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Role of Ca^{2+}/cAMP signalling in cancer with concurrent hypertension

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ABSTRACT: Cancer and hypertension have severely burdened the medical health system. Cumulative clinical findings suggest an association between hypertension and cancer development, although the underlying mechanisms remain unclear. Notably, a functional relationship between inflammation, hypertension, and cancer could explain the clinical link between these diseases. Ca^{2+} homeostasis dysregulation seems to play a key role in these diseases. Ca^{2+} signalling positively responds to inflammation. Furthermore, a core regulator of Ca^{2+} metabolism, cAMP, has been shown to indirectly regulate pro- and anti-inflammatory responses. In this review, by introducing the innate biological nano confinements and its potential function, we discussed the role of Ca^{2+}/cAMP signalling in inflammation, hypertension, and cancer to understand the interaction between Ca^{2+}/cAMP signalling pathways and these diseases and finally improve therapeutic strategies.

KEYWORDS: Ca^{2+}/cAMP signalling, cancer with concurrent hypertension, calcium homeostasis, calcium channel blocker, inflammation

INTRODUCTION

Cancer and hypertension pose huge social and economic burdens to human society. Hypertension is assumed to be closely associated with high incidence of cancer [1]. Atrial natriuretic peptide (ANP) is a hormone secreted by the heart tissue and plays an important role in lateral spread of tumour transforming into colorectal cancer. The ANP not only regulated the Wnt/β-catenin signalling pathway but also participated in the hypertension-induced atrial dysfunction [2]. Interestingly, a functional relationship between inflammation, hypertension, and cancer might explain the link between these diseases [3, 4]. It was speculated that cancers resulted from chronic inflammation, whereby the inflammatory environment with overexpressed growth factors, activated stroma, and unstable DNA damage initiate cancer development [5–7].

Immune responses triggered by immunogenicity factors, such as specific immune cell types, cytokines, toll-like receptors, and components of inflammasomes, have a significant impact on the incidence of hypertension. Therefore, immunoregulation is considered a promising target for hypertension management [4]. Ca^{2+} and cAMP signalling regulate diverse functions and their over-activation is associated with many diseases. The Ca^{2+} and cAMP signalling pathways interact on numerous levels. They regulate the activity of each other to determine the intensity of their response and cooperate to determine the physiological response by integration of their stimulatory/inhibitory activities. Mutual regulation of the Ca^{2+} and cAMP signals is referred to as crosstalk, while integration of their effects can result in an additive or synergistic physiological response. An increased expression of cAMP, the major regulator of Ca^{2+} homeostasis, has been shown to exhibit antitumor effects [8]. Moreover, cAMP can affect pro- and anti-inflammatory responses; for instance, an increasing intracellular cAMP level reduces pro-inflammatory mediators, promoting an anti-inflammatory effect [9–12]. The cAMP signal is determined by the balance between the activities of adenylyl cyclases (ACs) and the phosphodiesterases (PDEs). Intracellular Ca^{2+} homeostasis plays a vital role in the pathogenesis of inflammation, hypertension and cancer, that is, Ca^{2+} dysregulations was critically associated with the development and progression of cancer [13, 14]. Therefore, maintaining a balance of intracellular Ca^{2+} has high potential in controlling cancer progression and hypertension [15–19]. In addition, there is much evidence indicating a strong relationship between Ca^{2+} signalling and inflammatory responses [20, 21].

Several Ca^{2+} channel blockers (CCBs) have been successfully administered in cancer therapy, while they have been previously used to control hypertension empirically, a possible mechanism of action could rest in the fact that these pharmaceuticals may restore the

dysregulation of Ca^{2+} homeostasis [22–26]. Their role in maintaining Ca^{2+} homeostasis might be an underlying mechanism for their use in cancer treatment [27–32]. Additionally, we have proposed that substances (particularly small molecules and ions associated with signal transduction, such as Ca^{2+}) existing both intra- and intercellularly are orderly distributed in a time and spatial manner under the control of our newly conceptualized innate biological nanoconfinements (iBNCs) [33]. This finding will enable cancer precision therapy [34] with a targeted drug delivery system at the nano dimension [35].

In this review, we discussed the association of Ca^{2+}/cAMP signalling in inflammation, hypertension, and cancer to understand the link between these three conditions. This will aid in improving therapeutic strategies.

