

## P2X receptors: New players in cancer pain

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### Abstract

Pain is unfortunately a quite common symptom for cancer patients. Normally pain starts as an episodic experience at early cancer phases to become chronic in later stages. In order to improve the quality of life of oncological patients, anti-cancer treatments are often accompanied by analgesic therapies. The P2X receptor are adenosine triphosphate (ATP) gated ion channels expressed by several cells including neurons, cancer and immune cells. Purinergic signaling through P2X receptors recently emerged as possible common pathway for cancer onset/growth and pain sensitivity. Indeed, tumor microenvironment is rich in extracellular ATP, which has a role in both tumor development and pain sensation. The study of the different mechanisms by which P2X receptors favor cancer progression and relative pain, represents an interesting challenge to design integrated therapeutic strategies for oncological patients. This review summarizes recent findings linking P2X receptors and ATP to cancer growth, progression and related pain. Special attention has been paid to the role of P2X2, P2X3, P2X4 and P2X7 in the genesis

of cancer pain and to the function of P2X7 in tumor growth and metastasis. Therapeutic implications of the administration of different P2X receptor blockers to alleviate cancer-associated pain sensations contemporarily reducing tumor progression are also discussed.

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**Key words:** Cancer; Pain; Adenosine triphosphate; P2X2; P2X3; P2X2/3; P2X4; P2X7

**Core tip:** Cancer pain is an increasing emergency as the number of oncological patients and survivors tends to growth. Oncological patients will greatly benefit of new therapies combining anti-tumor effects with a reduction of pain perception. This review gives an overview of latest literature on P2X receptors role in tumor progression and different types of cancer pain. The potential of P2X receptors as therapeutic targets in tumor is also discussed.

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### INTRODUCTION

Half of all oncological patients present pain symptoms<sup>[1]</sup>. This percentage arise in individuals undergoing cancer treatment getting worse, as tumor progress through its advanced stages<sup>[2-4]</sup>. Pain sensitization is also frequent in long-term cancer survivors following curative treatment<sup>[2,3]</sup>. Moreover, pain experience of oncological patients ranges from moderate to severe<sup>[3]</sup>. The most common pain locations in all cancer patients are back, abdomen and hips. Although there are many studies reporting an increased pain prevalence in cancer types involving head, bone, gynecological and gastrointestinal sites<sup>[2]</sup>, other meta-analysis found no significant relation-

ship between pain and cancer type<sup>[3]</sup>.

A growing body of literature attributed a crucial role in pain sensitization and transduction to adenosine triphosphate (ATP) and purinergic P2X receptors<sup>[5]</sup>. Moreover, P2X antagonists were successful in reducing neuropathic pain<sup>[6]</sup>. Furthermore, recent reports highlighted the role of P2X receptors in cancer development and progression<sup>[7,8]</sup>. Thus, it is tempting to speculate a possible P2X-dependent mechanism affecting both tumor growth and cancer pain. P2X receptors are ATP gated ion channels that, upon ligand stimulation, cause Na<sup>+</sup> and Ca<sup>2+</sup> cellular influx and K<sup>+</sup> efflux. The P2X family includes seven transmembrane proteins (P2X1-7) ranging in length from the 362 amino acids of P2X6 to the 595 of P2X7<sup>[9]</sup>. Single P2X subunits assemble as homo or hetero-trimers, with each subunit formed by N and C terminal intracellular tails, two membrane spanning domains and a long extracellular loop including the ATP binding site<sup>[9,10]</sup>. Several cell types including neuronal, immune and cancer cells express P2X receptors. The role of ATP and its receptors in pain sensation is well accepted and diverse kind of pain have been associated to activation of different P2X receptors, *i.e.*, acute pain with sensory neurons-P2X3, neuropathic pain with glial cells-P2X4, inflammatory pain with immune cells-P2X7<sup>[11]</sup>.

Here we give an overview of different forms of cancer pain, identifying the role of P2X receptors in each of them.

