

Hormonal Regulation of Calcium Signaling in Endocrine Cancers

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ABSTRACT

The calcium ion (Ca^{2+}) plays a fundamental role in a number of physiological functions including bone formation, muscle contraction, secretion, enzyme cofactor, stabilization of membrane potentials, blood coagulation, etc. Calcium is homeostatically regulated by hormones that determines calcium balance within the body. The hormones PTH, 1,25-(OH) $_2$ D $_3$ and calcitonin are altered in endocrine cancers which are in turn regulated by calcium. The main focus of this review is how hormones can regulate calcium homeostasis in endocrine cancers.

Keywords: Endocrine cancers, Calcium homeostasis, Hormones PTH, 1,25-(OH) $_2$ D $_3$ and calcitonin.

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INTRODUCTION

Importance of Calcium in Biological System

Calcium (Ca^{2+}) is a useful ubiquitous ion in biology. It has an oxidation state of +2 which gives greater strength in interacting with anionic complexes compared to sodium, potassium or other monocations. Ca^{2+} is the fifth most abundant element in the body but 99% of it is sequestered in bone. Among the roles for Ca^{2+} , a major role is acting as a secondary signal to convert signals from the extracellular environment into specific intracellular responses. Also, Ca^{2+} is involved in the rapid depolarization of cells in neurons and muscle cells. These actions need to be tightly controlled. Therefore, Ca^{2+} is kept at low levels in the cell's cytosol

until needed. Ca^{2+} is stored in the endoplasmic reticulum (ER) and mitochondria for quick release that initiates Ca^{2+} dependent actions.¹ Calcium ions play vital roles in a variety of important physiological functions of the cell, including control of cell cycle progression, cell differentiation, mitosis, apoptosis, ETosis, cell mobility, macrophage activation, chromatin packaging and modifications, protein folding and control of potassium and calcium channels. Often Ca^{2+} is serving as a secondary messenger.² Calcium interacts with cyclic AMP, NO, phosphatidylinositol-3-OH kinase, feedback interactions and mitogen-activated protein kinase in different signaling pathways.

Major Hormones which take Part in Calcium Homeostasis

In endocrine cancers, the major hormones which are altered mainly include PTH, 1,25-(OH) $_2$ D $_3$ and calcitonin. The extracellular fluid (or plasma) calcium concentration is tightly controlled by a complex homeostatic mechanism involving fluxes of calcium between the extracellular fluid (ECF) and the kidney, bone, and gut. These fluxes are carefully regulated by three major hormones: parathyroid hormone (PTH), calcitonin, and 1,25-dihydroxyvitamin D[1,25(OH) $_2$ D $_3$]. Important cellular functions are dependent on the maintenance of the extracellular calcium concentration within a narrow range.³ Since, these enzymes play a major part in the calcium homeostasis, it is important to give a crosstalk on the alterations in calcium homeostasis of these hormones due to occurrence endocrine cancers.

Role of Calcium through Hormonal Regulation in Different Endocrine Cancers

The major endocrine cancers in which the calcium signaling is altered by the hormonal regulation are prostate cancer, parathyroid cancer and breast cancer. Cancer that forms in tissues of the prostate (a gland in the male reproductive system found below the bladder and in front of the rectum). Prostate cancer usually occurs in older men. Parathyroid cancer is a rare cancer that forms in tissues of one or more of the parathyroid glands (four pea-sized glands in the neck that make parathyroid hormone, which helps the body store and use calcium). The most common type of breast cancer is ductal carcinoma, which begins in the lining of the milk ducts

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(thin tubes that carry milk from the lobules of the breast to the nipple). Another type of breast cancer is lobular carcinoma, which begins in the lobules (milk glands) of the breast.

In prostate cancer, PTH plays a mitogen role through alterations in calcium homeostasis. There are several studies on breast cancer and prostate cancer with its relation to PTH and 1,25(OH)₂D. In most of other endocrine cancers the changes in calcium homeostasis with respect to PTH, 1,25(OH)₂D and calcitonin is well studied. The main focus of this review is how hormones can regulate calcium homeostasis in endocrine cancers.

