma membrane pumps, exchangers, and channels are likely to trigger only transient changes in extracellular calcium. Long-term increases in this cation concentration such as those observed in bone may result from different mechanisms.

5. Prostatic calcification: stones and calculi

Calcium stones and calculi are the result of deposition of calcium salts and are caused by high local calcium concentrations. Although also found in pancreas [18], kidney [16], and breast [17], we shall focus here on their involvement in benign prostatic hyperplasia (BPH) and prostate cancer. We propose that there is a link between inflammation and CaSR expression and activity.

Prostatic calculi are usually classified as endogenous (also known as primary) stones or extrinsic (also referred to as secondary) stones. Endogenous stones are commonly caused by obstruction of the prostatic ducts around the enlarged prostate resulting from BPH or chronic inflammation [78]. Several hypothesis have been proposed regarding the

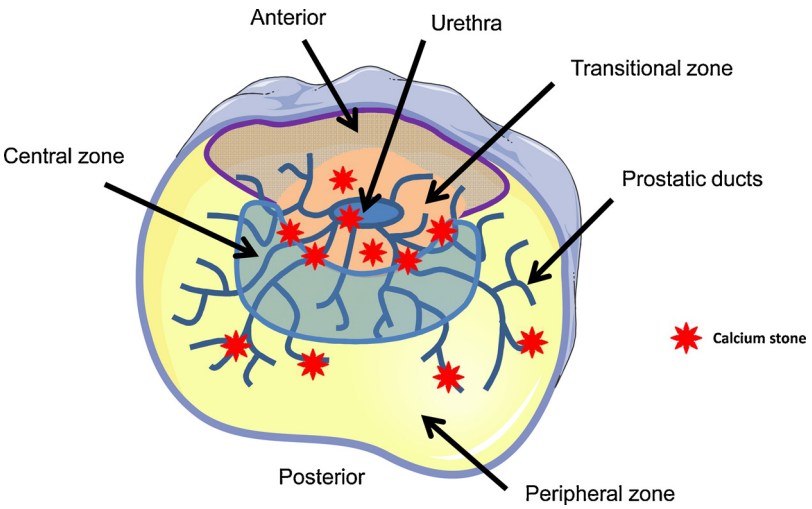

Fig. 1. Schematic representation of the different prostate zones and putative localization of prostate calculi or stones in human. Calcium stones are mainly located inside the main prostatic ducts in the peripheral zone and outside the ducts in transitional and central zones [129].

etiology of prostatic calculi but none are supported by definitive evidence [79,80]. Reflux of urine into the ejaculatory ducts upon voiding is not an uncommon phenomenon and is more likely to occur if there is a degree of urine flow obstruction. Hence, intraprostatic urinary reflux and the constituents of refluxing urine may contribute to the formation of prostatic stones [80]. Inflammation associated with prostatic lithiasis, the deposition of hydroxyapatite crystals in the corpora amylacea and the mineralization of these with calcium, and intraprostatic reflux have also been proposed to lead to formation of prostate calculi [81].

Extrinsic stones occur mainly around the urethra and are caused by reflux of urine into the prostate [78]. The exact prevalence of prostatic calculi is not known, and it has been reported to vary widely, from 7% to 70%. Many patients have several small stones ranging from 0.5 to 5.0 mm in size. Most cases of prostatic calculi are not accompanied by symptoms. Therefore, most cases are found incidentally during the diagnosis of BPH using transrectal ultrasonography [19]. Magnetic resonance imaging can also detect prostatic calculi as well as intra-vascular stones [82]. Intra-vascular stone formation is mediated by inflammation as indicated by analysis of cytokine expression [83]. Intra-vascular stones are systemic and generally occur in large vessels [84]; they are not included in our discussion.

The first step in the formation of prostatic calcification is accumulation of desquamated acinar cells to form corpora amylacea [85]. Corpora amylacea are luminal secretions commonly present in benign prostatic acini [81,86] that have also been noted in other organs including lung and uterus [87]. Corpora amylacea are present in the benign acini of prostates of approximately 25% of men aged 20–40 years, and they are common among men with prostate cancer [88]. The intraluminal contents of prostatic acini also include mucin, crystalloids, and proteinaceous debris. A variation in density of the matrix of the corpora produces a laminated structure. Formation of corporal calculi results from the deposition of hydroxyapatite crystallites in corpora amylacea and is linked to further growth and mineralization that can lead to the development of prostatic calculi, which are more readily identifiable upon clinical examination [85,89].

The exact mechanism underlying the formation of prostatic calcification is still unclear. Urine reflux into prostatic ducts, the penetration of spermatozoa into prostatic tissue, and desquamation of prostate epithelium due to chronic inflammation are believed to favor the formation of prostatic corpora amylacea [90]. Subsequent chronic inflammation of the prostate epithelium may promote the formation of calculi due to calcification of the corpora amylacea [85]. It is widely accepted that prostatic calculi are uncommon in children, rare in men below 40 years old, and common in men over the age of 50 [81]. Prostatic calcifications are frequently observed in men who are being tested for prostate cancer and in those with symptomatic BPH, although an association between prostatic calcification and these two diseases has not yet been established [90]. Further, no direct association between stone type and the severity of prostate inflammation was detected in more than 200 patients with BPH who were evaluated by transurethral electroresection of the prostate gland [90,91].

One important point should be emphasized: Prostatic calcification could result in an obstruction of the intraprostatic ducts stimulating the inflammatory response of the prostate with cytokine activation or the opposite could be the case. Chronic inflammation of the prostate tissue, triggered by any of a wide variety of factors such as diet, autoimmune response, urine reflux, or infections of the prostate epithelium could promote prostatic calcification. Age-related prostatic calcification in patients aged over 50 years may induce a cascade of events including obstruction of the intraprostatic ducts stimulating an inflammatory response in the prostatic tissue and damage of the epithelial and stromal cells. Subsequent wound healing may result in excessive extracellular matrix and stromal proliferation [92].