## DIFFERENT TYPES OF PAIN IN CANCER

Although the sensation of pain, at different levels, is a common experience in various pathologies including cancer, it is very difficult to catalog it. Responding to this need the International Association for the Study of Pain (IASP) classified Chronic Pain originally in 1986, and later on in 1994. The IASP system of classification considers the main site of pain, the system affected, the pattern of occurrence, the time since pain onset, and etiology (<http://www.iasp-pain.org>). In 2010, Woolf<sup>[12]</sup> proposed another way to classify pain in three main classes: nociceptive, inflammatory, and neuropathic.

Nociceptive pain can be associated with peripheral nerve sensitization and defined as a high-threshold pain only activated in the presence of intense stimuli such as thermal, mechanical and chemical. These stimuli are transduced and encoded to the brain by nociceptive neurons, whose cell bodies are located in both the dorsal root ganglia (DRG) or the trigeminal ganglia<sup>[12,13]</sup>. Inflammatory pain is spontaneous pain arising by activation of the immune system due to tissue injury or infection<sup>[12,13]</sup>. The inflammatory response is normally protective towards pathogens, however, when deregulated can cause pathological processes, such as autoimmune diseases and pain<sup>[14]</sup>. Neuropathic pain is defined by IASP (<http://www.iasp-pain.org>) as a pain “caused by a lesion or disease of the somatosensory nervous system”; thus, a nerve injury could determine a peripheral sensitization, characterized by an altered sensitivity at the peripheral

and central nervous system (PNS and CNS) level<sup>[15]</sup>. Infections and inflammation are other potential causes for neuropathic pain<sup>[16]</sup>.

Considering different cancer types, patients' experiences are ascribable to all the three subclasses of pain. In fact, cancer patients' pain sensations are characterized by different sensory abnormalities or a combination of them: hypersensitivity or hyposensitivity; paresthesia (abnormal sensation that is not painful or unpleasant), dysaesthesia (unpleasant abnormal sensation); allodynia (pain produced by normally non-painful stimuli); or hyperalgesia (increased response to a stimulus that is normally painful)<sup>[4]</sup>.

Cancer-related pain is present at any stage of cancer progression, with different intensity of frequency, and it is progressively increasing<sup>[17]</sup>. Initially cancer pain is the direct consequence of primary or metastatic tumor masses themselves, and then arises as side effect of treatments to eradicate cancer<sup>[1-3,15]</sup>. Pain perception could be considered also a useful alarm: most of nociceptive syndromes are easily discovered, and in some cases, their diagnosis could precede that of the neoplasia. On the other hand cancer associated-neuropathic syndromes are highly variable by individual<sup>[18]</sup>. Considering the impact of pain in patients' quality of life, it is not possible to define it as a simple side effect of tumor progression, for this reason a great interest is arising about the specific origin and mechanism of cancer pain (Figure 1).

Based on cancer stage and treatment, it is possible to define three diverse classes of cancer pain.

### **Tumor mass-induced pain**

Cancer itself is the first source of pain: the extension and invasiveness of primary/metastatic cancer masses generates obstruction, infiltration, or peripheral nerve sensitization inducing nociceptive or neuropathic pain<sup>[4,19]</sup>.

Bone cancer pain is an explicative example: it is caused by tumors arising in bone as osteosarcomas<sup>[20]</sup>, or it is a consequence of skeletal metastases of lung, breast and prostate tumors<sup>[21]</sup>. When tumor cells infiltrate into bone, different processes begin including bone resorption, compression and damage of the sensory fibers, infiltration of immune cells followed by release of inflammatory cytokines<sup>[22]</sup>. Thus, cancer bone pain can be defined as nociceptive and inflammatory pain. Furthermore, neuropathic and inflammatory pain pathway activation occurs even at the spinal cord level<sup>[23]</sup>.