Role of PTH-dependent Calcium Homeostasis in Different Endocrine Cancer

In 1962, Ludwig observed that metastases from prostate cancer cause increased serum levels of PTH. However, the epidemiologic and clinical implications of that observation have been little appreciated, PTH is now understood to be a mitogen for prostate cancer cells.⁴ In case of prostate cancer serum, PTH levels are very high and it promotes the progression of prostate cancer in bones. There are several studies on the role of PTH on CaR modulations in Ca²⁺ homeostasis. Some studies show increased bone turnover produced by PTH helps to increase prostate cancer metastasis to bone⁵ and the bone re-absorption induced by the dietary deficiency of calcium leads to the bony metastasis. The PTHrP is believed to be a mediator for 70% of breast and prostate cancer: (1) higher PTHrP expression in prostatic dysplasia (prostate intraepithelial neoplasia) than in normal prostate epithelium and (2) higher PTHrP expression in prostate carcinoma than in benign hyperplasia suggests that there are promalignant or proliferative effects of PTHrP that participate in the pathophysiology of prostate cancer.⁶⁻⁸

In normal breast cells, similarly to PTH release, the secretion of PTHrP is inhibited by increase in the Ca²⁺ concentration. Interestingly, in breast and prostate cancer cells, PTHrP release is augmented, rather than inhibited, by activation of the CaR.^{9,10} CaR expressions are high in a lactating mother and it is due to the presence of Ca²⁺ in high levels (200 mg Ca²⁺ daily in lactating mothers). During lactation breast participates in Ca²⁺ homeostasis by monitoring Ca²⁺ concentrations through the CaR and adjusting PTHrP secretion and milk production accordingly. Elevated PTHrP release increases skeletal Ca²⁺ secretion and renal Ca²⁺ retention. The resultant increased blood Ca²⁺, by activating the CaR, promotes transport of Ca²⁺ from blood to milk.¹¹ There are some studies supporting dietary calcium decreases breast cancer risk. Zheng et al¹² found out that the dietary Ca²⁺ will elevate the PTH levels in serum and it enhances bone turnover and leads to breast cancer in bones. They showed that treatment of osteoprotegerin, a naturally occurring inhibitor

of osteoclast formation and activity and dietary intake of calcium in mice reduces the risk of breast cancer. Recently, it has been revealed that the change between inhibition and stimulation of PTHrP release by Ca²⁺ occurs as a result of a switch in G protein activation by the cancerous cells. Thus, in normal mammary cells, it was shown that the CaR couples to G_i, leading to inhibition of cAMP formation and, consequently, PTHrP release, whereas in cancerous cells, (MCF7 and Comma-D cells), the CaR was shown to activate G_s, thereby promoting PTHrP release.¹³

In parathyroid cells, high Ca²⁺ levels activate the CaR, leading to inhibition of PTH secretion, PTH gene expression, and parathyroid cell proliferation.¹⁴ It leads to the regulation of PTH synthesis and involve modulation of intracellular cAMP and Ca²⁺ levels as well as activation of ERK1/2 and other kinases.¹⁵⁻¹⁷ In parathyroid adenomas, the Ca²⁺ inhibits PTH secretion and it results in hyperparathyroidism and abnormal control of Ca²⁺ homeostasis.¹⁸

1,25(OH)₂D

1,25(OH)₂D is very important hormone because of its protective role and is mediated by the calcium homeostasis. The major mechanism for the protective effect of vitamin D is believed to be the prostatic conversion of the vitamin D prohormone, 25-hydroxyvitamin D, into the active hormone, 1,25(OH)₂D, which binds to the prostatic receptor for 1,25(OH)₂D (the vitamin D receptor) and exerts prodifferentiating, antiproliferative, and antimetastatic effects on prostatic cells.¹⁹