Calcium phosphate or calcium oxalate with carbonate-apatite and hydroxyapatite are the main components of prostate calculi [19,89,93]. Prostatic calculi, often observed in patients with acute or chronic prostatitis, may lead to chronic prostatitis [94]. Hypercalciuria can be one of the underlying causes of prostate calculi as evidenced by the fact that stone formers (whose urine is more likely to be supersaturated with stone-forming salts) are more likely to form prostatic calculi than non-stone formers [89]. Hence, patients with calcifications often suffer from inflammation, and there is a casual association between inflammation and cancer development [95].

The prostate can be divided into three main zones: central, transitional, and peripheral (Fig. 1). The peripheral zone accounts for almost 70% of the tissue of the prostate gland in the posterior and lateral regions, and 70% of cases of prostate cancer occur in this area. The peripheral zone is also the site where chronic prostatitis occurs. Therefore zonal calcification could be important in the development of cancer, and it has been proposed that prostatic calculi detected in the peripheral zone of the gland represent a significant risk factor for prostate cancer and therefore could be used as predictors of high cancer risk [19,20,96].

6. Inflammation and high calcium concentrations

Inflammation, prostatic calculi, and prostate cancer progression are

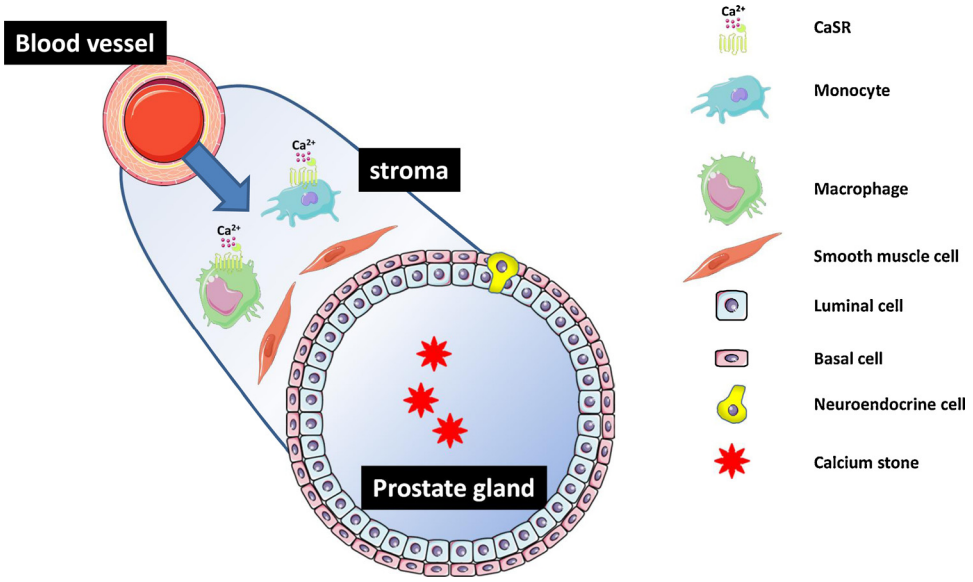

Fig. 2. Monocytes and macrophages are attracted to sites of inflammation by high local calcium concentrations (as indicated by the blue-shaded oval). This could be the source of prostate calcium stones observed in the lumen of the gland. Monocytes and macrophages that express CaSR are stimulated by extracellular calcium to release inflammatory cytokines such as IL6 and CXCL12. These cytokines in turn stimulate CaSR expression in prostate epithelial cells.

clearly related [19,97]. An important question remains, however: What is the connection between these processes and CaSR activity in the prostate? The relationship between extracellular calcium and inflammation works both ways (Fig. 2). First, inflammation can up-regulate CaSR expression. Several inflammatory cytokines can induce CaSR expression [98,99], and immune cells such monocytes, eosinophils, and macrophages express CaSR [100–104]. Second, inflammatory lesions often contain dead cells due to necrosis resulting in the release of cellular constituents after membrane rupture [105]. High levels of calcium are observed at sites of infections and calcifications are detected at sites of chronic inflammation [106] and ischemic necrosis [107] and are related to activation of NLRP3 inflammasome [108]. It is now thought that necrotic cell death can be induced by biomolecules known to initiate inflammation such as the cytokine TNFα and the pathogen component lipopolysaccharide.

The role of the CaSR in the inflammation was investigated by Zeng et al. in a model of acute myocardial infarction [109]. In this recent work, the authors showed that expression of CaSR by T lymphocytes enhanced expression of inflammatory cytokines. CaSR also activates pulmonary inflammation as shown in a mouse model of pulmonary inflammation using the CaSR inhibitor NPS2143 [110]. Immune responses are facilitated via the accumulation of immune cells attracted by chemokines that are produced by almost all cell types in human [111]. Localization of monocytes and macrophages to sites of injury or inflammation is crucial for initiation of their role in host defense and elevated extracellular calcium concentrations measured at sites of inflammation (94) are known to induce monocyte chemotaxis [112–114].

At sites of infection, immune cells secrete numerous cytokines that are implicated in tumorigenesis. For example, interleukins 6 and 1β, TNFα, TGFβ, and CXCL12 (also known as SDF-1) play important roles in prostate cancer progression [115–119]. IL6, IL1β, and TNFα all rapidly induce large increases in CaSR expression [98–100], and it is likely that CXCL12-activated CXCR4 trigger similar activation through STAT1, STAT3, and NFκB activation [118] as these three transcription factors bind to the *CaSR* promoter region [120,121]. Thus, activation of CaSR by high concentrations of calcium leads to inflammation, which in turn further up-regulates CaSR expression. Hence, the chronic inflammation induced may enhance rick of prostate cancer.

