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## Oxytocin and cancer: An emerging link

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### Abstract

The neuropeptide hormone oxytocin, which is released from the posterior pituitary gland, is involved in a number of physiological processes. Understanding of its effects is gradually increasing due to new research in this area. While mostly recognized as a reproductive system hormone, oxytocin also regulates other organ systems such as the brain and cardiovascular system. Recently, research has focused on unraveling its involvement in cancer, and emerging evidence suggests a potential role for oxytocin as a cancer biomarker. This review summarizes observations linking oxytocin and cancer, with a special emphasis on prostate cancer, where it may promote cell proliferation. Research suggests that oxytocin effects may depend on cell type, concentration of the hormone, its interactions with other hormones in the microenvironment, and the precise localization of its receptor on the cell membrane. Future research is needed to further elucidate the involvement of oxytocin in cancer, and whether it could be a clinical cancer biomarker or therapeutic target.

**Key words:** Oxytocin; Cancer; Prostate; Pancreas; Exercise

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**Core tip:** Oxytocin's role outside of the reproductive system and social bonding has yet to be fully elucidated. Apparently, its role in cancer may vary depending on location and cell type. This review summarizes the current state of our understanding of the potential role of oxytocin in cancer.

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## INTRODUCTION

Oxytocin is a central nervous system (CNS) neuropeptide hormone, which is composed of nine amino acids. The synthesis of oxytocin begins in the hypothalamus, where the paraventricular nucleus and supra-optic neurons express high levels of oxytocin, which is released from the posterior pituitary gland<sup>[1]</sup>. Oxytocin is biologically similar to vasopressin (also known as antidiuretic hormone), and they are often studied in parallel, as both hormones also share some functions. Originally thought of as a hormone with a role limited to the uterus and milk ejection - oxytocin means "quick birth" in Greek<sup>[2]</sup> - further research has expanded understanding of its function across sexes and organ systems. Furthermore, it has become clear that in addition to physical function, oxytocin also wields important impact on social behaviors, which include stress and trust, anxiety, social interaction and bonding, and parental care<sup>[3]</sup>, and thereby on neuropsychiatric disorders linked to these social behaviors. Interestingly, emerging evidence has linked oxytocin to somewhat conflicting roles in carcinogenesis, as oxytocin is implicated in either fostering development or, conversely, inhibition of cancer-related cellular functional phenomena.

## PHYSIOLOGICAL FUNCTIONS OF OXYTOCIN

### *Oxytocin in the reproductive system*

Oxytocin exerts its effects primarily through a single receptor, which has been well characterized. The oxytocin receptor is a class- I G-protein-coupled receptor with seven transmembrane domains, and can be bound by several ligands, including oxytocin, oxytocin agonists and antagonists, as well as vasopressin<sup>[4]</sup>. These receptors are found in the endometrium, myometrium, trophoblast, osteoblasts, reproductive organs, and throughout the CNS (Table 1). Notably, oxytocin receptor has also been implicated in various cancers related to tissues in which it is expressed, including endometrial cancer, glioblastomas, neuroblastomas<sup>[5]</sup>, and others. Several oxytocin receptor antagonists have been identified, with the most common being Atosiban<sup>[6,7]</sup>. While studies of oxytocin antagonist in cancer has been limited, atosiban has been implicated in inhibiting cell growth of DU145 prostate cancer<sup>[8]</sup> and various breast cancer cell lines<sup>[9]</sup>. However, little evidence indicates whether this strategy is efficacious *in vivo*.

The effectors of the oxytocin receptor may vary. While the primary signaling mechanisms of oxytocin have not been fully elucidated, recent studies show that the main mitogenic signaling mechanism of the oxytocin

receptor involves the Gq alpha subunit protein (G $\alpha$ q)/phospholipase C (PLC)/inositol 1, 4, 5 triphosphate (InsP3) pathway. Through this activation, the G protein couples to PLC-B, resulting in the release of calcium from intracellular stores<sup>[10]</sup>, triggering smooth muscle contractions<sup>[11]</sup>, for example in the uterus or in the myoepithelial cells of the mammary gland. The main oxytocin pathways described in this paper are depicted in Figure 1.