CANCER AND HYPERTENSION

Basic mechanisms

Cancer has long been ranked as the second most lethal disease [3]. The design and exploration of safer and more efficacious drugs have become the primary strategies for cancer therapy. Inflammation has been recognized to influence cancer development and stimulate several stages of tumorigenesis. Cancer and inflammatory cells are involved in a well-orchestrated reciprocal interaction that forms an inflammatory tumour microenvironment. The cells within this microenvironment are highly plastic and continuously shift their phenotypic characteristics. Therefore, elucidating the cellular mechanisms underlying tumour-promoting inflammation is essential for the development of anticancer therapies [3, 36, 37].

The consequences or comorbidities of hypertension, such as inflammation, dysregulated immunity, and cardiovascular diseases, make it a leading cause of mortality [1, 4, 38]. Based on the speculation that elevation in blood pressure result from inflammation and immune activation, patients with pre-hypertension should be more cautious to avoid a severe hypertensive state [4, 38]. However, this speculation requires further validation so that the possible effect of immunotherapy on malignant hypertension, especially in patients with concurrent cancer can be investigated.

Clinical evidence

Previous studies have shown an observational association between hypertension and cancer development. However, the causality and mechanisms have not been fully uncovered [1, 39–42]. An international longitudinal cohort study examining the association between metabolic syndrome and cancer among populations from Norway, Austria, and Sweden from 1972 to 2005 showed a significantly increased risk of developing cancer in several organs, with a cancer risk increase per 10-mmHg increment. Furthermore, these clinical findings indicated that this cancer risk association was common regardless of some variables, such as sex [1, 39]. However, the older population was at more risk of cancer [1, 39].

A meta-analysis comprising 18 studies revealed that the incidence of renal cell carcinoma was 1.6 times higher among patients with hypertension than those with normal blood pressure. This result suggests that hypertension is a risk for renal cell carcinoma occurring [40, 41]. In another analysis based on 85 prospective studies, drawn from 148 publications focusing on any type of cancer, revealed that hypertension was closely associated with a high risk of kidney, colorectal, and breast cancer [42].

Several studies have demonstrated that CCBs exert promising anticancer effects by reducing the intracellular influx of Ca^{2+} [13, 22–26, 43–47]. However, it remains unclear how this anti-hypertension Ca^{2+}/cAMP signalling exerts its anticancer effect.

ROLE OF Ca^{2+}/CAMP SIGNALLING IN HYPERTENSION AND CANCER CROSS-LINK

Ca^{2+}/cAMP signalling is a vital biochemical process that exists in almost all mammals. The Ca^{2+}/cAMP signalling pathway is regulated by various enzymes, molecules, and is affected by other signalling pathways, depending on the specific demands and cellular heterogeneity, including ACs, PDEs, and Ca^{2+} channel proteins [20, 48–55] (Fig. 1). The endoplasmic reticulum (ER) systems and Ca^{2+} channel protein families play an important role in the Ca^{2+}/cAMP pathway [20, 48–55]. Finally, the endothelial system which represents the largest barrier in the body, ensures Ca^{2+} homeostasis [56, 57]. Previous studies have reported that Ca^{2+}/cAMP signalling can modulate the behaviour of neurons and neuroendocrine cells through the release of neurotransmitters [20, 48, 51], and may even impact neuronal death [58–60] and cancer development [27, 61].

The sympathetic hyperactivity leads to elevated blood pressure owing to a high level of serum catecholamines, as demonstrated by experiments in a spontaneously hypertensive rat model. Intracellular Ca^{2+} concentration is modulated by the endoplasmic reticulum, which in turn activates catecholamine release [17–19]. Additionally, we have previously demonstrated that urocortin II administration can effectively regulate the calcification of vessels to restore blood pressure [62–65].

