REVIEW ARTICLE

The role of P2X7R purinoreceptor in osteosarcoma

Manish Yadav, Ajai Singh, Nazia Rizvi, Sabir Ali, Salma S, Vineet Kumar, Syed Rizwan Hussain

Department of Orthopaedic Surgery, King George’s Medical University, Lucknow, Uttar Pradesh, India.

Abstract: Osteosarcoma is the most common type of bone cancer, which appears mainly in the metaphysis of long bones, especially in males between the age of 0–14 years. Malignancy usually emerges with the abnormal growth of tumor-forming bone cells. These tumor cells act like new bones that are responsible for the spread of sarcoma throughout the bone matrix. In this review, we focused on the expression and function of the P2X7 receptor (P2X7R) as a therapeutic target in osteosarcoma malignancy. Two known human P2X7R functional splice variants in osteosarcoma cell growth are the full length P2X7RA and the truncated P2X7RB. The stimulation of growth is attributed to an increase (i) in the mobilization of Ca²⁺ ions, and (ii) in the nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) activity. Furthermore, Te85 P2X7RA+B cells caused membrane depolarization and spontaneous release of extracellular adenosine triphosphate (ATP). The P2X7R agonist, benzoyl adenosine triphosphate (BzATP), may increase the liberation of ATP and this may be regulated by P2X7R. As a result, cell proliferation occurs with the spread of osteosarcoma throughout the bone matrix. BzATP also increases cell growth and activates NFATc1 to make it cancerous. In this review, we have highlighted the crucial role of the P2X7R purinoreceptor in osteosarcoma pathogenesis. It is an upstream regulator of all paths that may inhibit the receptor activator of nuclear factor kappa-B ligand (RANKL) and a mechanistic target of rapamycin (mTOR) blockers. This review suggests that P2X7R is an attractive therapeutic target for osteosarcoma.

Keywords: osteosarcoma; purinergic receptor; osteoprotegerin; bone tumor; metastasis; osteoblast; osteoclast


©Correspondence to: Syed Rizwan Hussain, Department of Orthopaedic Surgery, King George’s Medical University, Chowk, Lucknow, Uttar Pradesh, 226018, India, rizwan59elmc@gmail.com

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Osteosarcoma is the most common type of cancer that arises in bones. This type of cancer occurs in bone-forming cells and the cancer-filled bone is weak compared to normal bones. The disease predominantly affects children and teenagers but it may also occur at any age. Osteosarcoma usually arises in the metaphysis of long bones (Figure 1) [1], such as the distal end of femur, proximal end of tibia, and proximal humerus during the second decade of one’s life [2]. Individuals with this kind of malignancy generally complained about deep-seated pain, and teenagers who are active in sports tend to experience pain in the distal end of their femur. Sudden bone fracture is an initial symptom as the affected bone becomes relatively weak and fractures may occur as a result of minor trauma. A previous study reported that the frequency of pain may be intermittent with varying intensities [3]. In osteosarcoma, swelling is typically not visible unless the disease develops closer to the surface of the body (e.g., pelvis). In addition, pain, swelling, and redness start at the site of the tumor and the feeling of pain increases with physical activities such as lifting or limping.

Osteosarcoma is an aggressive malignant neoplasm that originates from previously transformed cells of me-
Senchymal origin and produces malignant osteoid bone tissues as a result of osteoblastic differentiation\cite{4}. The characteristic feature of osteosarcoma is the presence of non-mineralized bone tissue (immature bone) within the tumor. The tumor cells are pleomorphic (variable in shape, size, and their nuclei), with several giant cells. These cells produce irregular trabeculae with or without central calcification of the tumor-filled bone. These tumor cells are incorporated in the osteoid matrix\cite{5,6}.

**Figure 1** Prevalence of skeletal osteosarcoma malignancy (adapted from Thompson 2013\cite{1})

The incidence of osteosarcoma for all races and both sexes are 4.0 and 5.0 per year per million people in the age range of 0–14 and 0–19 years old, respectively (Figure 2)\cite{6}. It should be noted that bone sarcoma is more prevalent in males than females in the age range of 0–14 years old.

