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Mini-review

Diabetes and cancer: Debating the link through Ca^{2+}/cAMP signalling

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ABSTRACT

The incidence of both cancer and diabetes is dramatically increasing in worldwide population, costing many millions from governments into expenditures related to medical health systems. Diabetes has been clinically linked to an increased risk for developing several types of cancer. The cellular mechanisms involved in this link are still under intensive debate in literature. In addition, a Ca^{2+} homeostasis dysregulation has been intensively debated as an issue involved in both cancer and diabetes. Calcium (Ca^{2+}) channel blockers (CCBs), prescribed for treating hypertension, have also been showing anti-cancer effects along with reducing diabetes symptoms. A debated mechanism of action could rest in the fact that CCBs may restore Ca^{2+} homeostasis dysregulations, involved in both diseases. Our studies about Ca^{2+}/cAMP signalling may add some new light in this field. In this review, I have debated the possible involvement of Ca^{2+}/cAMP signalling in the clinical link between diabetes and a higher risk for the development of several types of cancer, including the plausible involvement in both anti-cancer and anti-diabetic effects of CCBs.

1. Introduction

Cancer and diabetes have become problematic issues for medical health systems around the world, costing millions and millions from governments worldwide. Diabetes has been associated with a higher risk for developing several types of cancer [1]. Then, debating this link might improve our understanding of the risk factors involved in developing cancer [1].

An imbalance of intracellular Ca^{2+} homeostasis (e.g. intracellular Ca^{2+} excess) is now being intensively discussed as an issue involved in both cancer and diabetes, contributing to the pathogenesis of both diseases [2–10]. Calcium (Ca^{2+}) channel blockers (CCBs), pharmaceuticals typically administered for treating hypertension, have been showing both anti-cancer and anti-diabetic effects [6–10]. Our studies have discussed that a possible working principle for these anti-cancer and anti-diabetic effects could result from the fact that these pharmaceuticals may be restoring the dysregulation of Ca^{2+} homeostasis [11–15].

The phenomenon entitled as ´calcium paradox', which has been clarified by us in 2013, has also been correlated with CCBs [16]. This ´paradox' effect results into CCBs paradoxically increasing the release of neurotransmitters (a ´paradox' because intracellular Ca^{2+} concentration is being decreased by these medicines), very often when these pharmaceuticals have been used in low doses/concentrations. We discovered that Ca^{2+}/cAMP signalling interaction is involved in this phenomenon. In this review, I have discussed the plausible participation of Ca^{2+}/cAMP signalling in anti-cancer and anti-diabetic effects of CCBs, including the role of Ca^{2+}/cAMP signalling in the link between diabetes and a higher risk for the development of several types of cancer.

2. Diabetes and a higher risk for the development of cancer

A link between diabetes and a higher risk for the development of several types of cancer has been reported by epidemiological and clinical studies [1,17–19]. However, the working principle of this clinical association is not completely elucidated, and has been highly debated in literature [1,17,19]. A systematic study was conducted by Ohkuma T et al. [1] in PubMed for cohort reports published up to December 2016. Data concerning cancer events (incident or fatal only) were achieved from 121 cohorts (19,239,302 individuals from 1,082,592 events). The report showed an association between diabetes and an increased risk for the development of several types of cancer. Ohkuma T et al. [1] concluded that diabetes is a risk factor for several types of cancer in both sexes (men and women). Another report, which was conducted by Hiroshi Noto et al. [17], obtained similar conclusions. The report searched MEDLINE and Cochrane Library looking for pertinent articles which had been published as of 4 April 2011 and included them in a meta-analysis of the risk for several cancer types, including mortality and incidence in diabetic subjects. The study

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Abbreviations

ACs	adenylyl cyclases
CCBs	Calcium (Ca^{2+}) channel blockers
ER	endoplasmic reticulum
PDEs	phosphodiesterases
RyR	ryanodine receptor
VACC	voltage-activated Ca^{2+} channels

Symbols

$[\ Ca^{2+}\ ]_c$ intracellular concentration of Ca^{2+}

concluded that diabetes is correlated with an increased risk for several types of cancer. Other reports obtained similar conclusions, particularly for both pancreatic and colorectal cancers [18,19]. Concerning possible cellular mechanisms, it is postulated a basic mechanism by which hyperglycemia, in diabetes subjects, may achieve carcinogenic effects by inducing DNA damage, which could result from an enhanced oxidative stress [1]. However, additional explanations, more specific, are clearly needed. These data highlight the necessity of clinical consideration, and better-designed reports, trying to elucidate the exact working principles of this association (between diabetes and cancer).