Among the Ca^{2+} channel protein families, the L-type channel protein is closely related to cancer progression, whereby an increase in its expression level increases the risk for cancer progression, particularly for colon and oesophageal cancers [27, 61]. Concordantly, a high expression level of the L-type Ca^{2+} channel protein has been shown in pan-cancer samples via microarray assays. Moreover, similar results were

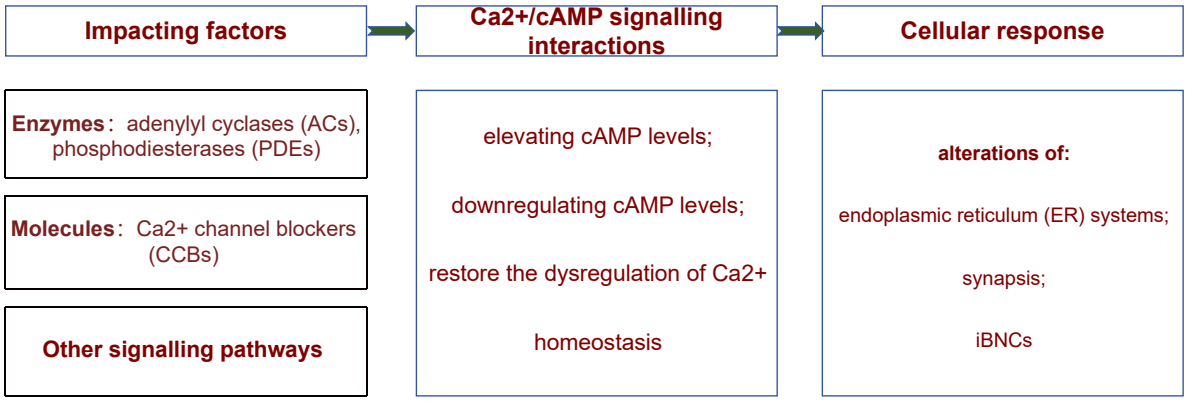

Fig. 1 Regulation on Ca^{2+}/cAMP signalling pathways and cellular responses. Briefly, the reduction of Ca^{2+} influx through L-type Ca^{2+} channels, produced by CCBs (calcium channel blockers) and the innate biological nanoconfinements (iBNCs) has the potential to restore the unexpected cellular response, such as endoplasmic reticulum disruption or iBNCs collapse.

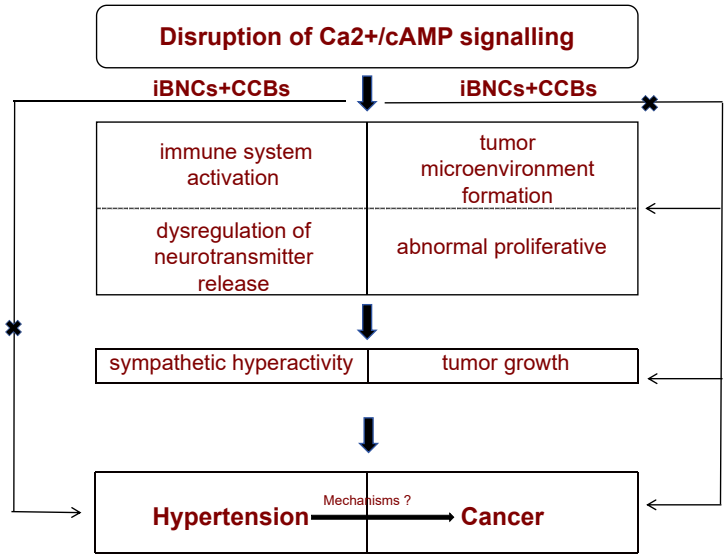

Fig. 2 Correlation between Ca^{2+} dysregulation, cancer, and hypertension. Disruption of Ca^{2+}/cAMP will influence the sympathetic activity and cellular microenvironment, then possibly initiated the hypertension or cancer. This pathway will be inhibited or restored under the invention of iBNCs and CCBs synergistically.

found for the detection of L-type CCBs [22–26].

The elevated expression of cAMP may be partially attributed to the induction of ACs activators, which promote anticancer effects [27, 66–68]. However, the comprehensive mechanisms underlying this phenomenon are unclear. Nevertheless, we may obtain valuable clues from the following findings: activated cAMP signalling may promote further cAMP synthesis, hinder degradation of cAMP, and activate cAMP receptors [68–76]. In a basic cell biology study, an analogue of cAMP, 8-Cl-cAMP, was demonstrated to have significant antiproliferative effects, whereby its underlying mechanisms were speculated to be growth arrest or proapoptotic effects [69]. Other studies have identified significant alterations in the expression levels of cAMP signalling in haematological malignancies compared to normal hematopoietic cells [74–76].