In breast cancer cells, 1,25(OH)₂D₃ activates the voltage-dependent and voltage-insensitive Ca²⁺ entry and triggers Ca²⁺ release from the ER stores through the inositol 1,4,5-trisphosphate and ryanodine receptors. 1,25(OH)₂D₃ induces apoptosis in breast cancer cells and this apoptosis induced by 1,25(OH)₂D₃ in these cells depends on Ca²⁺ signaling.²⁰⁻²² 1,25(OH)₂D₃ triggers apoptosis in breast cancer cells by causing an increase in Ca²⁺ entry through VICC and depletion of the ER Ca²⁺ stores. The resulting elevated (Ca²⁺) appears to be sufficient to elicit apoptosis.²³

In parathyroid adenomas Ca²⁺ levels and 1,25(OH)₂D₃ negatively regulate PTH synthesis and parathyroid proliferation through the activation of vitamin D receptor (VDR).

Calcitonin

Calcitonin is a hormone known to participate in calcium and phosphorus metabolism. In mammals, the major source of calcitonin is from the parafollicular or C cells in the thyroid gland. Calcitonin regulates the blood calcium levels. Calcitonin is used as a tumor marker for medullary thyroid cancers. Increase in ionized calcium enhances release of



calcitonin. Clinical observations support the notion that calcitonin has little chronic effect, because neither calcitonin-deficient patients (athyroid) nor patients with medullary thyroid cancer and excess calcitonin production experience alterations in calcium homeostasis. The calcitonin receptor has been cloned²⁴ and is structurally similar to the PTH receptor in that it also has seven transmembrane domains. Calcitonin is metabolized in minutes in the circulation, predominantly in the kidney. The calcitonin receptor is related structurally to the PTH/PTH-rP and secretin receptors. The calcitonin receptor exists in several isoforms, and its expression seems to be influenced by ambient concentrations of calcitonin itself. This may be the reason for down-regulation of the receptor and the escape phenomenon that occurs in the continued presence of calcitonin.²⁵

Recent studies have revealed that pituitary, testicular, pancreatic, and brain cancers may be influenced by the CaR. This receptor is expressed in the human pituitary, in both normal cells and in pituitary adenomas,²⁶ as well as in normal and malignant mouse and rat pituitary cells.^{27,28}

DISCUSSION

Calcium (Ca^{2+}) is a ubiquitous intracellular signal responsible for controlling numerous cellular processes. Ca^{2+} signaling is used throughout the life history of an organism. Life begins with a surge of Ca^{2+} at fertilization and this versatile system is then used repeatedly to control many processes during development and in adult life. Ca^{2+} signaling toolkit emerges from the use of an extensive molecular repertoire of signaling components which makes it versatile.

One of the fascinating aspects of Ca^{2+} is that it plays a direct role in controlling the transcriptional events that select out the types of Ca^{2+} signaling systems that are expressed in specific cell types. Such a role for Ca^{2+} in differential gene transcription is still in its infancy but is rapidly developing into an active area of research.

Ca^{2+} is needed at several steps of the cell cycle, such as early G_1 , at the G_1/S , and G_2/M transitions. Ca^{2+} -mediated signaling pathways have also been shown to play important roles in carcinogenesis, such as transformation of normal cells to cancerous cells, tumor formation and growth, invasion, angiogenesis and metastasis. The transformation of a normal cell into a malignant derivative is associated with a major rearrangement of Ca^{2+} pumps, Na/Ca exchangers and Ca^{2+} channels, which leads to enhanced proliferation and invasion under compromised/impaired ability to die.

Parathyroid hormone is the major hormone which plays a role in many endocrine cancers through altering the calcium signaling. PTH mediated cancers are regulated by the calcium homeostasis at times. It is very important to go deep into the molecular mechanism of PTH hormone

actions and Ca^{2+} homeostasis, because it can help in the drug development and cancer treatment. The protective nature of 1,25(OH)2D3 is also very important in the treatment and curing of endocrine cancers. 1,25(OH)2D3 acts through the regulation of PTH and regulates calcium levels in blood. It has also got a major role in apoptosis in breast cancer. Calcitonin regulates the blood Ca^{2+} levels. In conclusion better management of the hormonal level can probably become a treatment for the endocrine cancers.

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