### **Pain induced by anti-cancer treatments**

Oncologic patients also suffer pain induced not directly by cancer itself, but by the different treatments that they are undergoing, *i.e.*, chemotherapy, radiation or surgery<sup>[18]</sup>. These pain experiences belong principally to nociceptive and neuropathic pain syndromes.

Surgery represents one of the most used therapeutic approaches to eradicate cancer. Thus, it is quite common that removal of tumor masses causes nerve sensitization or damage, inducing nociceptive pain. In case of amputation, patients develop multiple form of discomfort in the

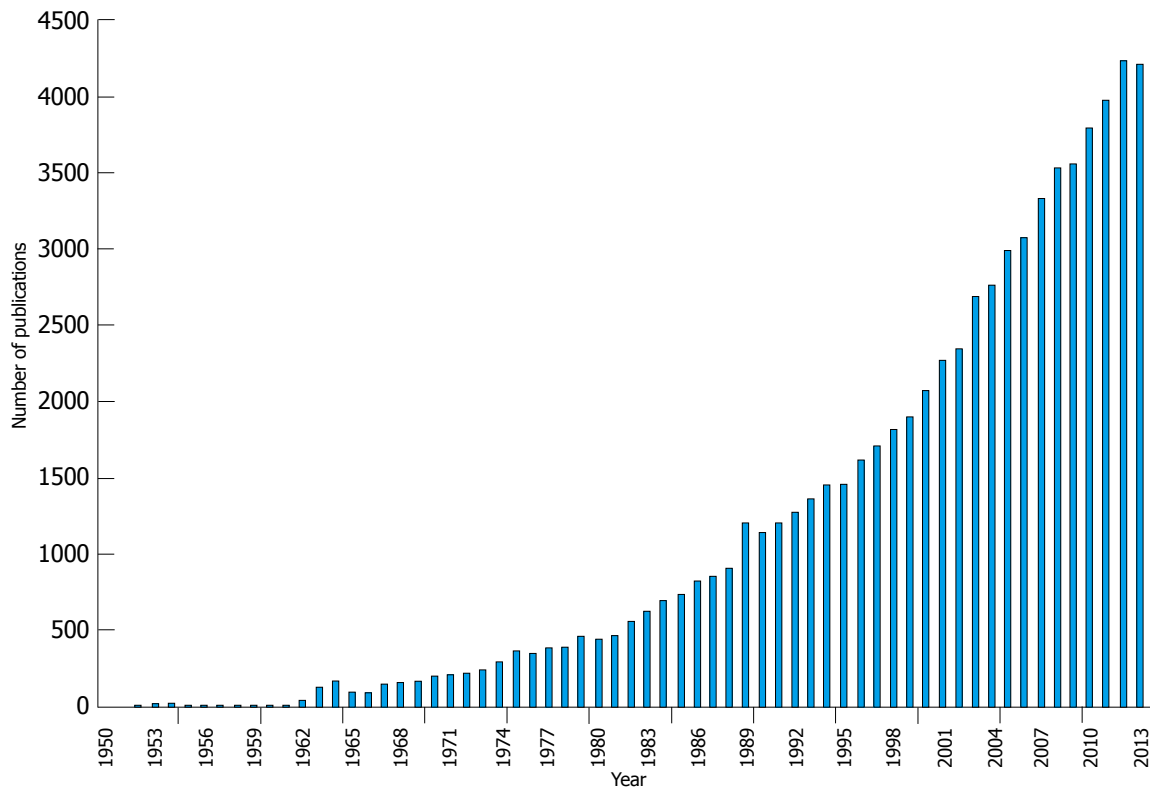


Figure 1 Number of publications per year with keywords "cancer pain". From MEDLINE®/PubMed®, a database of the United States National Library of Medicine.

missing limb. Both painful and non-painful sensation are defined as phantom limb phenomenon: a painful sensation in the residual portion of the amputated limb (stump pain) is associated with a painless sensation originating in the limb that no longer exists (phantom sensation)<sup>[24]</sup>. In this particular form of pain, the pathophysiology is not clearly defined, as it is not clear whether this is a phenomenon univocally dependent on PNS or CNS<sup>[24]</sup>. However, it was demonstrated that DRG neurons are a critical source of ectopic impulse discharge<sup>[25]</sup>.