Based on these findings, we speculate that because the alteration of L-type Ca^{2+} channel proteins induces a decrease in Ca^{2+} influx [20, 48–55, 58–61] and the cAMP-stimulating compounds induce CCBs effects, targeting the Ca^{2+}/cAMP signalling pathway may be a novel anti-cancer therapy. Furthermore, we speculate that dysregulation of Ca^{2+} homeostasis might be the underlying mechanism of cancer development [27, 61]. Notably, changes in Ca^{2+} concentration caused by other factors, affect the cAMP signalling pathway, resulting in a risk of cancer development. For instance, a high increase in Ca^{2+} concentration through the inhibition of ACs isoforms [59, 68] and

anticancer effects have been demonstrated in several studies whereby the expression level of cAMP signalling is upregulated [8, 27, 68, 69]. In contrast, some studies have shown that a high, Ca^{2+} concentration can inhibit cAMP signalling pathways, reducing the anticancer effect. Consequently, a lower influx of Ca^{2+} through CCBs can improve the anticancer effects [22–26]. Furthermore, eukaryotic elongation factor 2 kinase (eEF-2K) was also known as calcium/calmodulin (Ca^{2+}/CaM)-dependent protein kinase III and initially identified as a Ca^{2+}/CaM-dependent protein kinase (CaM-PK) that phosphorylates an abundant substrate of 100 kDa in mammalian cells. It is critical for eEF-2K that the precise coordinate of these signals to appropriately regulate protein translation rates. eEF-2K have been reported owning different functions in many kinds of cancer, due to its overexpress and overactivation in cancer cells [77].

In the hypertension research field, strong evidence have been found between the dysregulation of Ca^{2+} signalling and a high blood pressure level owing to an abnormal catecholamine release [17–19]. This Ca^{2+}/cAMP signalling disruption is shown in Fig. 2. Briefly, patients with hypertension presented a feature of imbalance of Ca^{2+} homeostasis, who will expose to a higher risk of malignant cellular response, such as ER disruption and dis-controllable of iBNCs, eventually resulting in cancer development. Mutually, cancer patients often had an abnormal tumor microenvironment and the Ca^{2+}/cAMP signalling pathway. These two sides are possibly interacted and exacerbated the outcomes.

CONCLUSION

Ca^{2+} and Ca^{2+}/cAMP signalling play vital roles in both the process of hypertension and cancer development. The targeted molecules, CCBs, have potential anticancer effects in addition to their antihypertensive function. The mechanisms by which Ca^{2+}/cAMP signalling and CCBs, along with the extraordinary function of iBNCs, synergistically modulate hypertension and cancer development need to be further investigated in large-scale clinical cohort studies.