There is evidence, however, that CaSR can moderate inflammation. CaSR has been shown to protect against colon cancer development [122], and evidence has been accumulating that this receptor might also prevent colonic inflammation [123]. However, due to the complexity of the gut homeostasis in large part due to the microbiota, the exact role of CaSR in the intestine inflammation remains unclear [124]. Thus, CaSR may promote or moderate inflammation, depending on the situation [100].

7. Conclusion - Calcium supplements and cancer

The currently available data indicate that calcium has a deleterious effect on prostate cancer progression [42,125], probably resulting from a combination of factors. As described in this review, high levels of calcium increase inflammation and urinary calcium and can cause calcium stones to be disseminated in different prostate zones. Furthermore, low bone mineral density is common in men with prostate cancer, even in those not treated with androgen-deprivation therapy (ADT) [126]. The prevalence of low bone mineral density is higher in men on ADT than untreated controls [127], and ADT is correlated with an increased risk of fracture [128]. Calcium supplementation provided to overcome this risk is likely to further increase urinary calcium concentration, the formation of calcium stones, immune cell chemotaxis, and increased secretion of pro-inflammatory cytokines able to increase CaSR expression and eventually tumorigenesis. Thus, as we argued previously [125], men at risk of or diagnosed with prostate cancer should avoid excessive calcium dietary intake.

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References

[1] R. Filadi, E. Basso, K. Lefkimmiatis, T. Pozzan, Beyond intracellular signaling: the ins and outs of second messengers microdomains, Adv. Exp. Med. Biol. 981 (2017) 279–322.
[2] P. Pizzo, V. Lissandron, P. Capitanio, T. Pozzan, Ca(2+) signalling in the Golgi apparatus, Cell Calcium 50 (2011) 184–192.
[3] D. Burdakov, O.H. Petersen, A. Verkhratsky, Intraluminal calcium as a primary regulator of endoplasmic reticulum function, Cell Calcium 38 (2005) 303–310.
[4] J. Krebs, L.B. Agellon, M. Michalak, Ca(2+) homeostasis and endoplasmic reticulum (ER) stress: an integrated view of calcium signaling, Biochem. Biophys. Res. Commun. 460 (2015) 114–121.
[5] D.L. Medina, S. Di Paola, I. Peluso, A. Armani, D. De Stefani, R. Venditti, S. Montefusco, A. Scotto-Rosato, C. Prezioso, A. Forrester, C. Settembre, W. Wang,