Anti-tumor chemotherapeutic agents are known to cause pain<sup>[26]</sup>. Chemotherapy-induced neuropathy, that causes pain increase in drug-dose-dependent manner<sup>[4]</sup>, include neuropathic, non-neuropathic<sup>[27]</sup> and inflammatory pain, inflicting damage both on sensory neurons and satellite glial cells in DRG<sup>[28]</sup>.

Even radiotherapy causes pain as side effect. For example, in breast cancer, radiotherapy successfully decreases mortality but can determine a long-lasting breast pain<sup>[29]</sup>. The administration of opioids is a good approach to prevent predictable pain due to radiotherapy in bone cancer patients<sup>[30]</sup>.

### Chronic non-cancer pain in cancer patients

Chronic non-cancer pain is a debilitating problem that compromises every aspect of patients' life. Normally, it could be defined as a nociceptive or neuropathic pain, lasting longer than the expected period of healing. Chronic pain sensation is due by persistent stimulation, changes or damages to the CNS or PNS, or both<sup>[31]</sup>. There is not a common therapeutic approach for these

different types of patients' pain, because the pain type and severity is a result of genotype, and administered treatment has to be customized<sup>[31]</sup>.

## ATP AND P2X RECEPTORS IN TUMOR

A growing body of evidence indicates ATP and purinergic signaling as key players in both cancer and pain<sup>[32-34]</sup>. ATP is released in physiologic conditions by healthy cells exerting beneficial effects *via* several mechanisms for example acting as fast excitatory neurotransmitter or playing long-term (trophic) roles in cell proliferation, growth and development<sup>[5,35,36]</sup>. Nonetheless, high levels of ATP can have detrimental effects as this nucleotide acts as pain stimulus and is involved in different inflammatory and non-inflammatory pathologies, including cancer<sup>[9,37]</sup>. *In vivo* measure of extracellular ATP in tumor microenvironment allowed to estimate a cancer surrounding concentration of the nucleotide in the micromolar range<sup>[38]</sup>. Tumor cells can actively secrete ATP<sup>[39]</sup> or release it as consequence of spontaneous or chemotherapy-induced cell death<sup>[40]</sup>. Platelets are an extra source of ATP in tumor context, and thanks to release of the nucleotide they facilitate cancer cell extravasation and spreading<sup>[41]</sup>. Another, good candidate for ATP secretion is its own receptor P2X7 as its stimulation with the synthetic agonist BZ-ATP caused release of ATP requiring P2X7 large pore opening<sup>[42,43]</sup>. Once in the cancer milieu, ATP acts as growth promoting and pro-metastatic factor<sup>[7,8]</sup>, neuronal and immune-cells stimulus<sup>[5,44]</sup> and main source of the immunosuppressant adenosine<sup>[45]</sup>.

Several studies implicated ATP-receptor P2X7 in cell proliferation under nutrient deprivation conditions, similar to those present in cancer microenvironment, such as growth factors and glucose reduced availability<sup>[43,46-48]</sup>. Moreover, it was recently demonstrated that P2X7 facilitates tumor engraftment, growth and vascularization<sup>[7]</sup> and that P2X7 blockade or silencing effectively reduces tumor growth in animal models of colon cancer, melanoma and neuroblastoma<sup>[7,49]</sup>. P2X and P2Y receptors expression has been reported both in tumor and tumor-associated cells in several cancers (for a recent review see<sup>[34]</sup>). However, and in depth characterization of the role of ATP in the crosstalk among tumor and immune or neuronal surrounding cells is still missing.