Indeed, the first functional role attributed to oxytocin centered on the female reproductive system, specifically in uterine contraction and in lactation. Uterine sensitivity to oxytocin increases around the onset of labor, and upon labor oxytocin stimulation becomes more efficient. Therefore, exogenous administration of oxytocin is also clinically used to induce labor. Following parturition, the density of oxytocin receptors declines. In lactation, the oxytocin pathway is activated when the infant begins sucking on the nipple<sup>[12]</sup>. A sensory impulse is sent from the nipple to the spinal cord, and from there transmitted to the oxytocinergic neurons in the hypothalamus. These neurons generate action potentials that lead to a substantial release of oxytocin into the blood stream, which subsequently elicits milk ejection via a contraction of myoepithelial cells<sup>[4]</sup>. Interestingly, this cascade can be triggered even before suckling occurs, by an event such as a baby crying<sup>[13]</sup>, suggesting that it may involve reflex neural pathways. Increased plasma oxytocin has also been linked to an increased risk of pregnancy-induced hypertension<sup>[14]</sup>, and exogenous oxytocin administration has been associated with angiotensin II-induced hypertension<sup>[15]</sup>. Interestingly, though, there is also a potential link between increased oxytocin and reduced risk of hypertension (which might be acquired *in utero* in association with intrauterine growth retardation)<sup>[16]</sup>, so that oxytocin has been attributed with eliciting a reduction in blood pressure<sup>[17,18]</sup>.

The reproductive function of oxytocin is not limited to females, as it stimulates contractility of the seminiferous tubules, epididymis, and the prostate gland<sup>[19]</sup>. Due to its production locale in the testes, oxytocin has been studied as a paracrine regulator of the prostate gland, specifically of growth and muscle contractility<sup>[20]</sup>. In males, oxytocin has been thought to induce erection and play a role in ejaculation<sup>[19,21]</sup>. Specifically, in the prostate, oxytocin has been suggested to induce prostatic smooth muscle cell contraction<sup>[22]</sup>. Its postulated involvement in ejaculation includes stimulation of the reproductive tract to promote sperm release<sup>[19]</sup>. Oxytocin's role in aggravating and potentially facilitating the development of benign prostatic hyperplasia, and the oxytocin-induced proliferative effect, are likely mediated through the extracellular signal regulated kinase (ERK) pathway<sup>[23]</sup>.

### *Oxytocin in the CNS*

Given its ubiquitous distribution in the CNS, the role of oxytocin in cognition and social behavior has also been studied extensively, especially over the past decade.

**Table 1 Human tissue with known expression of the oxytocin receptor**

Tissue	Expression type
Myometrium	mRNA and protein <sup>[7,11]</sup>
Lung	mRNA <sup>[109]</sup>
Breast	mRNA and protein <sup>[16]</sup>
Prostate	mRNA <sup>[22,79]</sup>
Uterus	mRNA and Protein <sup>[11]</sup>
Heart	mRNA <sup>[17]</sup>
Vascular endothelium	mRNA <sup>[110]</sup>
Brain	mRNA <sup>[31,42,43]</sup>
Thymus	mRNA <sup>[111]</sup>
Pancreas	mRNA <sup>[112]</sup>
Blood	mRNA and protein <sup>[113]</sup>
Bone	mRNA <sup>[114]</sup>

It has been shown that oxytocin can enhance positive social interactions, and importantly can enhance trust<sup>[24]</sup>. Oxytocin activity was found to be decreased in women who suffered abuse in their youth<sup>[25]</sup>. Conversely, and perhaps related to this, a study reported increased oxytocin levels in individuals enjoying heightened levels of partner support<sup>[26]</sup>. Oxytocin also has been reported to improve social cognition<sup>[27,28]</sup>. However, it must be noted that studies on the social effects of oxytocin are somewhat inconsistent<sup>[29]</sup>, suggesting that at least socially, additional factors are likely to be at play.

One of the aims of oxytocin research stems from an attempt to establish it as a tool to predict, diagnose, and potentially treat neuropsychiatric disorders<sup>[30]</sup>, and has mostly focused on anxiety and depression. Oxytocin intake has been shown to reduce anxiety symptoms<sup>[31,32]</sup>. In concordance with its pivotal role during birth, the majority of the research regarding depression in humans has revolved around pregnancies and the mother's ability to recover from postnatal depression (PND). Studies in this field have discovered lowered oxytocin in mothers with PND, and that increased oxytocin levels bestow positive effects on mothers with PND and on their interactions with infants<sup>[33,34]</sup>. On the other hand, abnormal post-prandial oxytocin secretion has also been demonstrated in women with anorexia nervosa, possibly as an adaptive response to food-related symptoms of anxiety and depression<sup>[35]</sup>. One of the emerging "hot topics" in neuropsychiatric research links oxytocin with autism<sup>[36-38]</sup>, with recent studies beginning to identify oxytocin as a potential medical therapy to alleviate social anxiety caused by autism<sup>[39]</sup>.