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REFERENCES

1. Stocks T, Van Hemelrijck M, Manjer J, Bjørge T, Ulmer H, Hallmans G, Lindkvist B, Selmer R, et al (2012) Blood pressure and risk of cancer incidence and mortality in the metabolic syndrome and cancer project. *Hypertension* **59**, 802–810.
2. Zhang XY, Wang Q, Jia CY, Li D, Lv ZW, Yang JS (2022) Role of atrial natriuretic peptide receptor in inhibition of laterally spreading tumors via Wnt/β-catenin signaling. *Arch Med Sci Atheroscler Dis* **7**, e104–e108.
3. Coussens LM, Werb Z (2002) Inflammation and cancer. *Nature* **420**, 860–867.
4. De Miguel C, Rudemiller NP, Abais JM, Mattson DL (2015) Inflammation and hypertension: new understandings and potential therapeutic targets. *Curr Hypertens Rep* **17**, 507.
5. Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? *Lancet* **357**, 539–545.
6. Yang JS, Li WJ, Jin XD, Jing XG, GuoCL, Wei W, Gao QX (2006) Survival and initial chromatid breakage in normal and tumour cells exposed *in vitro* to gamma rays and carbon ions at the HIRFL. *Br J Radiol* **79**, 518–521.
7. Jia CY, Wang Q, Yao XH, Yang JS (2021) The role of DNA damage induced by low/high dose ionizing radiation in cell carcinogenesis. *Explor Res Hypothesis Med* **6**, 177–184.
8. Murray F, Insel PA (2013) Targeting cAMP in chronic lymphocytic leukemia: a pathway-dependent approach for the treatment of leukemia and lymphoma. *Expert Opin Ther Targets* **17**, 937–949.
9. Raker VK, Becker C, Steinbrink K (2016) The cAMP pathway as therapeutic target in autoimmune and inflammatory diseases. *Front Immunol* **7**, 123.
10. Moore AR, Willoughby DA (1995) The role of cAMP regulation in controlling inflammation. *Clin Exp Immunol* **101**, 387–389.
11. Erdogan S, Aslantas O, Celik S, Atik E (2008) The effects of increased cAMP content on inflammation, oxidative stress and PDE4 transcripts during Brucella melitensis infection. *Res Vet Sci* **84**, 18–25.
12. Tavares LP, Negreiros-Lima GL, Lima KM, E Silva PMR, Pinho V, Teixeira MM, Sousa LP (2020) Blame the signaling: role of cAMP for the resolution of inflammation. *Pharmacol Res* **159**, 105030.
13. Gomez-Ospina N, Tsuruta F, Barreto-Chang O, Hu L, Dolmetsch R (2006) The C terminus of the L-type voltage-gated calcium channel Ca(V)1.2 encodes a transcription factor. *Cell* **127**, 591–606.
14. Duan Y, Wang T, Wu SS, Liu D, Zhao J, Liu B (2023) The role of the phosphatidylinositol 3-kinase/protein kinase B signaling pathway in the pulmonary vascular remodeling of pulmonary arterial hypertension in rats. *ScienceAsia* **49**, 56–62.
15. Okuno K, Xu C, Pascual-Sabater S, Tokunaga M, Takayama T, Han H, Fillat C, Kinugasa Y, et al (2023) Andrographis reverses gemcitabine resistance through regulation of ERBB3 and calcium signaling pathway in pancreatic ductal adenocarcinoma. *Biomedicines* **11**, 119.
16. Bong AHL, Monteith GR (2018) Calcium signaling and the therapeutic targeting of cancer cells. *Biochim Biophys Acta Mol Cell Res* **1865**, 1786–1794.
17. Vavřínová A, Behuliak M, Vaněčková I, Zicha J (2021) The abnormalities of adrenomedullary hormonal system in genetic hypertension: Their contribution to altered regulation of blood pressure. *Physiol Res* **70**, 307–326.
18. Alejandre-García T, Segura-Chama P, Parada-Parra OJ, Millán-Aldaco D, Hernández-Cruz A (2023) Calcium imaging and amperometric recording in cultured chromaffin cells and adrenal slices from normotensive, wistar kyoto rats and spontaneously hypertensive rats.