**Figure 2** Incidence in relation to different cancers worldwide

**Risk factors and pathogenesis**

In the older population, around one-third of malignancy cases are due to Paget’s disease of bone, followed by osteosarcoma\cite{7}. The precursor conditions for osteosarcoma may be Paget’s disease and other benign bony lesions\cite{8}, with chemotherapy, irradiation, as well as inherited conditions (i.e., Li-Fraumeni, Rothmund-Thomson, and Bloom and Werner syndromes)\cite{9} being listed as potential causes.

Osteosarcoma occurs at the sites of bone growth and its proliferation creates a tendency for the osteoblastic cells of the cancer to acquire mutations, which could lead to the transformation of cells (Rb and p53 genes are commonly involved). The tumors are solid, hard, and irregular owing to the tumor spicules of calcified bone radiating in triangles. These triangles are known as the Codman’s triangle, which is characteristic of osteosarcoma.

Microscopically, the presence of osteoid (bone formation) is the characteristic feature of osteosarcoma within the tumor. A previous study by Smida et al. showed the amplification of chromosomes 6p21, 8q24, and 12q14, as well as the loss of heterozygosity of chromosome 10q21.1, which are the most common genomic alterations in osteosarcoma\cite{10}.

When human cells are exposed to a molecular level attack, the DNA of somatic cells may get damaged. Nonetheless, this type of DNA damage may not necessarily lead to malignancy as there are a number of tumor suppressor mechanisms in place. These mechanisms involve either the repair of DNA damage or inducing the apoptosis of these cells. The p53 and retinoblastoma (Rb) genes are well-known tumor suppressor genes. However, tumor suppressor genes may themselves become mutated resulting in the loss of their protective function. Mutations in the p53 and Rb genes have been proven to be involved in osteosarcoma pathogenesis\cite{11}. The molecular pathogenesis (Table 1) of this malignant disease is due to abnormalities like the dysfunction of the tumor suppression gene (p533), transcriptional factors (c-fos and c-jun proto-oncogenes), connective tissue growth factors (CTGF), and secretion of cytokines (PTHrP, interleukin 6, and 11).

**P2X7R gene**

P2X7R is a human protein encoded by the P2X7R gene that is located on chromosome 12. The product of this gene belongs to the purinoreceptors of the ATP family\cite{17,18}. The P2X7R is a ligand-gated cation channel, which opens in response to ATP binding and leads to cell depolarization. The P2X7R receptors require higher levels of ATP than other P2X receptors, though this could be due to a reduction in the concentration of divalent cations such as calcium or magnesium. The continuous binding results in increased permeability to N-methyl-D-gluc-
mine (NMDG)\(^{[20]}\).

P2X7R is not readily desensitized and a continuous signaling leads to increased permeability and an increase in current amplitude. The activation of P2X7R by ATP helps to recruit pannexin pores\(^{[21]}\), which allow small molecules such as ATP to leak out of the cells. This permits the activation of purinergic receptors and physiological responses such as the spread of cytoplasmic calcium waves\(^{[19]}\). P2X7R has been implicated in ATP-mediated cell death, regulating receptor trafficking and inflammation\(^{[22]}\).

There are two types of purinergic receptors, P1 and P2. Adenosine acts on the P1 receptors while ATP and its breakdown products (adenosine diphosphate, ADP and adenosine monophosphate, AMP), act on the P2 receptors\(^{[23]}\). A previous study has proposed the subclassification of the P2 receptors, i.e., P2X (seven subtypes) and P2Y (eight subtypes) receptors, and P2X7R consists of two types: P2X7RA and P2X7RB\(^{[24]}\).

Although the growth-promoting function of P2X7R seems at odd with its established role in apoptosis, this receptor is highly expressed in some malignancies, seemingly consistent with its growth-promoting role. The apparent anti-apoptotic property of P2X7R is based on studies using ATP and KN-93. The initial activation of P2X7R (via autocrine/paracrine release of extracellular ATP) promotes cell growth\(^{[25]}\). P2X7R-transfected human embryonic kidney (HEK293) cells have a huge amount of intracellular ATP, higher mitochondrial resting potential, and increased basal mitochondrial Ca\(^{2+}\) ions compared to HEK293 mock-transfected cells. This growth-promoting function of P2X7R is dependent on pore formation since it does not take place in cells transfected with a truncated form of P2X7R, which cannot form a pore. P2X7R-transfected Henrietta Lacks (HeLa) cells are ATP-challenged, resulting in mitochondrial fragmentation and subsequent cell death (Figure 3).