### Oxytocin in the cardiovascular system

The potential regulatory role of oxytocin in other organ systems has also raised considerable interest. Oxytocin contributes to several forms of cardiovascular regulation, as it has been shown that preconditioning rats with oxytocin reduces cardiac arrhythmias<sup>[40]</sup>, and that oxytocin can lower blood pressure<sup>[41]</sup>, increase anti-inflammatory and antioxidant activity, and exert beneficial metabolic effects. Therefore, its cardiovascular

activity seems to aim largely at restoring homeostasis.

Notably, oxytocin seems to also exert cardiovascular regulation during elevated levels of physical activity. Oxytocin levels have been shown to rise in response to exercise<sup>[42]</sup>, which activates oxytocinergic projections<sup>[43]</sup> and oxytocinergic modulatory loops that adjust cardiac output, assisting in keeping cardiovascular control over the blood supply<sup>[44]</sup>. The rise in oxytocin has been traced to the lumbar spinal cord<sup>[45]</sup>. Oxytocin also reduces the rise of exercise-induced adrenocorticotrophic hormone (ACTH) and cortisol<sup>[46,47]</sup>, furthering support on its effects on cortisol levels. Furthermore, exogenously administered oxytocin along with exercise have been shown to protect ovariectomized rats from myocardial infarction<sup>[48]</sup>. On the other hand, its contribution to cardiovascular regulation may depend on the type or intensity of exercise, because plasma oxytocin in cyclists remains unchanged during intense exercise<sup>[49]</sup>.

## OXYTOCIN IN CANCER

Less is understood about the connection between oxytocin and cancer, partly due to lack of adequate research in this area, and partly due to some inconsistency in the current data (Figure 2). The first link of oxytocin to cancer was reported in 1984, when oxytocin was described to be structurally and genomically related to vasopressin, an endogenous hormone that is also secreted by the pituitary, and that in addition to its physiological functions has been found to constitute a biomarker of small-cell lung cancer<sup>[50]</sup>. Furthermore, oxytocin and vasopressin are co-expressed in these cells, where they have been proposed to induce mitogenic effects<sup>[51]</sup>. Oxytocin's link to vasopressin and its potential role as a biomarker was subsequently proposed in 1990<sup>[52]</sup>. Shortly thereafter, it was suggested that oxytocin may modulate growth in breast cancer<sup>[53]</sup>, which was subsequently demonstrated<sup>[54]</sup>. These observations have instigated additional research into oxytocin's potential involvement in various forms of cancer.

### Oxytocin in breast cancer

Interestingly, subsequent studies have shown that oxytocin in fact inhibits proliferation of breast cancer cell lines, such as MDA-MB231, MCF7, and T47D<sup>[55,56]</sup>, as well as the canine mammary cell line CMT-U27<sup>[57]</sup>, mouse mammary carcinoma cell line TS/A, and rat mammary carcinoma cell line D-R3230AC<sup>[9]</sup>. This effect was shown to be mediated via the cyclic adenosine monophosphate protein kinase A in human cell lines<sup>[58]</sup>. Importantly, anti-proliferative and tumor inhibitory properties were also observed *in vivo* in both rat and mouse experimental models, and attributed to both oxytocin and its analogue F314<sup>[9]</sup>. Recently, it was suggested that exercise training, by inducing oxytocin secretion, may reduce the expression of specific signaling proteins involved in breast cancer<sup>[59]</sup>.