Methods Mol Biol **2565**, 129–151.
19. Martínez-Ramírez C, Gil-Gómez I, G de Diego AM, García AG (2021) Acute reversible SERCA blockade facilitates or blocks exocytosis, respectively in mouse or bovine chromaffin cells. *Pflugers Arch* **473**, 273–286.
20. Bergantin LB, Caricati-Neto A (2016) Challenges for the pharmacological treatment of neurological and psychiatric disorders: Implications of the Ca^{2+}/cAMP intracellular signalling interaction. *Eur J Pharmacol* **788**, 255–260.
21. Dalal PJ, Muller WA, Sullivan DP (2020) Endothelial cell calcium signaling during barrier function and inflammation. *Am J Pathol* **190**, 535–542.
22. Monteith GR, Davis FM, Roberts-Thomson SJ (2012) Calcium channels and pumps in cancer: changes and consequences. *J Biol Chem* **287**, 31666–31673.
23. Munaron L, Genova T, Avanzato D, Antoniotti S, Fiorio Pla A (2013) Targeting calcium channels to block tumor vascularization. *Recent Pat Anticancer Drug Discov* **8**, 27–37.
24. Kim KH, Kim D, Park JY, Jung HJ, Cho YH, Kim HK, Han J, Choi KY, et al (2015) NNC 55-0396, a T-type Ca^{2+} channel inhibitor, inhibits angiogenesis via suppression of hypoxia-inducible factor-1α signal transduction. *J Mol Med (Berl)* **93**, 499–509.
25. Yoshida J, Ishibashi T, Nishio M (2007) G1 cell cycle arrest by amlodipine, a dihydropyridine Ca^{2+} channel blocker, in human epidermoid carcinoma A431 cells. *Biochem Pharmacol* **73**, 943–953.
26. Liu J, Guo Y, Zhang R, Xu Y, Luo C, Wang R, Xu S, Wei L (2023) Inhibition of TRPV4 remodels single cell polarity and suppresses the metastasis of hepatocellular carcinoma. *Cell Death Dis* **14**, 379.
27. Bergantin LB (2019) Diabetes and cancer: debating the link through Ca^{2+}/cAMP signalling. *Cancer Lett* **448**, 128–131.
28. Bergantin LB (2020) A hypothesis for the relationship between depression and cancer: role of Ca^{2+}/cAMP signalling. *Anticancer Agents Med Chem* **20**, 777–782.
29. Errante PR, Menezes-Rodrigues FS, Leite AA, Caricati-Neto A, Bergantin LB (2017) New antitumoral pharmacological strategies involving Ca^{2+}/cAMP signaling pathways. *J Cancer Epidem Prev* **2**, 1–6.
30. Sorrin AJ, Liu C, Cicalo J, Reader J, Najafali D, Zhang Y, oque DM, Huang HC (2021) Photodynamic priming improves the anti-migratory activity of prostaglandin E receptor 4 antagonist in cancer cells *in vitro*. *Cancers (Basel)* **13**, 5259.
31. Dale P, Head V, Dowling MR, Taylor CW (2018) Selective inhibition of histamine-evoked Ca^{2+} signals by compartmentalized cAMP in human bronchial airway smooth muscle cells. *Cell Calcium* **71**, 53–64.
32. Shi H, Sun X, Kong A, Ma H, Xie Y, Cheng D, Wong CKC, Zhou Y, et al (2021) Cadmium induces epithelial-mesenchymal transition and migration of renal cancer cells by increasing PGE2 through a cAMP/PKA-COX2 dependent mechanism. *Ecotoxicol Environ Saf* **207**, 111480.
33. Zhao Z, Deng S, Lv Z, Yang J (2023) Cellular innate biological nano confinements control cancer metastasis through materials seizing and signaling regulating. *Technol Cancer Res Treat* **22**, 15330338231158917.