## P2X IN CANCER PAIN

Extracellular ATP triggers pain perception through activation of different P2X receptors. Indeed, P2X receptors are essential players in nociceptive, inflammatory and pathological pain transduction<sup>[38,50,51]</sup>. All the different compartments involved in pain transduction, sensory ganglia, DRG and spinal cord, are characterized by high expression of P2X receptors in excitable and non-excitable cells<sup>[51]</sup>.

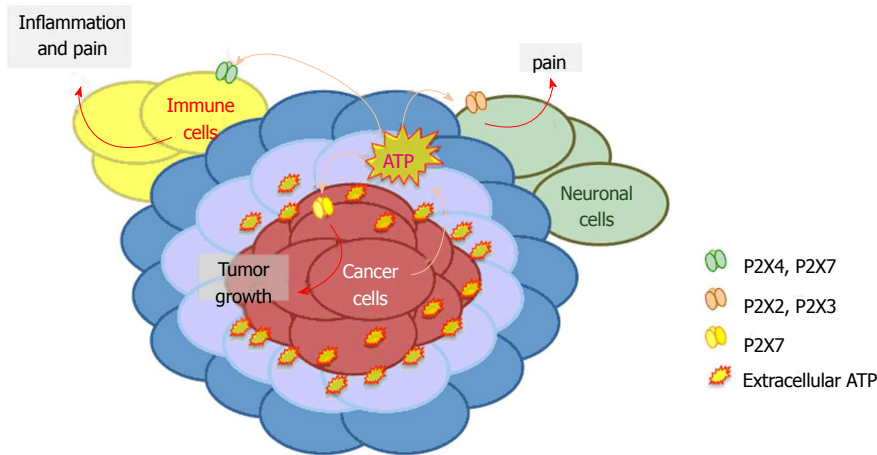
Different studies demonstrated the involvement of ATP and P2X receptors in cancer pain<sup>[22]</sup>. The use of diverse animal pain models allowed identifying P2X receptors as mediators of cancer pain perception through DRG and spinal cord<sup>[28,52,53]</sup>.

As mentioned before, one of the most studied cancer pain models is bone cancer: many common tumors preferentially metastasize to multiple bones and bone cancer patients suffer of moderate to severe chronic pain<sup>[20,54]</sup>. Interestingly, up-regulation of P2X3 receptor was found in DRG of animals experiencing bone cancer pain<sup>[52,53,55]</sup>. Homomeric P2X3 and heteromeric P2X2/3 receptors are the main responsible for ATP evoked nociceptive pain<sup>[56,57]</sup>, and were accordingly involved in bone cancer pain perception<sup>[55]</sup>. Recently, Liu *et al.*<sup>[52]</sup> (2013) showed that, in rat bone cancer, DRG neurons-P2X3 receptor is functionally up-regulated by the neuronal calcium sensor VILIP-1, and contributes to the development of bone cancer pain. Moreover, P2X3 receptor antagonist A-317491, which successfully reduces chronic inflammatory and neuropathic pain behavior in animals<sup>[58,59]</sup>, also relieves cancer bone pain<sup>[60]</sup>. However, A-317491 effect was limited to attenuation of bone pain related behaviors in the early stage of tumor development, while had no effect as tumor progressed to an advanced point. Similarly, oral administration of AF-353, another potent and selective P2X3 and P2X2/3 receptor antagonist, attenuated bone cancer pain, but had no preventing effect on cancer-induced bone destruction<sup>[55]</sup>. P2X receptors blockade was found to be an efficacious pain easing strategy also in a model of melanoma developed in mice paw<sup>[61]</sup>. In this context, tumor cell inoculation caused a pain related behavior that was increased by intra-plantar injection of ATP, and reduced, in a dose-dependent fashion, by P2