Lactation has long been linked to a reduced risk

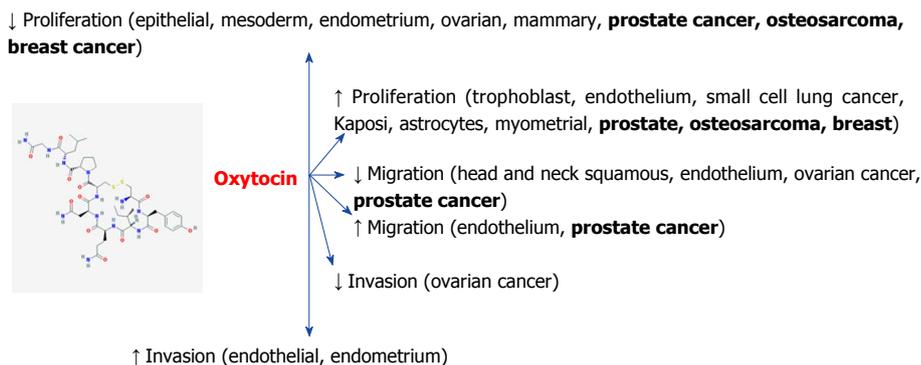


Figure 1 The potential role of oxytocin in various cancers and cell types. Bold font indicates conflicting observations.

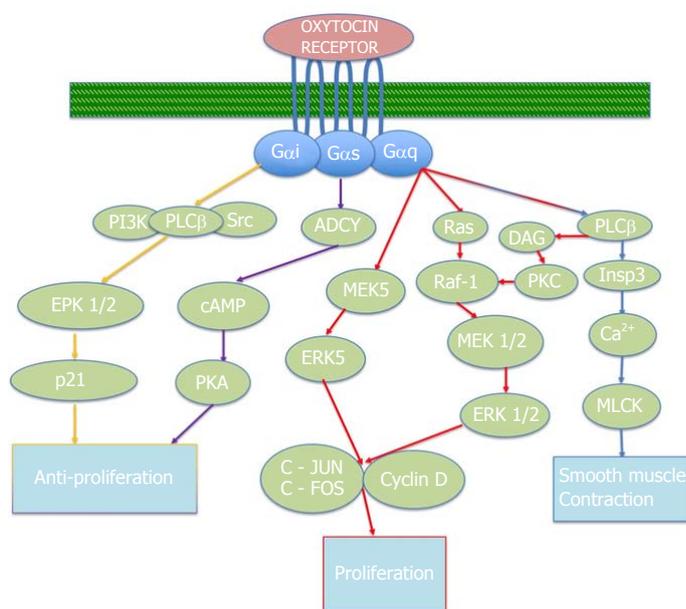


Figure 2 Mechanisms of action of oxytocin. Yellow and purple are anti-proliferation (via different subunits), red is proliferation, and blue is smooth muscle contraction. Gαi: Guanine nucleotide binding protein subunit alpha i; Gαs: Guanine nucleotide binding protein subunit alpha s; Gαq: Guanine nucleotide binding protein subunit alpha q; PI3K: Phosphoinositide 3-kinase; PLCβ: Phospholipase beta; Src: Tyrosine protein kinase; ERK: Extracellular signal-regulated kinase; p21: Cyclin-dependent kinase inhibitor 1; ADCY: Adenylate cyclase; cAMP: Cyclic AMP; PKA: Protein kinase A; DAG: Diacylglycerol; PKC: Protein kinase C; Insp3: Inositol triphosphate 3; MLCK: Myosin light chain kinase.

of cancer, with research dating back to as early as the 1950's<sup>[60-63]</sup>. Worldwide, it has been shown that breastfeeding reduces the risk of both breast and uterine cancer, with prolonged durations of breastfeeding (usually involving multiple children breastfed) correlating with a progressive fall in the risks of both breast and uterine cancer<sup>[64-68]</sup>. The relationship with uterine cancer might be related to the action of oxytocin as a paracrine and endocrine hormone in lactation. Nevertheless, while the relationship between oxytocin, lactation, and breastfeeding with reduced risk of breast and uterine cancer are all well documented individually, more research needs to be conducted to determine if the relationship between oxytocin, lactation, and breastfeeding with reduced breast and uterine cancer is causal. Elucidating such a connection may establish new therapeutic targets in cancer.

### Oxytocin in ovarian cancer

In addition to breast and uterine cancer, the potential participation of oxytocin in the pathogenesis of other cancers in the reproductive system has been investigated. Oxytocin was found to inhibit the progression of ovarian carcinoma (Figure 2) both *in vitro* and *in vivo*. Using cell viability, invasion, and migration assays, it was demonstrated that oxytocin inhibited proliferation, migration and invasion of ovarian cancer cells *in vitro*, and its administration also attenuated the dissemination of ovarian cancer using mean tumor burden as a measure<sup>[69]</sup>. The same investigators had demonstrated in a previous study expression of the oxytocin receptor in various human ovarian carcinoma tissues and cell lines, and identified placental leucine aminopeptidase (P-LAP) as an oxytocin-degrading oxytocinase in certain adenocarcinoma tissues<sup>[70]</sup>. This team of investigators,