### The role of the P2X7R gene in osteosarcoma

The P2X7R gene is attracting attention for its involvement in cancer. Recent studies have reported the crucial role of P2X7R in tumor cell growth, angiogenesis, and invasiveness. Two variants of P2X7R, the full length P2X7RA and truncated P2X7RB, are found in osteosarcoma.

#### Table 1 Molecular pathogenesis of osteosarcoma

<table>
<thead>
<tr>
<th>No.</th>
<th>Process</th>
<th>Mechanism</th>
<th>References</th>
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<tbody>
<tr>
<td>1.</td>
<td>Chromosomal abnormalities</td>
<td>Amplification of chromosome 6p21, 8q24, and 12q14 causes genomic alteration in osteosarcoma.</td>
<td>Ta et al., 2009(^{[12]})</td>
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<td>2.</td>
<td>Tumor suppression gene dysfunction</td>
<td>p53 is a well-known tumor suppressor gene. It undergoes mutations occasionally, giving rise to cells that cause osteosarcoma. When exposed to molecular level assaults (e.g., radiation), somatic DNA may get damaged or apoptosis takes place.</td>
<td>Chandar et al., 1992(^{[13]})</td>
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<td>3.</td>
<td>Transcription factor</td>
<td>AP-1 comprised of fos and jun protein products of c-fos and c-jun proto-oncogenes. C-fos and c-jun are responsible for benign osteoblastic lesions and low-grade osteosarcoma. The activator protein-1 complex (AP-1) is a regulator of transcription that controls cell proliferation, differentiation, and bone metabolism.</td>
<td>Franchi et al., 1998(^{[14]})</td>
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<td>4.</td>
<td>Osteosarcoma cell proliferation, apoptosis, anchored independent growth</td>
<td>Cancer cells are resistant to apoptosis/proliferation without restriction. Apoptosis consists of initiation and execution phases. During initiation, the caspase enzyme (responsible for cleaving cellular proteins) is activated. The execution phase refers to the hydrolysis process performed by an activated caspase. Anoikis is a form of apoptosis involving osteosarcoma cells that are resistant to regular cell death and continue to proliferate despite of deranged cell-cell and cell-matrix attachment. This resistance to anoikis is termed as anchored independent growth (AIG).</td>
<td>Broadhead et al., 2009(^{[15]})</td>
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<td>5.</td>
<td>Tumor angiogenesis</td>
<td>Tumor angiogenesis is essential for sustained osteosarcoma growth and metastasis without vasculature. Osteosarcoma cells would be unable to obtain nutrients and oxygen for proliferation.</td>
<td>Hicklin et al., 2005(^{[16]})</td>
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<td>6.</td>
<td>Osteoclast function</td>
<td>Osteosarcoma invasion of bone relies on bone matrix, osteosarcoma cells, osteoblast, and osteoclast. During the initial stage of osteosarcoma invasion, growth factor such as TGF-β is released from degraded bone matrix and acts on osteosarcoma cells, stimulating the release of PTHrP and interleukins (IL-6,11). These cytokines stimulate osteoclast resorption. As a result, the bone remodels itself from cancerous cell.</td>
<td>Quis et al., 2003(^{[17]})</td>
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Recently, in vitro and in vivo evidence show that P2X7R has a main role in carcinogenesis, enhancing tumor cell growth\textsuperscript{[28,29]}, tumor-associated angiogenesis, and cancer invasiveness\textsuperscript{[30]}. These data further support previous in vitro reports, demonstrating that P2X7R expression increases cell proliferation\textsuperscript{[31,32]}, mitochondria and endoplasmic reticulum Ca\textsuperscript{2+} levels\textsuperscript{[33]}, vascular endothelial growth factor (VEGF) secretion\textsuperscript{[34]}, and agaroose infiltration\textsuperscript{[35]}. P2X7R is expressed in both osteoblasts\textsuperscript{[36]} and osteoclasts\textsuperscript{[37-39]}, and may play a vital role in osteoblasts-osteoclasts cross-talk through calcium oscillations\textsuperscript{[40]} and other signaling pathways\textsuperscript{[41]}. P2X7R promotes osteogenesis by stimulating osteoblast proliferation as well as osteodeposition\textsuperscript{[42]}, through a series of different pathways, including c-fos\textsuperscript{[43]}, extracellular signal-regulated kinases (ERK)\textsuperscript{[44]}, phosphotoinositide 3-kinase (PI3K)\textsuperscript{[45]} and cyclooxygenase (COX)\textsuperscript{[46]}. Finally, it is likely that P2X7R mediates osteoblast ATP release as P2X7R blockers inhibit ATP secretion.