Q. Gao, H. Xu, M. Sandri, R. Rizzuto, M.A. De Matteis, A. Ballabio, Lysosomal calcium signalling regulates autophagy through calcineurin and TFEB, Nat. Cell Biol. 17 (2015) 288–299.
[6] M.D. Bootman, C. Fearnley, I. Smyrnias, F. MacDonald, H.L. Roderick, An update on nuclear calcium signalling, J. Cell. Sci. 122 (2009) 2337–2350.
[7] E.M. Brown, G. Gamba, D. Riccardi, M. Lombardi, R. Butters, O. Kifor, A. Sun, M.A. Hediger, J. Lytton, S.C. Hebert, Cloning and characterization of an extracellular Ca(2+)-sensing receptor from bovine parathyroid, Nature 366 (1993) 575–580.
[8] M.J. Berridge, Calcium signalling remodelling and disease, Biochem. Soc. Trans. 40 (2012) 297–309.
[9] F.M. Hannan, E. Kallay, W. Chang, M.L. Brandi, R.V. Thakker, The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases, Nat. Rev. Endocrinol. 15 (2018) 33–51.
[10] E.M. Brown, R.J. MacLeod, Extracellular calcium sensing and extracellular calcium signaling, Physiol. Rev. 81 (2001) 239–297.
[11] G.J. Augustine, E. Neher, Calcium requirements for secretion in bovine chromaffin cells, J. Physiol. (Paris) 450 (1992) 247–271.
[12] J.E. Chad, R. Eckert, Calcium domains associated with individual channels can account for anomalous voltage relations of CA-dependent responses, Biophys. J. 45 (1984) 993–999.
[13] E. Neher, G.J. Augustine, Calcium gradients and buffers in bovine chromaffin cells, J. Physiol. (Paris) 450 (1992) 273–301.
[14] E.M. Brown, Extracellular Ca2+ sensing, regulation of parathyroid cell function, and role of Ca2+ and other ions as extracellular (first) messengers, Physiol. Rev. 71 (1991) 371–411.
[15] A. Gerbino, M. Colella, The Different Facets of Extracellular Calcium Sensors: Old and New Concepts in Calcium-Sensing Receptor Signalling and Pharmacology, Int. J. Mol. Sci. 19 (2018).
[16] W. Cheungpasitporn, C. Thongprayoon, O.A. O'Corragain, P.J. Edmonds, P. Ungprasert, W. Kittanamongkolchai, S.B. Erickson, The risk of kidney cancer in patients with kidney stones: a systematic review and meta-analysis, QJM 108 (2015) 205–212.
[17] S. O'Grady, M.P. Morgan, Microcalcifications in breast cancer: from pathophysiology to diagnosis and prognosis, Biochim. Biophys. Acta Rev. Cancer 1869 (2018) 310–320.
[18] F. Verde, E.K. Fishman, Calcified pancreatic and peripancreatic neoplasms: spectrum of pathologies, Abdom. Radiol. (NY) 42 (2017) 2686–2697.
[19] J.S. Hyun, Clinical significance of Prostatic Calculi: a review, World J. Mens Health 36 (2018) 15–21.
[20] M. Smolski, R. Turo, S. Whiteside, S. Bromage, G.N. Collins, Prevalence of prostatic calcification subtypes and association with prostate cancer, Urology 85 (2015) 178–181.
[21] N. Prevarskaya, R. Skryma, Y. Shuba, Ion Channels in Cancer: Are Cancer Hallmarks Oncochannelopathies? Physiol. Rev. 98 (2018) 559–621.
[22] S. Tennakoon, A. Aggarwal, E. Kallay, The calcium-sensing receptor and the hallmarks of cancer, Biochim. Biophys. Acta 1863 (6 Pt B) (2016) 1398–1407.
[23] S.A. Lietman, E.L. Germain-Lee, M.A. Levine, Hypercalcemia in children and adolescents, Curr. Opin. Pediatr. 22 (2010) 508–515.
[24] D.A. Goldstein, Serum Calcium, R.D.H.K. Walker, W.D. Hall, J.W. Hurst (Eds.), Clinical Methods: The History, Physical, and Laboratory Examinations, 1990 Boston.
[25] W.G. Robertson, R.W. Marshall, Calcium measurements in serum and plasma–total and ionized, CRC Crit. Rev. Clin. Lab. Sci. 11 (1979) 271–304.
[26] E.M. Brown, Role of the calcium-sensing receptor in extracellular calcium homeostasis, Best Pract. Res. Clin. Endocrinol. Metab. 27 (2013) 333–343.
[27] T. Capiod, Extracellular calcium has multiple targets to control cell proliferation, Adv. Exp. Med. Biol. 898 (2016) 133–156.
[28] A.S. Borowiec, G. Bidaux, N. Pigat, V. Goffin, S. Bernichtein, T. Capiod, Calcium channels, external calcium concentration and cell proliferation, Eur. J. Pharmacol. 739 (2014) 19–25.
[29] A.B. Parekh, J.W. Putney Jr., Store-operated calcium channels, Physiol. Rev. 85 (2005) 757–810.
[30] M.J. Berridge, Inositol trisphosphate and calcium signalling mechanisms, Biochim. Biophys. Acta 1793 (2009) 933–940.
[31] M.J. Berridge, M.D. Bootman, H.L. Roderick, Calcium signalling: dynamics, homeostasis and remodelling, Nat. Rev. Mol. Cell Biol. 4 (2003) 517–529.
[32] J. Karlstad, Y. Sun, B.B. Singh, Ca(2+) signaling: an outlook on the characterization of Ca(2+) channels and their importance in cellular functions, Adv. Exp. Med. Biol. 740 (2012) 143–157.
[33] A.J. Laude, A.W. Simpson, Compartmentalized signalling: Ca2+ compartments, microdomains and the many facets of Ca2+ signalling, FEBS J. 276 (2009) 1800–1816.
[34] K. Samanta, A.B. Parekh, Spatial Ca(2+) profiling: decrypting the universal cytosolic Ca(2+) oscillation, J. Physiol. (Paris) 595 (2017) 3053–3062.
[35] G. Diaz-Soto, A. Rocher, C. Garcia-Rodriguez, L. Nunez, C. Villalobos, The calcium-sensing receptor in health and disease, Int. Rev. Cell Mol. Biol. 327 (2016) 321–369.
[36] G.N. Hendy, L. Canaff, Calcium-sensing receptor gene: regulation of expression, Front. Physiol. 7 (2016) 394.
[37] M. Colella, A. Gerbino, A.M. Hofer, S. Curci, Recent advances in understanding the extracellular calcium-sensing receptor, F1000Res 5 (2016).
[38] K. Leach, P.M. Sexton, A. Christopoulos, A.D. Conigrave, Engendering biased signalling from the calcium-sensing receptor for the pharmacotherapy of diverse disorders, Br. J. Pharmacol. 171 (2014) 1142–1155.
[39] A.D. Conigrave, D.T. Ward, Calcium-sensing receptor (CaSR): pharmacological properties and signaling pathways, Best Pract. Res. Clin. Endocrinol. Metab. 27 (2013) 315–331.
[40] R.T. Dorsam, J.S. Gutkind, G-protein-coupled receptors and cancer, Nat. Rev. Cancer 7 (2007) 79–94.