therefore, proposed that a system involving P-LAP and oxytocin plays a role in the regulation of human endometrial adenocarcinoma, in which P-LAP exerts a functionally positive impact on carcinoma cell growth by degrading suppressive peptides such as oxytocin. More recently, these effects have also been linked with a cross-talk network between oxytocin and the stress hormone cortisol, whereby oxytocin reversed the carcinogenic effects of cortisol via autophagy (cellular self-degradation)<sup>[71]</sup>. Interestingly, pertinent to the postulated connection between oxytocin and symptoms of autism<sup>[39]</sup>, oxytocin and cancer have also demonstrated an inverse relationship in autistic children<sup>[72]</sup>.

### **Oxytocin in the gastrointestinal tract**

Oxytocin receptors are expressed throughout the gastrointestinal (GI) tract<sup>[73]</sup>, but little is known about their function in the GI tract, especially in relation to cancer. Some studies have suggested a link between oxytocin and its receptor in GI-related cancers, such as esophageal, gastric, and pancreatic cancers. For example, some studies showed an inverse relationship between the duration of breastfeeding and risk of esophageal cancer<sup>[74,75]</sup>, gastric cancer<sup>[76]</sup>, and pancreatic cancer<sup>[77]</sup>. In fact, Yu *et al.*<sup>[78]</sup> showed a 54% decreased risk of developing esophageal cancer in women who breastfed for over 12 mo.

Unpublished data from our laboratory shows that the messenger ribonucleic acid (mRNA) expression of oxytocin is twofold higher in PANC-1 (a human pancreatic cancer cell line highly unresponsive to the chemotherapeutic agents, gemcitabine and 5-FU) compared to L3.6pl (a highly responsive human pancreatic cancer cell line). We also found that oxytocin receptor protein expression is also higher in PANC-1 than in L3.6pl. Further, inhibition of the oxytocin receptor decreased cell proliferation of PANC-1 and L3.6pl cells. Our analysis of data from the cBioPortal database revealed that up to 5% of pancreatic cancer patients included in The Cancer Genome Atlas showed genetic alterations (primarily upregulation of mRNA expression) in oxytocin and its receptor. Patients with these alterations had poorer survival outcomes as compared to those without these alterations. These interesting data warrant further investigation on the molecular mechanisms implicating oxytocin and its receptor in pancreatic cancer and other GI cancers.

### **Oxytocin in prostate cancer**

As a role for oxytocin in the regulation of prostate function is established, its potential involvement in the development of prostate cancer has been proposed. Data from over two decades ago implicated oxytocin in the pathophysiology of benign prostatic hyperplasia, where the peptide might contribute to both the physical enlargement and dynamic tone of the gland<sup>[19]</sup>. More recently, immunohistochemical staining has detected oxytocin expression in stromal and epithelial cell lines and in tissue from patients with benign prostatic hyperplasia,

which was significantly reduced in tissues of invasive prostate cancer in comparison to both benign prostatic hyperplasia tissues and normal human prostate epithelial cells<sup>[79]</sup>. This inverse relationship might implicate a fall in oxytocin levels in progression of prostate cancer. Within the prostate, oxytocin has been shown to affect gland growth both directly and *via* its interaction with androgen metabolism, and oxytocin concentrations are positively correlated with androgens<sup>[20,80]</sup>. Indeed, while in the absence of androgens oxytocin had no effect on prostate cancer cell lines (LNCaP and PC-3), in the presence of testosterone low oxytocin doses stimulated proliferation of PC-3 cells<sup>[81]</sup>, supporting the notion that changes in levels of oxytocin in the prostate in aging and cancer may promote prostate epithelial cell proliferation. It is possible that increased levels of oxytocin might be involved in the mechanisms by which high ejaculation frequency is related to decreased risk of prostate cancer<sup>[82]</sup>. This hypothesis needs to be further investigated.