For Te85 cells that are transfected either with P2X7RA, P2X7RB, or co-transfected with both (P2X7RA+B) genes, the expression of plasma membrane P2X7RA is higher than P2X7RB. Nonetheless, the highest level of cell surface expression has been achieved in Te85 cells transfected with both P2X7RA and P2X7RB. The stimulation of BzATP (corresponding to the EC\textsubscript{50} for P2X7RB, which has a lower affinity for ATP than the full length P2X7RA) triggers a rise in Ca\textsuperscript{2+} level in all transfected clones\textsuperscript{[40]}. The Ca\textsuperscript{2+} increments occur in the following order: Te85-P2X7RB<Te85-P2X7RA<Te85-P2X7RA+B. This response may be dependent on the different plasma membrane expression levels of the diverse isoforms (P2X7RB being the lowest whereas P2X7RA+B is the highest), or on the activation of the receptor-associated large conductance pore. In order to reproduce the typical P2X7R signature in the Te85 osteosarcoma cells, the expression of both P2X7RA and B isoforms is required. Among all cell lines tested, only Te85 cells transfected with both P2X7RA and B show a significantly higher value than the Te85 wild-type (wt) cells. Hence, the pore formation found in Te85 P2X7RA+B cells appears to be related to the extracellular ATP release. Giuliani et al.\textsuperscript{[25]}, who used P2X7R-transfected Te85 clones, found that a majority of human osteosarcomas express both P2X7RA and B; however, the expression of either isoform is differently coupled to cell growth/activity. Intracellular calcium mobilization is one of the main stimuli leading to the activation of NFATc1, which has been associated with P2X7R dependent proliferation\textsuperscript{[47]}, and is well-known in osteoblast biology\textsuperscript{[48]}. Analysis of NFATc1 nuclear translocation also showed...
The role of P2X7R purinoreceptor in osteosarcoma

that all P2X7R-transfected Te85 clones had significantly higher nuclear NFATc1 levels\(^{[25]}\). Combined evidence from various laboratory testing shows that both P2X7RA and B provided a strong growth-promoting activity\(^{[49-52]}\), and in particular P2X7RA is over-expressed in many human malignant tumors\(^{[53-56]}\). The P2X7R expression is indeed a powerful stimulus for cell growth, in which P2X7RB is the most efficient growth-promoting isoform. Treatment with either apyrase or A740003 significantly reduces the proliferative capability of all transfectants, whilst increasing BzATP stimulation. This strongly suggests an ATP-mediated loop controlling and sustaining of cell proliferation.

The function of P2X7R in osteosarcoma biology has also been investigated by scrutinizing the expression of two vital molecules for bone homeostasis, the receptor activator of RANKL and osteoprotegerin (OPG)\(^{[23]}\). The OPG mRNA is significantly increased only in P2X7RB-transfected cells. However, the RANKL/OPG ratio is decreased in all P2X7R clones. The expression of P2X7R, which affects mineralization, is another evidence of osteoblastic activity, with the transfection of the two gene isoforms producing different effects. P2X7RA alone does not significantly modify mineralization as compared to Te85 wt cells. However, the expression of P2X7RB causes a striking reduction in mineralization, with respect to Te85 wt and Te85-P2X7RA; whereas a marked increase is observed in cells transfected with both P2X7RA and B variants\(^{[25]}\).