[41] R. Mamillapalli, J. VanHouten, W. Zawalich, J. Wysolmerski, Switching of G-protein usage by the calcium-sensing receptor reverses its effect on parathyroid hormone-related protein secretion in normal versus malignant breast cells, J. Biol. Chem. 283 (2008) 24435–24447.
[42] S. Bernichtein, N. Pigat, N. Barry Delongchamps, F. Boutillon, V. Verkarre, P. Camparo, E. Reyes-Gomez, A. Mejean, S.M. Oudard, E.M. Lepicard, M. Viltard, J.C. Souberbielle, G. Friedlander, T. Capiod, V. Goffin, Vitamin D3 prevents calcium-induced progression of early-stage prostate tumors by counteracting TRPC6 and calcium sensing receptor upregulation, Cancer Res. 77 (2017) 355–365.
[43] S.C. Brennan, U. Thiem, S. Roth, A. Aggarwal, I. Fetahu, S. Tennakoon, A.R. Gomes, M.L. Brandi, F. Bruggeman, R. Mentaverri, D. Riccardi, E. Kallay, Calcium sensing receptor signalling in physiology and cancer, Biochim. Biophys. Acta 1833 (2013) 1732–1744.
[44] A.M. Hofer, K. Lefkimmiatis, Extracellular calcium and cAMP: second messengers as "third messengers"? Physiology Bethesda (Bethesda) 22 (2007) 320–327.
[45] P. Wellendorph, L.D. Johansen, H. Brauner-Osborne, Molecular pharmacology of promiscuous seven transmembrane receptors sensing organic nutrients, Mol. Pharmacol. 76 (2009) 453–465.
[46] I.R. Reid, M.J. Bolland, A. Avenell, A. Grey, Cardiovascular effects of calcium supplementation, Osteoporos. Int. 22 (2011) 1649–1658.
[47] N. Chattopadhyay, A. Mithal, E.M. Brown, The calcium-sensing receptor: a window into the physiology and pathophysiology of mineral ion metabolism, Endocr. Rev. 17 (1996) 289–307.
[48] J.A. Ramirez, W.G. Goodman, J. Gornbein, C. Menezes, L. Moulton, G.V. Segre, I.B. Salusky, Direct in vivo comparison of calcium-regulated parathyroid hormone secretion in normal volunteers and patients with secondary hyperparathyroidism, J. Clin. Endocrinol. Metab. 76 (1993) 1489–1494.
[49] A.D. Conigrave, The Calcium-Sensing Receptor and the Parathyroid: Past, Present, Future, Front. Physiol. 7 (2016) 563.
[50] J.H. Green, C. Booth, R. Bunning, Postprandial metabolic responses to milk enriched with milk calcium are different from responses to milk enriched with calcium carbonate, Asia Pac. J. Clin. Nutr. 12 (2003) 109–119.
[51] G.E. Breitwieser, L. Gama, Calcium-sensing receptor activation induces intracellular calcium oscillations, Am. J. Physiol., Cell Physiol. 280 (2001) C1412–1421.
[52] S.C. Brennan, H.C. Mun, K. Leach, P.W. Kuchel, A. Christopoulos, A.D. Conigrave, Receptor expression modulates calcium-sensing receptor mediated intracellular Ca2+ mobilization, Endocrinology 156 (2015) 1330–1342.
[53] S.J. Quinn, C.P. Ye, R. Diaz, O. Kifor, M. Bai, P. Vassilev, E. Brown, The Ca2+-sensing receptor: a target for polyamines, Am. J. Physiol. 273 (1997) C1315–1323.
[54] E.F. Nemeth, Calcimimetic and calcilytic drugs: just for parathyroid cells? Cell Calcium 35 (2004) 283–289.
[55] C. Zhang, Y. Huang, Y. Jiang, N. Mulpuri, L. Wei, D. Hamelberg, E.M. Brown, J.J. Yang, Identification of an L-phenylalanine binding site enhancing the cooperative responses of the calcium-sensing receptor to calcium, J. Biol. Chem. 289 (2014) 5296–5309.
[56] C. Zhang, T. Zhang, J. Zou, C.L. Miller, R. Gorkhali, J.Y. Yang, A. Schilmiller, S. Wang, K. Huang, E.M. Brown, K.W. Moremen, J. Hu, J.J. Yang, Structural basis for regulation of human calcium-sensing receptor by magnesium ions and an unexpected tryptophan derivative co-agonist, Sci. Adv. 2 (2016) e1600241.
[57] A.D. Conigrave, D.R. Hampson, Broad-spectrum L-amino acid sensing by class 3 G-protein-coupled receptors, Trends Endocrinol. Metab. 17 (2006) 398–407.
[58] A.D. Conigrave, H.C. Mun, H.C. Lok, Aromatic L-amino acids activate the calcium-sensing receptor, J. Nutr. 137 (2007) 1524S–1527S discussion 1548S.
[59] P.J. Marie, The calcium-sensing receptor in bone cells: a potential therapeutic target in osteoporosis, Bone 46 (2010) 571–576.
[60] I.A. Silver, R.J. Murrills, D.J. Etherington, Microelectrode studies on the acid microenvironment beneath adherent macrophages and osteoclasts, Exp. Cell Res. 175 (1988) 266–276.
[61] A.M. Hofer, Another dimension to calcium signaling: a look at extracellular calcium, J. Cell. Sci. 118 (2005) 855–862.
[62] R. Caroppo, A. Gerbino, L. Debellis, O. Kifor, D.I. Soybel, E.M. Brown, A.M. Hofer, S. Curci, Asymmetrical, agonist-induced fluctuations in local extracellular [Ca(2+)] in intact polarized epithelia, EMBO J. 20 (2001) 6316–6326.
[63] E. Perez-Armendariz, I. Atwater, Glucose-evoked changes in [K+] and [Ca2+] in the intercellular spaces of the mouse islet of Langerhans, Adv. Exp. Med. Biol. 211 (1986) 31–51.
[64] M.C. Ashby, A.V. Tepikin, Polarized calcium and calmodulin signaling in secretory epithelia, Physiol. Rev. 82 (2002) 701–734.
[65] O.H. Petersen, Localization and regulation of Ca2+ entry and exit pathways in exocrine gland cells, Cell Calcium 33 (2003) 337–344.
[66] G.E. Breitwieser, Extracellular calcium as an integrator of tissue function, Int. J. Biochem. Cell Biol. 40 (2008) 1467–1480.
[67] R. Caroppo, A. Gerbino, G. Fistetto, M. Colella, L. Debellis, A.M. Hofer, S. Curci, Extracellular calcium acts as a "third messenger" to regulate enzyme and alkaline secretion, J. Cell Biol. 166 (2004) 111–119.
[68] T. Andersson, P.O. Berggren, E. Gylfe, B. Hellman, Amounts and distribution of intracellular magnesium and calcium in pancreatic beta-cells, Acta Physiol. Scand. 114 (1982) 235–241.
[69] G. Nicaise, K. Maggio, S. Thirion, M. Horoyan, E. Keicher, The calcium loading of secretory granules. A possible key event in stimulus-secretion coupling, Biol. Cell 75 (1992) 89–99.