Conversely, a different study recently revealed that oxytocin increased the expression of APPL1, a protein with the ability to interact with tumor suppressor proteins. *In vitro* studies showed that oxytocin increased prostate cancer cell proliferation, and expression of APPL1. Analysis of serum and tissue samples identified increased oxytocin levels in the serum of prostate cancer patients, and high expression of oxytocin and its receptor in prostate tissues collected from prostate cancer patients in comparison to those collected from patients without prostate cancer. The oxytocin receptor has also been implicated in the migration of prostate cancer cells, and possibly modulation of prostate cancer metastasis<sup>[83]</sup>. Taken together, these observations of oxytocin in prostate cancer cells both *in vivo* and *in vitro*, suggest that oxytocin could serve as a prostate cancer biomarker<sup>[84]</sup>.

Several explanations have been offered for the apparent differences in the data from different studies regarding the role of oxytocin in prostate cancer. One explanation is the notable difference in the numbers of participants involved in each study. Secondly, some of the studies included prostate cancer patients that had undergone neo-adjuvant therapy, which can affect oxytocin levels<sup>[85]</sup>. Thirdly, oxytocin is likely to activate a wide range of signaling mechanisms to elicit variable cellular responses, possibly depending on the density or precise localization of the oxytocin receptor on the plasma membrane<sup>[86]</sup>. This may also account for the dichotomy in the observations reported regarding the role of oxytocin in cancer. Clearly, additional studies are needed to elucidate the involvement of oxytocin and oxytocin receptor in progression or regression of human prostate cancer.

### **Perspectives and future directions**

There is clearly some evidence implicating oxytocin in carcinogenesis, although its precise effect and underlying mechanisms are still unclear. It is possible that in some

individuals, cell types, or types of cancers, oxytocin may not act as a sole regulator of carcinogenesis, but may mediate or modulate other coexisting factors in the microenvironment.

For example, research generally supports the hypothesis that exercise can inhibit the progression of cancer<sup>[87-89]</sup>. The positive impact of exercise in blunting development of cancer and facilitating recovery may potentially be partly mediated through oxytocin. For example, oxytocin has been proposed to mediate an exercise-induced reduction in the expression of specific signaling molecules involved in breast cancer<sup>[59]</sup>. It has also recently been shown *in vivo* that the combination of exogenous oxytocin with exercise improves cardiac function, which might be associated with improved cancer survival. Cardiac dysfunction and cancer have such a strong link that it has even spawned its own subspecialty in cardio-oncology<sup>[90-93]</sup>, although much of the research has centered around long-term survival and cardiac complications in cancer patients. While this potential mediating effect of oxytocin has been hypothesized<sup>[94]</sup>, it appears that little primary research has been conducted to address this postulation. The ability to knockout or silence oxytocin is available, and its social effects are already documented<sup>[95,96]</sup>. Thus, a thorough study is certainly possible. Similarly, oxytocin may mediate the inhibitory effects of lactation on development of breast cancer, and of ejaculation on development of prostate cancer, and additional studies could prove to be invaluable in revealing its involvement.

It must be noted that most systems and bodily processes in living organisms are tightly inter-connected. Untangling this complexity in the presence of confounding elements is often difficult, especially in relation to psychosocial factors. Therefore, interpretation of oxytocin's expression and levels alone might be over-simplistic and under-informative. For example, instead of being increased as a direct response to exercise, oxytocin may be induced to assist its "companion" hormone, vasopressin, a well-known hormonal regulator of body fluid homeostasis<sup>[97]</sup>. Cortisol, the "stress hormone" and the rhythm surrounding its release has been linked to the progression and survival from various cancers<sup>[98-101]</sup>, and has also been linked to oxytocin<sup>[71,72]</sup>. The ability to completely elucidate various pathways and mechanisms of actions would go a long way to showing if the established connection between the different hormones extends to cancer. Furthermore, while outside the scope of this review, there are several other diseases and pathologic states possibly linked to oxytocin. Pain, depression, and anxiety have all been linked to oxytocin<sup>[102,103]</sup>. Oxytocin's role in depression management was mentioned previously in this article, but oxytocin also seems to be a promising target in pain management<sup>[104-107]</sup>, and in immunotherapy, especially through its interactions in the gut<sup>[108]</sup>.

## CONCLUSION

Most knowledge of oxytocin centers on its role as a reproductive hormone. Since its discovery, its other

roles have progressively become clearer, including involvement in social behavior, cardiovascular regulation, and carcinogenesis. While it is currently difficult to pinpoint and precisely define oxytocin's oncogenic roles, it is hoped that this review will encourage greater intensity in researching the details of the role of oxytocin in cancer. Future research has a number of plausible and exciting directions to follow and will hopefully clarify some of the ambiguities concerning the role of oxytocin in cancer.

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