In accordance with the concepts discussed above, several studies suggest that diets which are low in both red and processed meats, and that are also high in vegetables, fruits and whole grains are associated with a lower risk of both many types of cancer and diabetes [20–24]. Diets that are low in both red and processed meats, and that are also high in monounsaturated fatty acids, fruits, vegetables, whole grain cereals and dietary fiber may protect against type 2 diabetes possibly through improving insulin sensitivity [23,24]. Several studies suggest that diets which are high in foods with high glycemic index are associated with an increased risk of type 2 diabetes. Thus, considering that both energy-dense and sugary foods contribute to overweight and to obesity, the American Cancer Society, the World Cancer Research Fund and the American Institute for Cancer Research recommend limiting consumption of these foods [20–24]. As it is postulated that regular consumption of both fruits and vegetables may reduce the risk of several types of cancers, and that dysregulations of Ca^{2+} signalling have been correlated to an increased risk for developing several types of cancer [2–8], Meng-Wong Taing et al., 2015 [25] confirmed that fruit extracts exhibited growth inhibitory effects by restoring Ca^{2+} homeostasis dysregulations.

On the other hand, in laboratory studies, metformin, the most commonly used therapy in patients with type 2 diabetes, has been shown to: 1) inhibit cell proliferation, 2) reduce colony formation and 3) cause partial cell cycle arrest in cancer cell lines [26–29]. These studies suggest that a metformin-induced activation of AMP-activated protein kinase (AMPK) in tumor cells may lead to growth inhibition, at least in part, by inhibiting protein synthesis [26,30]. In vitro studies have also suggested that metformin may selectively kill cancer stem cells, and also enhance the effectiveness of breast cancer treatment regimens [31,32]. Metformin has also been shown to reduce mammary tumor growth in rodent models [33].

Considering the complexity of the link between diabetes and cancer, including their treatments, it is vital to not neglect glucose as a relevant mediator for this link (between diabetes and cancer). Both Warburg hypothesis [34] and cancer energetics highlight the dependence of many cancers on glycolysis for energy, then creating a high necessity for glucose. This principle outcomes into the basis for FDG-PET imaging of cancers, which distinguishes tissues with high rates of glucose uptake. Thus, the hypothesis that an untreated hyperglycemia facilitates neoplastic proliferation deserves further consideration [34].

In addition to the known classical effects of insulin, type 2 diabetes and/or related obesity might probably dysregulate other signalling pathways, resulting into malignant progression. Nowadays, adipose tissue is considered an active endocrine organ, producing free fatty acids, adiponectin, leptin, interleukins and tumor necrosis factor [35]. These factors might play an important role in regulating malignant transformation or cancer progression. In some cases, the role of these signalling pathways in cancer progression is well known, and in other cases, more studies are clearly needed [35]. For example, interleukin-6 is known to enhance cancer cell proliferation, survival and invasion [36]. Results from animal reports concerning an energy balance support the relationship between obesity and cancer mortality. Certain experimental cancers tend to outcome into a more aggressive pathway when animals overeat, and into a less aggressive pathway when animals have low caloric diets [37,38]. These reports suggest that diet-induced changes in interleukin-6, and/or insulin, may mediate the effect of diet on cancer progression, suggesting that diet influences tumor behavior [39]. Considering an imbalance of intracellular Ca^{2+} homeostasis is also being intensively discussed as an issue involved in both cancer and diabetes [2–10], CCBs, antihypertensive pharmaceuticals which reduce the influx of Ca^{2+} into the cells, have been showing both anti-cancer and anti-diabetic effects [6–10]. Thus, how could Ca^{2+}/cAMP signalling support the explanation of these effects, including the association between diabetes and a higher risk for developing cancer?

3. Diabetes and cancer: significance of Ca^{2+}/cAMP signalling

Ca^{2+}/cAMP signalling are assumed to virtually occur in almost all mammalian cells, regulated by adenylyl cyclases (ACs), phosphodiesterases (PDEs), Ca^{2+} channels and so on [40–48, Fig. 1]. Briefly, decreasing Ca^{2+} influx through L-type Ca^{2+} channels, induced by CCBs, enhances AC activity (elevating cAMP levels; entitled as Ca^{2+}/cAMP signalling interaction), and these CCBs-effects can be amplified by cAMP-stimulating compounds (like PDEs inhibitors [40–48]).