[70] I. Gillot, B. Ciapa, P. Payan, C. Sardet, The calcium content of cortical granules and the loss of calcium from sea urchin eggs at fertilization, Dev. Biol. 146 (1991) 396–405.
[71] J.C. Hutton, E.J. Penn, M. Peshavaria, Low-molecular-weight constituents of isolated insulin-secretory granules. Bivalent cations, adenine nucleotides and inorganic phosphate, Biochem. J. 210 (1983) 297–305.
[72] N.R. Mahapatra, M. Mahata, P.P. Hazra, P.M. McDonough, D.T. O'Connor, S.K. Mahata, A dynamic pool of calcium in catecholamine storage vesicles. Exploration in living cells by a novel vesicle-targeted chromogranin A-aequorin chimeric photoprotein, J. Biol. Chem. 279 (2004) 51107–51121.
[73] Y. El Hiani, A. Ahidouch, M. Roudbaraki, S. Guenin, G. Brule, H. Ouadid-Ahidouch, Calcium-sensing receptor stimulation induces nonselective cation channel activation in breast cancer cells, J. Membr. Biol. 211 (2006) 127–137.
[74] O. Rey, S.H. Young, R. Papazyan, M.S. Shapiro, E. Rozengurt, Requirement of the TRPC1 cation channel in the generation of transient Ca2+ oscillations by the calcium-sensing receptor, J. Biol. Chem. 281 (2006) 38730–38737.
[75] K. Meng, J. Xu, C. Zhang, R. Zhang, H. Yang, C. Liao, J. Jiao, Calcium sensing receptor modulates extracellular calcium entry and proliferation via TRPC3/6 channels in cultured human mesangial cells, PLoS One 9 (2014) e98777.
[76] M. Ranieri, G. Tamma, A. Di Mise, G. Vezzoli, L. Soldati, M. Svelto, G. Valenti, Excessive signal transduction of gain-of-function variants of the calcium-sensing receptor (CaSR) are associated with increased ER to cytosol calcium gradient, PLoS One 8 (2013) e79113.
[77] Z.V. Vysotskaya, C.R. Moss 2nd, C.A. Gilbert, S.A. Gabriel, Q. Gu, Modulation of BK channel activities by calcium-sensing receptor in rat bronchopulmonary sensory neurons, Respir. Physiol. Neurobiol. 203 (2014) 35–44.
[78] D.H. Mc, W.E. Upchurch, Treatment of prostatic calculi, J. Am. Med. Assoc. 157 (1955) 787–788.
[79] R.A. Moore, Morphoplogy of prostatic corpora amylacea and calculi, Archiv Pathology 22 (1936) 22–40.
[80] R.S. Kirby, D. Lowe, M.I. Bultitude, K.E. Shuttleworth, Intra-prostatic urinary reflux: an aetiological factor in abacterial prostatitis, Br. J. Urol. 54 (1982) 729–731.
[81] R. Klimas, B. Bennett, W.A. Gardner Jr., Prostatic calculi: a review, Prostate 7 (1985) 91–96.
[82] Y.X. Kitzing, A. Prando, C. Varol, G.S. Karczmar, F. Maclean, A. Oto, Benign conditions that mimic prostate carcinoma: MR imaging features with histopathologic correlation, Radiographics 36 (2016) 162–175.
[83] I. Parra-Izquierdo, I. Castanos-Mollor, J. Lopez, C. Gomez, J.A. San Roman, M. Sanchez Crespo, C. Garcia-Rodriguez, Calcification induced by type I interferon in human aortic valve interstitial cells is larger in males and blunted by a Janus kinase inhibitor, Arterioscler. Thromb. Vasc. Biol. 38 (2018) 2148–2159.
[84] N.M. Rajamannan, F.J. Evans, E. Aikawa, K.J. Grande-Allen, L.L. Demer, D.D. Heistad, C.A. Simmons, K.S. Masters, P. Mathieu, K.D. O'Brien, F.J. Schoen, D.A. Towler, A.P. Yoganathan, C.M. Otto, Calcific aortic valve disease: not simply a degenerative process: a review and agenda for research from the National Heart and Lung and Blood Institute Aortic Stenosis Working Group. Executive summary: calcific aortic valve disease-2011 update, Circulation 124 (2011) 1783–1791.
[85] K.S. Sfanos, B.A. Wilson, A.M. De Marzo, W.B. Isaacs, Acute inflammatory proteins constitute the organic matrix of prostatic corpora amylacea and calculi in men with prostate cancer, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 3443–3448.
[86] G.C. Prather, D. Skinner, Prostatic corpora amylacea, J. Urol. 76 (1956) 107–114.
[87] J.D. Christian, T.C. Lamm, J.F. Morrow, D.G. Bostwick, Corpora amylacea in adenocarcinoma of the prostate: incidence and histology within needle core biopsies, Mod. Pathol. 18 (2005) 36–39.
[88] N.C. DuPre, R. Flavin, K.S. Sfanos, R.H. Unger, S. To, E. Gazeeva, M. Fiorentino, A.M. De Marzo, J.R. Rider, L.A. Mucci, P. Transdisciplinary Prostate Cancer, corpora amylacea in prostatectomy tissue and associations with molecular, histological, and lifestyle factors, Prostate 78 (2018) 1172–1180.
[89] D.J. Sutor, S.E. Wooley, The crystalline composition of prostatic calculi, Br. J. Urol. 46 (1974) 533–535.
[90] P.F. Engelhardt, S. Seklehner, H. Brustmann, C.R. Riedl, L. Lusuardi, Association between asymptomatic inflammatory prostatitis NIH category IV and prostatic calcification in patients with obstructive benign prostatic hyperplasia, Minerva Urol. Nefrol. 68 (2016) 242–249.
[91] S.H. Kim, K.I. Jung, J.S. Koh, K.O. Min, S.Y. Cho, H.W. Kim, Lower urinary tract symptoms in benign prostatic hyperplasia patients: orchestrated by chronic prostatic inflammation and prostatic calculi? Urol. Int. 90 (2013) 144–149.
[92] V. Ficarra, Is chronic prostatic inflammation a new target in the medical therapy of lower urinary tract symptoms (LUTS) due to benign prostate hyperplasia (BPH)? BJU Int. 112 (2013) 421–422.
[93] S.W. Park, J.K. Nam, S.D. Lee, M.K. Chung, Are prostatic calculi independent predictive factors of lower urinary tract symptoms? Asian J. Androl. 12 (2010) 221–226.
[94] S.E. Lee, J.H. Ku, H.K. Park, C.K. Jeong, S.H. Kim, Prostatic calculi do not influence the level of serum prostate specific antigen in men without clinically detectable prostate cancer or prostatitis, J. Urol. 170 (2003) 745–748.
[95] L.M. Coussens, Z. Werb, Inflammation and cancer, Nature 420 (2002) 860–867.
[96] L. Dell'Atti, A.B. Galosi, C. Ippolito, Prostatic calculi detected in peripheral zone of the gland during a transrectal ultrasound biopsy can be significant predictors of prostate cancer, Arch. Ital. Urol. Androl. 88 (2016) 304–307.
[97] A.M. De Marzo, E.A. Platz, S. Sutcliffe, J. Xu, H. Gronberg, C.G. Drake, Y. Nakai, W.B. Isaacs, W.G. Nelson, Inflammation in prostate carcinogenesis, Nat. Rev. Cancer 7 (2007) 256–269.