receptor broad-spectrum antagonists. Interestingly, the authors reported a contemporary up-regulation of P2X3 receptors in DRG. Discussed evidence suggests that specific blockade of P2X3 or P2X2/3 receptors will not be sufficient to minimize cancer related pain. In fact, the role of P2X receptors in cancer pain is not restricted to P2X3 and neuronal cells. On the contrary, non-neuronal cells play a pivotal role in chronic pain states<sup>[51,57,62]</sup> and immune-cancer cells expressed P2X4 and P2X7 receptors are involved in inflammatory and neuropathic pain development<sup>[29,30,47,53,54,60]</sup>. P2X4 or P2X7 null mice show reduced nociceptive sensitivity and development of neuropathic pain states. Moreover, similar results can be obtained by *in vivo* administration of P2X7 antagonists<sup>[6]</sup>. However, neither P2X7 genetic ablation nor receptors' antagonist administration was able to alleviate bone cancer pain<sup>[63]</sup>. The different efficacy of P2X7 antagonist in reducing inflammatory and neuropathic pain versus bone cancer pain can be ascribed to a diverse mechanism of generation of the painful stimulus, which is probably more complex in cancer than in other pathological situations.

## P2X RECEPTORS AS PHARMACOLOGICAL TARGETS FOR CANCER PAIN

Pharmacological approaches to different kind of cancer pain are based on patient's status. There are three main classes of drugs for cancer pain management: opioids, non-opioids and adjuvant analgesics<sup>[64]</sup>. Normally, pharmacotherapy consist in an appropriate selection of drugs, belonging to the three categories mentioned, and it is structured to optimize positive outcomes and minimize side-effects<sup>[4]</sup>. Terminal oncological patients generally experience chronic pain that can be eased by palliative care improving their quality of life and helping them to face the prospect of death<sup>[1]</sup>. Suramin, a broad spectrum P2 receptor antagonist, showed clinically relevant antitumor activity in prostate cancer, as reflected by reduction of prostate specific antigen levels, pain relief, and a relatively long time to disease progression<sup>[65,66]</sup>. Moreover, suramin underwent phase III clinical trials for refractory prostate cancer, giving encouraging results as palliative therapy and delaying disease progression<sup>[67]</sup>. However, the mechanism of action of suramin is essentially unknown as it binds to several proteins including growth factors and is not only a P2 receptor antagonist but also acts as agonist of ryanodine receptors. Nevertheless, pain-easing activity of suramin could be attributed, at least partially, to P2X3 or P2X2/3 blockade. Indeed, as mentioned before, different P2X3, P2X2/3 specific antagonists proved effective in reduce bone cancer pain perception in animal models<sup>[53,60,68]</sup> and refractory prostate cancer generally metastasize to bone. P2X2 and P2X2/3 receptors have also been involved in development of opioid treatment resistance in severe pain states associated to cancer metastasis<sup>[68]</sup>. Chizhnikov *et al.*<sup>[69]</sup> demonstrated that opioids



**Figure 2** Schematic representation of solid tumor generated by cancer cells (red) surrounded by the normal tissue cells (light and dark blue) releasing extracellular adenosine triphosphate in surrounding environment (in yellow). Adenosine triphosphate (ATP) acts through three different ways: (1) binding P2X7 receptors, ATP facilitates tumor growth; (2) binding the P2X2, P2X3, P2X2/3 receptors expressed by neuronal cells (in green), ATP triggers pain perception; and (3) binding P2X4 and P2X7 receptors expressed by immune cells (in yellow), ATP causes inflammation and pain.

are able to inhibit P2X3 and P2X2/3 receptor responses in sensory neurons<sup>[69]</sup>, but also that cancer cells, co-cultured with neurons, release diffusible factors able to alter opioid-dependent P2Xs inhibition, probably causing opioid resistance<sup>[69]</sup>.