In this field, endoplasmic reticulum (ER) Ca^{2+} channels have particularly been a forefront for the field, such as ryanodine receptors (RyR) [40–48]. Through our reports, we have recognized that Ca^{2+}/cAMP signalling play an essential role in controlling the neurotransmitter release from both neurons and neuroendocrine cells, including modulating neuronal death [40–43] and the development of

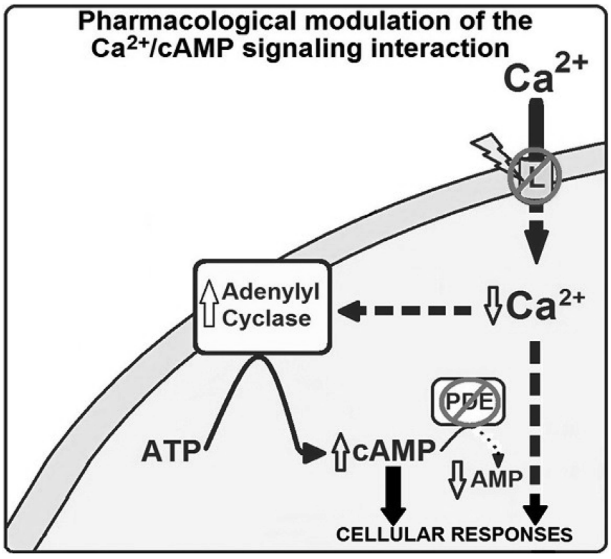

Fig. 1. Cellular effects achieved from pharmacological modulation of Ca^{2+}/cAMP signalling pathways. Briefly, decreasing Ca^{2+} influx through L-type Ca^{2+} channels, induced by CCBs, enhances AC activity (elevating cAMP levels; entitled as Ca^{2+}/cAMP signalling interaction), and these CCBs-effects can be amplified by cAMP-stimulating compounds (like PDEs inhibitors).

both cancer and diabetes [11–15,48]. In endocrine cells, Ca^{2+}/cAMP signalling modulate the release of various hormones, including insulin from pancreatic β-cells [48–50]; then, dysregulations of Ca^{2+} signalling have been implicated in the pathogenesis of diabetes [48]. While increasing cAMP levels by adrenaline may stimulate hepatic glucose production, enhancing cAMP levels into pancreatic β-cells can induce the release of insulin. The trigger for an exocytosis of insulin granules is due to enhancing cytoplasmic Ca^{2+} concentration, which is stimulated by cAMP [48–50]. In addition to the response of stimulating insulin synthesis, cAMP participates in homeostasis of β-cell by stimulating cell proliferation and differentiation, and by restoring cells from apoptosis [48–50].

Ca^{2+} dysregulations, such as up-regulations of L-type Ca^{2+} channels, have also been correlated in development and progression of cancer. A recent meta-analysis of microarray datasets demonstrated a mRNA gene profile of L-type Ca^{2+} channels in different types of cancer [51–56]. It was shown that L-type Ca^{2+} channels are expressively up-regulated in colon and esophageal cancer [51–56]. Thus, pharmacological blockade of these channels could be a goal as a therapeutic strategy for antitumor therapy. Some reports showed that L-type CCB such as amlodipine, mibefradil and NNC-55-0396 decreased proliferative responses in different tumor cells [6–8].

In addition, it was shown that an increase of cAMP, induced by ACs activators, stimulated significant antitumor effects [57]. The 8-Cl-cAMP, and PKA -selective cAMP analogs such as 8-piperidinoadenosine - 3′,5′-cyclic monophosphate (8-PIP-cAMP) and 8-hexylaminoadenosine - 3′,5′-cyclic monophosphate (8-HA-cAMP), induced significant anti-proliferative effects in human cancer cell lines [11,57]. The anti-proliferative effect of PKA -selective cAMP analogs was correlated to growth arrest, while 8-Cl-cAMP appears to be due to pro-apoptotic responses [11,57]. These discoveries suggest that cAMP analogs, such as 8-Cl-cAMP and PKA -selective cAMP analogs, could be administered in human tumor therapy. Thus, considering that our reports have shown that a decrease of Ca^{2+} influx through L-type Ca^{2+} channels, induced by CCBs, enhances AC activity (elevating cAMP levels; entitled as Ca^{2+}/cAMP signalling interaction) [11–15,58], and that these CCBs-effects can be amplified by cAMP-stimulating compounds (like PDEs inhibitors), then pharmacological modulation of Ca^{2+}/cAMP signalling could be a new therapeutic goal for tumor therapy. In addition, our discovery, which demonstrated the role of Ca^{2+}/cAMP signalling in neurotransmitter release and neuroprotection [40–43], may put some new ´light' in the association between diabetes and a higher risk for the development of cancer. If dysregulations of Ca^{2+} homeostasis may be an issue for the pathogenesis of both cancer and diabetes [11–15,48]; in this scenario, Ca^{2+}/cAMP signalling interaction may be disrupted as a consequence of rising $[Ca^{2+}]_c$ in development of both cancer and diabetes processes [11–15,48]. Considering ACs5 and ACs6 isoforms can be inhibited by rising Ca^{2+} concentrations [40–48], a rise of $[Ca^{2+}]_c$ may dramatically disturb cAMP signalling pathways. Up-regulations of cAMP signalling have been associated to both anti-cancer and anti-diabetic effects [11,15,48,57,59]. Thus, besides its own effect in enhancing cancer progression, a rise of $[Ca^{2+}]_c$ may also probably result into cancer-excitotoxic responses by reducing anti-cancer responses due to a down-regulation of cAMP signalling pathways (due to disruption of Ca^{2+}/cAMP signalling interaction). Then, CCBs could exert their anti-cancer effects [6–8] through Ca^{2+}/cAMP signalling interaction. Novel methodologies will allow researchers to explore these hypotheses!