The interaction between tumor cells and ligand molecules present in the tumor microenvironment is crucial in cancer growth and progression. ATP recently emerged as an extracellular messenger that is present at high levels in the tumor microenvironment\(^{[57-59]}\), but its effect on carcinogenesis is not completely understood. In a recent article, it has been demonstrated that P2X7R is involved in tumor growth and in vivo neo-vascularization\(^{[54]}\). P2X7R supports the proliferation of lymphocytes\(^{[60]}\), osteoblasts\(^{[61]}\), and osteosarcoma cells\(^{[62]}\). Human osteosarcomas express a high level of full length P2X7RA and truncated P2X7RB isoforms. As most osteosarcomas express both P2X7RA and P2X7RB, there is a possibility that other isoforms (i.e., different from P2X7RA or P2X7RB) are recognized by the anti-P2X7R-ec antibody. On the other hand, if expressed, the non-functional P2X7RC, P2X7RD, P2X7RF, and P2X7RH isoforms would be recognized by anti-P2X7R-Cter as they carry the same C-terminal tail as P2X7RA\(^{[63]}\). However, based on a 27.7% positive detection of anti-P2X7R-ec from known osteosarcoma cases, this strongly suggests that the only variant expressed by these tumors is P2X7RB\(^{[63]}\).

Furthermore, the discovery of P2X7RB-positive osteosarcomas, which show higher cell density and increased Ki67 expression than those expressing both isoforms, indicates a relationship between P2X7RB expression and enhanced cell proliferation. P2X7R might autonomously sustain osteosarcoma growth owing to the autocrine/paracrine ATP release. Furthermore, it might also modulate osteosarcoma cell interaction with other bone cells by regulating the release of key molecules such as RANKL and OPG, or by affecting osteodeposition\(^{[64]}\). All P2X7R-transfected Te85 osteosarcoma clones display increased proliferation compared to Te85 wt or Te85 mock cells, therefore confirming P2X7R’s trophic activity in the tumor. The receptor stimulation by BzATP significantly increases the proliferative activity of all transfected clones, with Te85 P2X7RB cells giving the highest growth ability.

Giuliani et al\(^{[23]}\) previously compared tumors cells that are positive for both P2X7RA and P2X7RB. They found that P2X7RB and P2X7RA+B have opposing roles on osteosarcoma cell growth and mineralization: the P2X7R anion channel is predominantly involved in cell proliferation (Tables 2 and 3), while the activation of the P2X7R-associated large conductance pore might be chiefly responsible for the differentiation-associated effects\(^{[25]}\).

Table 2 Opposing effects of P2X7RB and P2X7RA+B on osteosarcoma cell growth and mineralization

<table>
<thead>
<tr>
<th>P2X7RB</th>
<th>P2X7RA+P2X7RB</th>
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<tbody>
<tr>
<td>Data observation</td>
<td>Tumor cell number</td>
</tr>
<tr>
<td>Tumor matrix</td>
<td>Cell growth</td>
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<tr>
<td>NFATc1</td>
<td>OPG</td>
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<td>RANKL</td>
<td>Mineralization</td>
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<tr>
<td>Deduction</td>
<td>RANKL</td>
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<td>Osteosarcoma with undifferentiated phenotype</td>
<td>Osteosarcoma with differentiated phenotype</td>
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Recent reviews\(^{[80-83]}\) have mostly focused on the role, as well as therapeutic potential, of P2X7R in osteosarcoma. However, most of the evidence is based on in vitro studies, with limited studies on in vivo experiments and clinical studies. Therefore, further efforts must be invested
The P2X7R-mediated regulation of IL-1β has been demonstrated within the central nervous system where microglia are the resident monocyte cells. The ATP-induced IL-1β production in cultured microglial cells occurs through the activation of the P2X7R.