Another interesting target for the development of anti-cancer, pain-easing therapies is P2X7. At the moment different P2X7 antagonists are undergoing clinical trials for their efficacy in reducing neuropathic and inflammatory pain<sup>[70,71]</sup>, and its role in pain pathways is confirmed by the involvement of P2X7 receptor, expressed by spinal microglia, in induction of morphine tolerance<sup>[72]</sup>. Moreover, P2X7 potent and selective antagonists A-740003 and A-438079 both showed anti-nociceptive activity in rodents<sup>[69,73]</sup>. Accordingly, P2X7 receptor antagonist brilliant blue G reduced pain perception in a rat model of bone cancer<sup>[74]</sup>. However, in a similar mice model A-438079 failed to alleviate bone cancer pain<sup>[63]</sup>. These discrepancies could be ascribed to the different animal models, cell players examined, and dissimilar specificity of the drugs administered. A strategy based on P2X7 blockade could not only be efficacious in reducing cancer pain but also tumor growth, vascularization and spreading. In fact, we recently demonstrated that P2X7 receptor affects cancer development, causing increased tumor engraftment, growth rate and angiogenesis<sup>[75]</sup>. Interestingly, both P2X7 antagonist AZ-10606120 and P2X7 inhibitor oxidized-ATP caused an evident tumor regression accompanied by reduced vascular endothelial growth factor secretion and consequently a decrease in tumor blood vessels<sup>[76]</sup>. Accordingly, different studies show a P2X7 blockade dependent reduction of melanoma and glioma growth<sup>[49]</sup>. However, data on glioma are debatable, in fact Fang and colleagues also reported Brilliant Blue G dependent glioma growth acceleration<sup>[75]</sup>.

A growing body of literature has also attributed a role to P2X7 in tumor dissemination<sup>[65,77-80]</sup> and drugs acting at the receptor have been proposed as anti-metastatic agents<sup>[8,80]</sup>. Interestingly, drugs as different as the traditional Chinese medicine compound Emodin, and the statin atrovastatin both act at tumor cells inhibiting their migratory ability *via* P2X7 blockade<sup>[79,80]</sup>.

Treatment of oncological patients with intravenous

infusions of ATP at high doses was also proposed as strategy to fight tumor growth taking advantage of ATP cytotoxic properties. ATP administration intravenously proved to be effective in arresting tumor progression in rodent models of hormone-refractory prostate<sup>[81]</sup> and colon cancer<sup>[82]</sup>. However, the possible side effects due to pain development after intravenous administration of millimolar doses of ATP to patients have to be taken into account. In fact, it is known that application/injection of ATP causes pain perception associated with vascular changes<sup>[61,62]</sup> and this effect was also observed in clinical trials administering high doses of ATP to patients<sup>[83]</sup>. On the other hand, short infusion of low ATP concentrations did not cause pain when administered to terminal oncological patients, but improved their quality of life<sup>[84]</sup> and reduced cachexia<sup>[85]</sup>. However, administration of ATP to patients with less severe forms of cancer did not produce any positive effect on their quality of life or in tumor regression<sup>[84]</sup>.

Interestingly, ATP has been suggested also as adjuvant chemotherapy facilitating the passage of anticancer drugs such as doxorubicin and mytomicin C<sup>[81,86,87]</sup>. However, chemotherapy itself causes pain, which could be enhanced by ATP administration. Summarizing, even if ATP administration to cancer patients is representing an interesting strategy to eradicate tumor cells, probably will be causing pain as major side effect and will be, then, inadequate for the treatment of tumors associated with severe pain sensation.

## CONCLUSION

Cancer pain is one of the most serious problems in oncology, depending on the growing number of cancer patients and, luckily, of cancer survivors. For these reasons identification of adequate anti-pain therapies, improving the quality of life of oncological patients is attracting widespread interest. Due to the different cellular components involved in tumor, classically administered anti-pain pharmacological approaches not always satisfy cancer patient's needs. In this review, we underline a possible connection between pain perception and tumor growth in cancer mediated by P2X receptors (Figure 2). Described

evidence suggests that P2X receptors are good pharmacological targets for the treatment of cancer and associated pain. Reported literature supports the hypothesis that the ideal anti-cancer strategy will be obtained with a calibrated mixture or combination of P2X2, P2X3, P2X4 and P2X7 receptor antagonists, which will reduce/resolve at the same time tumor growth and relative pain.

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