34. Jiang M, Yang J, Li K, Liu J, Jing X, Tang M (2021) Insights into the theranostic value of precision medicine on advanced radiotherapy to breast cancer. *Int J Med Sci* **18**, 626–638.
35. Yang J, Jia C, Yang J (2021) Designing nanoparticle-based drug delivery systems for precision medicine. *Int J Med Sci* **18**, 2943–2949.
36. Greten FR, Grivennikov SI (2019) Inflammation and cancer: triggers, mechanisms, and consequences. *Immunity* **51**, 27–41.
37. Palliyagea GH, Ghosha R, Rojanasaku Y (2020) Cancer chemoresistance and therapeutic strategiestargeting tumor microenvironment. *ScienceAsia* **46**, 639–649.
38. Harrison DG, Guzik TJ, Lob HE, Madhur MS, Marvar PJ, Thabet SR, Vinh A, Weyand CM (2011) Inflammation, immunity, and hypertension. *Hypertension* **57**, 132–140.
39. Stocks T, Borena W, Strohmaier S, Bjørge T, Manjer J, Engeland A, Johansen D, Selmer R (2010) Cohort profile: the metabolic syndrome and cancer project (Me-Can). *Int J Epidemiol* **39**, 660–607.
40. Corrao G, Scotti L, Bagnardi V, Sega R (2007) Hypertension, antihypertensive therapy and renal-cell cancer: a meta-analysis. *Curr Drug Saf* **2**, 125–133.
41. Andreotti G, Boffetta P, Rosenberg PS, Berndt SI, Karami S, Menashe I, Yeager M, Chanock SJ (2010) Variants in blood pressure genes and the risk of renal cell carcinoma. *Carcinogenesis* **31**, 614–620.
42. Seretis A, Cividini S, Markozannes G, Tseretopoulou X, Lopez DS, Ntzani EE, Tsilidis KK (2019) Association between blood pressure and risk of cancer development: a systematic review and meta-analysis of observational studies. *Sci Rep* **9**, 8565.
43. Kale VP, Amin SG, Pandey MK (2015) Targeting ion channels for cancer therapy by repurposing the approved drugs. *Biochim Biophys Acta* **1848**, 2747–2755.
44. Dziegielewska B, Gray LS, Dziegielewski J (2014) T-type calcium channels blockers as new tools in cancer therapies. *Pflugers Arch* **466**, 801–810.
45. Gackière F, Bidaux G, Delcourt P, Van Coppenolle F, Katsogiannou M, Dewailly E, Bavencoffe A, Van Chuoï-Mariot MT, et al (2008) CaV3.2 T-type calcium channels are involved in calcium-dependent secretion of neuroendocrine prostate cancer cells. *J Biol Chem* **283**, 10162–10173.
46. Li RF, Man QW, Liu JY, Zheng YY, Gao X, Liu HM (2021) Overexpression of T-type calcium channel Cav3.1 in oral squamous cell carcinoma: association with proliferation and anti-apoptotic activity. *J Mol Histol* **52**, 511–520.
47. Subbamanda YD, Bhargava A (2022) Intercommunication between voltage-gated calcium channels and estrogen receptor/estrogen signaling: insights into physiological and pathological conditions. *Cells* **11**, 3850.
48. Bergantin LB, Souza CF, Ferreira RM, Smaili SS, Jurkiewicz NH, Caricati-Neto A, Jurkiewicz A (2013) Novel model for "calcium paradox" in sympathetic transmission of smooth muscles: role of cyclic AMP pathway. *Cell Calcium* **54**, 202–212.
49. Gonçalves CA, Sesterheim P, Wartchow KM, Bobermin LD, Leipnitz G, Quincozes-Santos A (2022) Why antidiabetic drugs are potentially neuroprotective during the SARS-CoV-2 pandemic: The focus on astroglial UPR and calcium-binding proteins. *Front Cell Neurosci* **16**, 905218.
50. Bergantin LB (2020) Diabetes and Parkinson's disease:

debating the link through Ca^{2+}/cAMP signalling. *Curr Diabetes Rev* **16**, 238–241.
51. Caricati-Neto A, Garcia AG, Bergantin LB (2015) Pharmacological implications of the Ca^{2+}/cAMP signaling interaction: from risk for antihypertensive therapy to potential beneficial for neurological and psychiatric disorders. *Pharmacol Res Perspect* **3**, e00181.
52. Bergantin LB (2021) Common issues among asthma, epilepsy, and schizophrenia: from inflammation to Ca^{2+}/cAMP signalling. *Antiinflamm Antiallergy Agents Med Chem* **20**, 229–232.
53. Moreno-Ortega AJ, Buendia I, Mouhid L, Egea J, Lucea S, Ruiz-Nuño A, López MG, Cano-Abad MF (2015) CALHM1 and its polymorphism P86L differentially control Ca^{2+} homeostasis, mitogen-activated protein kinase signaling, and cell vulnerability upon exposure to amyloid β. *Aging Cell* **14**, 1094–1102.
54. White A, Parekh RU, Theobald D, Pakala P, Myers AL, Van Dross R, Sriramula S (2022) Kinin B1R activation induces endoplasmic reticulum stress in primary hypothalamic neurons. *Front Pharmacol* **13**, 841068.
55. Isfandari S, Roosihermiatie B, Tuminah S, Mihardja LK (2023) The risk associated with psychiatric disturbances in patients with diabetes in Indonesia (2018): a cross-sectional observational study. *Osong Public Health Res Perspect* **14**, 368–378.
56. Zhang XC, Jiang M, Yang JS (2021) Potential value of circulating endothelial cells for the diagnosis and treatment of COVID-19. *Int J Infect Dis* **107**, 232–233.
57. Zhang RZ, Wang Q, Yang JS (2022) Potential of sphingosine-1-phosphate in preventing SARS-CoV-2 infection by stabilizing and protecting endothelial cells: narrative review. *Medicine (Baltimore)* **101**, e29164.
58. Bergantin LB (2020) The interactions between Alzheimer's disease and major depression: role of Ca^{2+} channel blockers and Ca^{2+}/cAMP signalling. *Curr Drug Res Rev* **12**, 97–102.
59. Bergantin LB (2020) The complex link between schizophrenia and dementia: targeting Ca^{2+}/cAMP signalling. *Curr Pharm Des* **26**, 3326-3331.
60. Bergantin LB (2020) A link between brain insulin resistance and cognitive dysfunctions: targeting Ca^{2+}/cAMP signalling. *Cent Nerv Syst Agents Med Chem* **20**, 103–109.
61. Bergantin LB (2020) A hypothesis for the relationship between depression and cancer: role of Ca^{2+}/cAMP signalling. *Anticancer Agents Med Chem* **20**, 777–782.
62. Zhang X, Zhou X, Huang Z, Fan X, Tan X, Lu C, Yang J (2021) Aldosterone is a possible new stimulating factor for promoting vascular calcification. *Front Biosci (Landmark Ed)* **26**, 1052–1063.
63. Zhang X, Huang Z, Fan X, Tan X, Lu C, Yang J (2022) Molecular mechanisms and effects of urocortin II on rat adventitial fibroblast calcification induced by calcified medium. *Vasc Biol* **4**, 19–27.
64. Lin WZ, Yang X, Zhang F, Yang JS, Zhang YG (2023) Smad2/3 signaling involved in urotensin II-induced phenotypic differentiation, collagen synthesis and migration of rat aortic adventitial fibroblasts. *Ital J Med* **17**, 1637.
65. Liao CJ, Huang Z, Chen LT, Fan XR, Peng J, Tan XQ, Yang JS, Zhang XS (2023) Urotensin II promotes the proliferation and secretion of vascular endothelial growth factor in rat dermal papilla cells by activating Wnt-β-catenin signaling pathway. *Ital J Med* **17**, 1607.
66. Liu C, Ke P, Zhang J, Zhang X, Chen X (2020) Protein kinase inhibitor peptide as a tool to specifically inhibit protein kinase A. *Front Physiol* **11**, 574030.
67. Naviglio S, Caraglia M, Abbruzzese A, Chiosi E, Di Gesto D, Marra M, Romano M, Sorrentino A (2009) Protein kinase A as a biological target in cancer therapy. *Expert Opin Ther Targets* **13**, 83–92.
68. Fajardo AM, Piazza GA, Tinsley HN (2014) The role of cyclic nucleotide signaling pathways in cancer: targets for prevention and treatment. *Cancers (Basel)* **6**, 436–458.
69. Campolo F, Assenza MR, Venneri MA, Barbagallo F (2023) Once upon a testis: the tale of cyclic nucleotide phosphodiesterase in testicular cancers. *Int J Mol Sci* **24**, 7617.
70. Pinto EM, Faucz FR, Paza LZ, Wu G, Fernandes ES, Bertherat J, Stratakis CA, Lalli E, et al (2020) Germline variants in phosphodiesterase genes and genetic predisposition to pediatric adrenocortical tumors. *Cancers (Basel)* **12**, 506.
71. Eskandari N, Bastan R, Esfahani SH, Peachell PT (2015) The effect of cyclic nucleotide analog drugs on the mediators release from basophils. *Adv Biomed Res* **4**, 125.
72. Tortorella C, Piazzolla G, Spaccavento F, Antonaci S (1998) Effects of granulocyte-macrophage colony-stimulating factor and cyclic AMP interaction on human neutrophil apoptosis. *Mediat Inflamm* **7**, 391–396.
73. Perez DR, Sklar LA, Chigaev A, Matlawska-Wasowska K (2021) Drug repurposing for targeting cyclic nucleotide transporters in acute leukemias: A missed opportunity. *Semin Cancer Biol* **68**, 199–208.
74. Chen Y, Wu Z, Wang L, Lin M, Jiang P, Wen J, Li J, Hong Y, et al (2023) Targeting nucleolin improves sensitivity to chemotherapy in acute lymphoblastic leukemia. *Cell Oncol (Dordr)* **46**, 1709–1724.
75. Zorn A, Baillie G (2023) Phosphodiesterase 7 as a therapeutic target – where are we now? *Cell Signal* **108**, 110689.
76. Robinson RB, Dun W, Boyden PA (2021) Autonomic modulation of sinoatrial node: Role of pacemaker current and calcium sensitive adenylyl cyclase isoforms. *Prog Biophys Mol Biol* **166**, 22–28.
77. Li S, Li Y, Bai Y (2019) What is the impact of eukaryotic elongation factor 2 kinase on cancer: A systematic review. *Eur J Pharmacol* **857**, 172470.