[98] L. Canaff, G.N. Hendy, Calcium-sensing receptor gene transcription is up-regulated by the proinflammatory cytokine, interleukin-1beta. Role of the NF-kappaB PATHWAY and kappaB elements, J. Biol. Chem. 280 (2005) 14177–14188.
[99] L. Canaff, X. Zhou, G.N. Hendy, The proinflammatory cytokine, interleukin-6, up-regulates calcium-sensing receptor gene transcription via Stat1/3 and Sp1/3, J. Biol. Chem. 283 (2008) 13586–13600.
[100] G.N. Hendy, L. Canaff, Calcium-sensing receptor, proinflammatory cytokines and calcium homeostasis, Semin. Cell Dev. Biol. 49 (2016) 37–43.
[101] J. Canton, D. Schlam, C. Breuer, M. Gutschow, M. Glogauer, S. Grinstein, Calcium-sensing receptors signal constitutive macropinocytosis and facilitate the uptake of NOD2 ligands in macrophages, Nat. Commun. 7 (2016) 11284.
[102] T. Yamaguchi, O. Kifor, N. Chattopadhyay, M. Bai, E.M. Brown, Extracellular calcium (Ca2+o)-sensing receptor in a mouse monocyte-macrophage cell line (J774): potential mediator of the actions of Ca2+o on the function of J774 cells, J. Bone Miner. Res. 13 (1998) 1390–1397.
[103] T. Yamaguchi, I. Olozak, N. Chattopadhyay, R.R. Butters, O. Kifor, D.T. Scadden, E.M. Brown, Expression of extracellular calcium (Ca2+o)-sensing receptor in human peripheral blood monocytes, Biochem. Biophys. Res. Commun. 246 (1998) 501–506.
[104] P.L. Yarova, A.L. Stewart, V. Sathish, R.D. Britt Jr., M.A. Thompson, A.P. P Lowe, M. Freeman, B. Aravamudan, H. Kita, S.C. Brennan, M. Schepelmann, T. Davies, S. Yung, Z. Cholisoh, E.J. Kidd, W.R. Ford, K.J. Broadley, K. Rietdorf, W. Chang, M.E. Bin Khayat, D.T. Ward, C.J. Corrigan, T.W. JP, P.J. Kemp, C.M. Pabelick, Y.S. Prakash, D. Riccardi, Calcium-sensing receptor antagonists abrogate airway hyperresponsiveness and inflammation in allergic asthma, Sci. Transl. Med. 7 (2015) 284ra260.
[105] D. Wallach, T.B. Kang, C.P. Dillon, D.R. Green, Programmed necrosis in inflammation: toward identification of the effector molecules, Science 352 (2016) aaf2154.
[106] R.S. Kaslick, A.I. Chasens, I.D. Mandel, D. Weinstein, R. Waldman, T. Pluhar, R. Lazzara, Quantitative analysis of sodium, potassium and calcium in gingival fluid from gingiva in varying degrees of inflammation, J. Periodontol. 41 (1970) 93–97.
[107] G.N. Tzimas, M. Afshar, A. Emadali, E. Chevet, H. Vali, P.P. Metrakos, Correlation of cell necrosis and tissue calcification with ischemia/reperfusion injury after liver transplantation, Transplant. Proc. 36 (2004) 1766–1768.
[108] M. Rossol, M. Pierer, N. Raulien, D. Quandt, U. Meusch, K. Rothe, K. Schubert, T. Schoneberg, M. Schaefer, U. Krugel, S. Smajilovic, H. Brauner-Osborne, C. Baerwald, U. Wagner, Extracellular Ca2+ is a danger signal activating the NLRP3 inflammasome through G protein-coupled calcium sensing receptors, Nat. Commun. 3 (2012) 1329.
[109] J. Zeng, Y. Pan, B. Cui, T. Zhai, S. Gao, Q. Zhao, Y. Sun, Calciumsensing receptors in human peripheral T lymphocytes and AMI: cause and effect, Int. J. Mol. Med. 42 (2018) 3437–3446.
[110] J.W. Lee, H.A. Park, O.K. Kwon, J.W. Park, G. Lee, H.J. Lee, S.J. Lee, S.R. Oh, K.S. Ahn, NPS 2143, a selective calcium-sensing receptor antagonist inhibits lipopolysaccharide-induced pulmonary inflammation, Mol. Immunol. 90 (2017) 150–157.
[111] A.D. Luster, Chemokines–chemotactic cytokines that mediate inflammation, N. Engl. J. Med. 338 (1998) 436–445.
[112] I.T. Olszak, M.C. Poznansky, R.H. Evans, D. Olson, C. Kos, M.R. Pollak, E.M. Brown, D.T. Scadden, Extracellular calcium elicits a chemokinetic response from monocytes in vitro and in vivo, J. Clin. Invest. 105 (2000) 1299–1305.
[113] T. Sugimoto, M. Kanatani, J. Kano, H. Kaji, T. Tsukamoto, T. Yamaguchi, M. Fukase, K. Chihara, Effects of high calcium concentration on the functions and interactions of osteoblastic cells and monocytes and on the formation of osteoclast-like cells, J. Bone Miner. Res. 8 (1993) 1445–1452.
[114] Q. Wu, H. Shao, E.D. Darwin, J. Li, J. Li, B. Yang, K.A. Webster, H. Yu, Extracellular calcium increases CXCR4 expression on bone marrow-derived cells and enhances pro-angiogenesis therapy, J. Cell. Mol. Med. 13 (2009) 3764–3773.
[115] Q. Liu, M.R. Russell, K. Shahriari, D.L. Jernigan, M.I. Lioni, F.U. Garcia, A. Fatatis, Interleukin-1beta promotes skeletal colonization and progression of metastatic prostate cancer cells with neuroendocrine features, Cancer Res. 73 (2013) 3297–3305.
[116] J. Massague, TGFbeta in Cancer, Cell 134 (2008) 215–230.
[117] M. Royuela, G. Rodriguez-Berriguete, B. Fraile, R. Paniagua, TNF-alpha/IL-1/NF-kappaB transduction pathway in human cancer prostate, Histol. Histopathol. 23 (2008) 1279–1290.
[118] A. Saha, S. Ahn, J. Blando, F. Su, M.G. Kolonin, J. DiGiovanni, Proinflammatory CXCL12-CXCR4/CXCR7 signaling Axis Drives myc-induced prostate Cancer in obese mice, Cancer Res. 77 (2017) 5158–5168.
[119] J. Pencik, R. Wiebringhaus, M. Susani, Z. Culig, L. Kenner, IL-6/STAT3/ARF: the guardians of senescence, cancer progression and metastasis in prostate cancer, Swiss Med. 145 (2015) w14215.
[120] I.S. Fetahu, D.M. Hummel, T. Manhardt, A. Aggarwal, S. Baumgartner-Parzer, E. Kallay, Regulation of the calcium-sensing receptor expression by 1,25-dihydroxyvitamin D3, interleukin-6, and tumor necrosis factor alpha in colon cancer cells, J. Steroid Biochem. Mol. Biol. 144 (Pt A) (2014) 228–231.
[121] G.N. Hendy, L. Canaff, D.E. Cole, The CASR gene: alternative splicing and transcriptional control, and calcium-sensing receptor (CaSR) protein: structure and ligand binding sites, Best Pract. Res. Clin. Endocrinol. Metab. 27 (2013) 285–301.
[122] A. Aggarwal, M. Prinz-Wohlgenannt, S. Tennakoon, J. Hobaus, C. Boudot, R. Mentaverri, E.M. Brown, S. Baumgartner-Parzer, E. Kallay, The calcium-sensing receptor: a promising target for prevention of colorectal cancer, Biochim. Biophys. Acta 1853 (2015) 2158–2167.
[123] L. Iamartino, T. Elajnaf, E. Kallay, M. Schepelmann, Calcium-sensing receptor in colorectal inflammation and cancer: current insights and future perspectives, World J. Gastroenterol. 24 (2018) 4119–4131.
[124] J.L. Owen, S.X. Cheng, Y. Ge, B. Sahay, M. Mohamadzadeh, The role of the