Similar to cancer, diabetes has also been linked to dysregulations of Ca^{2+} signalling [48,59]. In this scenario, Ca^{2+}/cAMP signalling interaction may be disrupted as a consequence of diabetes development process, like in cancer. Similar to cancer, novel methodologies will allow researchers to solve this conundrum! Then, dysregulations of Ca^{2+} signalling could provide a ´clinical link' between cancer and diabetes. The following diagram summarizes previous discussion:

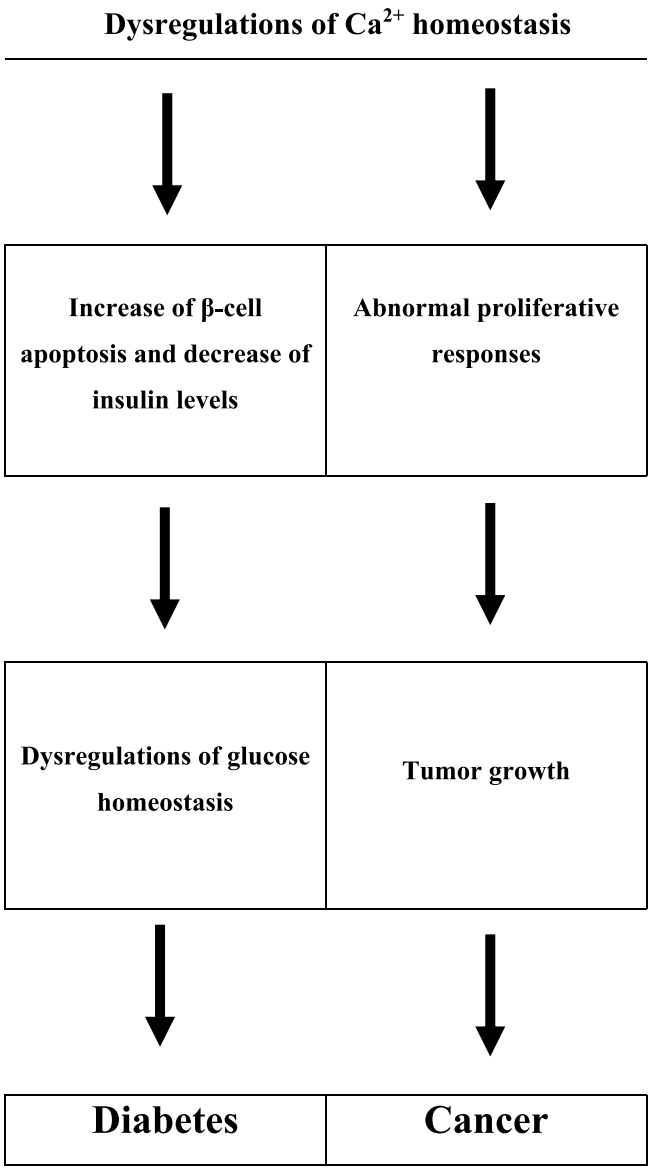

Diagram. Ca^{2+} homeostasis dysregulations and their endpoint consequences: cancer and diabetes.

4. Conclusions and future directions

Ca^{2+} signalling and its dysregulations have been associated to development of both diabetes [9,10,48,59] and cancer [51–56]. CCBs, despite their antihypertensive effect, have been showing both anti-cancer and anti-diabetic effects [6–10]. Ca^{2+}/cAMP signalling interaction has now been emerging as a possible new therapeutic target for treating both cancer and diabetes [11–15,48,59]. If Ca^{2+}/cAMP signalling are involved, in part, in both anti-cancer and anti-diabetic effects of CCBs deserves more consideration, including additional experiments with modern methodologies, and in clinical trials.

Conflicts of interest

None declared.

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