Neutrophil apoptosis is an important part of inflammatory regulation. The role of P2X7R is less established in neutrophils. P2X7R may have an additional and indirect role in the mediation of inflammatory arthritis via anti-apoptotic signaling in neutrophils. Serum amyloid (SAA) protein is an acute phase reactant that is often correlated with active joint inflammation and is elevated in many patients. P2X7R regulates the production of the pro-inflammatory cytokines IL-1β and IL-18 and potentially, the innate immune response. P2X7R is an activator of the inflammasome, an important complex of cytosolic proteins that are known to regulate caspase-1 processing of IL-1β and IL-18. With inflammasome dysregulation known to produce inflammatory disorders such as Muckle-Wells syndrome and neonatal onset multisystem inflammatory disease (NOMID), inhibiting inflammasome activation with P2X7R antagonists could affect the outcome of a range of inflammatory disorders.

**Table 3** Supporting roles of the P2X7R gene as reported in other diseases

<table>
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<tr>
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<tr>
<td><strong>Inflammation</strong></td>
<td>Nucleotides (such as ATP) are normally retained within the cytoplasm of cell and their presence during the process of cytolsis is thought to provide danger signals, inducing antigen-presenting cells to initiate the innate immune system. The innate immunity can be initiated by a variety of cytokines such as IL1β, IL-18, IL-16, and tumor necrosis factor-α, all of which can be produced by P2X7R activation.</td>
<td>Di Virgilio et al. 1996[85]</td>
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<td>The P2X7R-regulated release of the pro-inflammatory cytokines IL-1β and IL-18 is thought to control key signaling pathways. In particular, P2X7R is the most potent plasma membrane receptor responsible for inflammasome activation and the release of pro-inflammatory cytokines of the IL-1 family.</td>
<td>La Sala et al. 2003[90]</td>
</tr>
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<td>Savill et al. 2002[84]</td>
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<td>Mariathanasan et al. 2006[86]</td>
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<td>Volonte et al. 2012[69]</td>
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<td>Honore et al. 2006[70]</td>
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<td>Ferrari et al. 1997[71]</td>
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<td>Shigemoto-Mogami et al. 2001[72]</td>
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<td>Adinolfi et al. 2012[73]</td>
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<td><strong>Neuropathic pain</strong></td>
<td>The role of extracellular ATP and purinoceptors in cytokine regulation and neurological disorders has been discussed. P2X7R represents a critical communication link between the nervous and immune system. The systematic administration of A740003 and A 4438079 (selective inhibitors of P2X7R) reduced tactile allodynia in three different rat models, thus supporting the association between P2X7R and neuropathic pain.</td>
<td>Liu et al. 2006[83]</td>
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<td>The P2X7R expression in the spinal cord is increased after a nerve injury. The predominant type of cells expressing these receptors is microglia, and the intrathecal administration of A430879 attenuates the development of mechanical hyper-sensitivity.</td>
<td>Oh et al. 2000[82]</td>
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<td>P2X7R is one of the key players in the release of pro-inflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor-α (TNFα) from activated microglia. IL-1β is released from lipopolysaccharide (LPS)-primed microglia, following ATP stimulation in a manner that depends on P2X7Rs.</td>
<td>Yang et al. 2007[82]</td>
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<td>Cancer</td>
<td>P2X7R involves in many tumor-promoting and immune-modulatory effects of extracellular ATP. Like other members from the P2X7R family, P2X7R mediates cation fluxes across the plasma membrane but it also gates a large non-selective pore owing to its peculiar C terminal tail.</td>
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<td>Proliferation and other tumor transformation hallmarks seem dependent on channel activity since they are retained by cells expressing the C terminal-truncated P2X7 splice variants, which lack pore forming activity. Several reports have suggested an association between P2X7R and cancer.</td>
<td>El-Oram et al. 2001[75]</td>
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<td>The participation of P2X7R in tumor progression was demonstrated in a recent in vivo study. It showed that P2X7 inhibition by either pharmacological tools or RNA interference caused a dramatic reduction of tumor masses and vice versa. Interestingly, P2X7 showed a higher vascular endothelial growth factor (VEGF)</td>