calcium-sensing receptor in gastrointestinal inflammation, Semin. Cell Dev. Biol. 49 (2016) 44–51.
[125] T. Capiod, N. Barry Delongchamps, N. Pigat, J.C. Souberbielle, V. Goffin, Do dietary calcium and vitamin D matter in men with prostate cancer? Nat. Rev. Urol. 15 (2018) 453–461.
[126] A.C. Lassemillante, S.A. Doi, J.D. Hooper, J.B. Prins, O.R. Wright, Prevalence of osteoporosis in prostate cancer survivors II: a meta-analysis of men not on androgen deprivation therapy, Endocrine 50 (2015) 344–354.
[127] A.C. Lassemillante, S.A. Doi, J.D. Hooper, J.B. Prins, O.R. Wright, Prevalence of osteoporosis in prostate cancer survivors: a meta-analysis, Endocrine 45 (2014) 370–381.
[128] A. Wang, Z. Obertova, C. Brown, N. Karunasinghe, K. Bishop, L. Ferguson, R. Lawrenson, Risk of fracture in men with prostate cancer on androgen deprivation therapy: a population-based cohort study in New Zealand, BMC Cancer 15 (2015) 837.
[129] M. Balasar, N. Poyraz, Y.E. Goger, Y. Unal, M.M. Piskin, The incidence and location of prostatic calculi on noncontrast computed tomography images in patients with renal calculi, Urolithiasis 43 (2015) 375–378.