<td>La Sala et al. 2003[90]</td>
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<td>P2X7-dependent AP-1/Fos–B activation is responsible for the cycoxygenase-2 (COX-2) expression whereas mechanism stimulation triggers arsenic trioxide (ATO) release and P2X7-dependent activation of several kinases, including ERK and PI3.</td>
<td>Honore et al. 2006[70]</td>
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<td>The enhanced plasma tumor necrosis factor (TNF-α) has been associated with an increased incidence of prostate cancer, while a polymorphism increasing IL-1β production conferred a greater susceptibility to gastric cancer. Given the importance of P2X7R in regulating cell death and cytokine production, it is perhaps unsurprising that it may play a role in cancer. Therefore, the development of either P2X7R agonists or antagonists may result in useful anti-cancer agents (i.e., agonists could kill cells whereas antagonists would perhaps stop proliferation).</td>
<td>Ferrari et al. 1997[71]</td>
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<td><strong>Fever</strong></td>
<td>P2 receptors in P2X7R are coupled to the release of different autacoid and P2 receptor inhibition to reduce the fever induced by LPS.</td>
<td>El-Oram et al. 2001[75]</td>
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<td>ATP is released into the extra cellular space and activates P2X7R. This finding supports the view that the extracellular ATP is a bona fide, or prototypic, danger signal. P2X7R is widely expressed in many immune cells, where it controls key signaling pathways. In particular, P2X7R is the most potent plasma membrane receptor responsible for inflammasome activation and the release of pro-inflammatory cytokines of the IL-1 family.</td>
<td>La Sala et al. 2003[90]</td>
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<td>P2X7R activation also increases the generation of reactive oxygen species, induces the release of cathepsins, promotes the antigen-driven T-lymphocyte proliferation, and facilitates intracellular pathogen killing.</td>
<td>Yip et al. 2009[72]</td>
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<td><strong>Musculoskeletal</strong></td>
<td>Human lung alveolar macrophage releases sufficient amounts of lysosome cathepsins into the extracellular medium within minutes to degrade extracellular collagen matrix in vitro. The mechanism of lysosomal release does not require initial pathogen-associated molecular pattern PAMP-induced signaling and therefore, is independent of IL-1β and is abolished by specific P2X7R antagonist, but not anti-IL-1, anti-IL-6, or anti-TNF-α approaches or other drugs used in the treatment of rheumatoid arthritis (RA) and osteoarthritis (OA).</td>
<td>Vasiljeva et al. 2009[77]</td>
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<td>Cathepsins are a family of lysosomal protease known to play important roles in the development of both inflammatory and rheumatoid arthritis joint destruction. It is thought that their site of action is intracellular in acidic lysosome, where they could break down phagocytosed extracellular matrix protein at low pH level.</td>
<td>Collo et al. 1997[79]</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>P2X7R antagonist may be used for the treatment of several disorders including stroke, traumatic brain injury (TBI), multiple sclerosis, and Alzheimer’s disease.</td>
<td>Collo et al. 1997[79]</td>
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The role of P2X7R purinoreceptor in osteosarcoma

in exploring therapeutic potential of purinoceptor in cancer diseases, especially osteosarcoma.

Future prospect

Osteosarcoma is the primary form of malignant bone tumor but owing to its rarity, it is difficult to identify, classify, and treat. This disease has a major impact on the patient’s life. Currently, there is insufficient knowledge on the proper treatment of osteosarcoma. Studies on this molecular target may lead to future discoveries of effective diagnosis methods, as well as improved treatments, for osteosarcoma. In addition, a better understanding of P2X7R will also facilitate the management of various other diseases that are related to the expression of the P2X7R genes (i.e., other cancers, neuropathic pain, autoimmune hepatitis, tuberculosis, and inflammation).

The factors regulating the over-expression of P2X7RA and B in osteosarcoma can be controlled with various drugs. Drugs that can suppress the effect of P2X7R and decrease the size of bone tumor will be safe for humans. Since P2X7R is an upstream regulator of all cancer pathways, it can be inhibited to increase the secretion of RANKL and mTOR blockers. This is an attractive therapeutic target for osteosarcoma.

Conflict of interests

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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94
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