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Extracellular ATP and its derivatives provide spatiotemporal guidance for bone adaptation to wide spectrum of physical forces

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ABSTRACT

ATP is a ubiquitous intracellular molecule critical for cellular bioenergetics. ATP is released in response to mechanical stimulation through vesicular release, small tears in cellular plasma membranes, or when cells are destroyed by traumatic forces. Extracellular ATP is degraded by ecto-ATPases to form ADP and eventually adenosine. ATP, ADP, and adenosine signal through purinergic receptors, including seven P2X ATP-gated cation channels, seven G-protein coupled P2Y receptors responsive to ATP and ADP, and four P1 receptors stimulated by adenosine. The goal of this review is to build a conceptual model of the role of different components of this complex system in coordinating cellular responses that are appropriate to the degree of mechanical stimulation, cell proximity to the location of mechanical injury, and time from the event. We propose that route and amount of ATP release depend on the scale of mechanical forces, ranging from vesicular release of small ATP boluses upon membrane deformation, to leakage of ATP through resealable plasma membrane tears, to spillage of cellular content due to destructive forces. Correspondingly, different P2 receptors responsive to ATP will be activated according to their affinity at the site of mechanical stimulation. ATP is a small molecule that readily diffuses through the environment, bringing the signal to the surrounding cells. ATP is also degraded to ADP which can stimulate a distinct set of P2 receptors. We propose that depending on the magnitude of mechanical forces and distance from the site of their application, ATP/ADP profiles will be different, allowing the relay of information about tissue level injury and proximity. Lastly, ADP is degraded to adenosine acting via its P1 receptors. The presence of large amounts of adenosine without ATP, indicates that an active source of ATP release is no longer present, initiating the transition to the recovery phase. This model consolidates the knowledge regarding the individual components of the purinergic system into a conceptual framework of choreographed responses to physical forces.

1. Introduction

The human body constantly interacts with the physical world. Forces imposed externally, such as gravity and activity-generated, and forces imposed internally (due to blood flow, ventilation, etc.) are critical to the development, maintenance, and adaptation of various tissues in the body. Bone is known for its adaptive responses to mechanical loads (Willie et al., 2020). Reduced forces, such as in microgravity (Stavnichuk et al., 2020) and immobilized patients (Jo and Shin, 2015), are associated with bone loss, whereas activity-related impact forces are conversely associated with bone gain (Kohrt et al., 2009). While daily physical activity is critical for healthy bones (Burr et al., 1996; Fritton et al., 2000), in extreme physical activity, such as in elite sports, bone strains can reach levels resulting in irreversible deformations and failure

Abbreviations: ADA, Adenosine deaminase; ADK, Adenosine kinase; ADP, Adenosine diphosphate; ALP, Alkaline phosphatase; AMP, Adenosine monophosphate; AR, Adenosine receptor; ATP, Adenosine triphosphate; cAMP, Cyclic AMP; Cyto-5′NT, Cytosolic 5′ nucleotidase; eN, Ecto-5′-nucleotidase; ENTs, Equilibrative nucleoside transporter; NO, Nitric Oxide; NPP, Ecto-nucleotide pyrophosphatase/phosphodiesterases; NTPDases, Ecto-nucleoside triphosphate diphosphohydrolases; PG, Prostaglandins; PLC, Phospholipase C; PMD, Plasma membrane disruptions; SAH, S-adenosyl-L-homocysteine; SNP, Single nucleotide polymorphism; TRAP, Tartrate resistant acid phosphatase.

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(Lynch and Fischbach, 2014; Reilly and Burstein, 1975). Eventually, external forces will reach magnitudes resulting in traumatic bone fracture; however, different individuals demonstrate significant variability in their susceptibility to fracture (Mikolajewicz et al., 2020). These forces can be modeled in *in vitro* experiments by applying pressure, fluid shear stress (FSS), strain and compression to study the responses of individual cells (Michael Delaine-Smith et al., 2015). Thus, bone tissue experiences a wide range of physical forces and can adapt accordingly to these different mechanical environments.

The architecture and mineral-collagen composition of the bone effectively transfers mechanical loads through the skeletal structure, so that mechanical perturbations are perceived by bone cells that mediate the adaptive response. Bone is a highly cellular organ, which is maintained throughout our adult lives by three main cell types: *osteoclasts*, cells that specialize in bone resorption; *osteoblasts*, cells that actively produce extracellular matrix that later mineralizes; and *osteocytes*, cells that are embedded in bone matrix and are considered the main mechanosensors and coordinators of bone adaptation (Willie et al., 2020). Together, these cells orchestrate the growth, modeling, and remodeling of bone, adapting the mineralized structure to systemic signals and mechanical stimuli.

Following mechanical stimulation, there is a temporal cascade of signaling events that ultimately manifests in cell- and tissue-level adaptations. Within seconds, fluid shears and substrate strains distort the extracellular matrix, integrin/focal adhesion complexes reorganize the cytoskeleton, and mechanosensitive channels are activated as the membrane yields to applied forces (Robling and Turner, 2009). Transient intracellular free calcium ($[Ca^{2+}]_i$) elevations are among the earliest detectable events after cells are mechanically stimulated (Chen et al., 2000; Hung et al., 1995; Robling and Turner, 2009). $[Ca^{2+}]_i$ signals exhibit various features such as transient or sustained signatures and single or multiple oscillatory peaks, which are believed to encode information (Semyanov, 2019; Tian et al., 2020). On a similar timescale as the calcium response, seconds following mechanical stimulation, adenosine triphosphate (ATP) release is detected (Mikolajewicz et al., 2018a; Robling and Turner, 2009). Within minutes, nitric oxide (NO) is released into the extracellular space from osteoblasts and osteocytes (Mullender et al., 2004), acting as a bone anabolic agent in low to moderate concentrations (Kapur et al., 2003; Wimalawansa, 2010) and similarly prostaglandins (PG), lipid autocrine and paracrine mediators, are produced (Blackwell et al., 2010). Among these early mediators orchestrating bone adaptation to the mechanical stimulus, this review focuses on the mechanotransductive role of extracellular ATP, one of the earliest signals generated upon mechanical stimulation of bone cells.

Extracellular ATP is known to stimulate multiple receptors of the purinergic receptor family (Illes et al., 2021; Jacobson et al., 2020; von Kügelgen, 2021) and to undergo enzymatic degradation that leads to generation of metabolites, such as adenosine diphosphate (ADP) and adenosine (Zimmermann et al., 2012), which are also ligands for different subsets of purinergic receptors (Fredholm, 2007; Illes et al., 2021; Jacobson et al., 2020; von Kügelgen, 2021). Here we build a conceptual model of how this complex system acts to convey the information regarding the degree, proximity to, and time from the event of mechanical force application.

2. ATP release is proportional to the amount of cellular damage

Mechanical forces applied to bone result in the release of ATP into the extracellular environment (Mikolajewicz et al., 2018a). Osteoblasts have been demonstrated to release ATP in response to fluid shear stress (Genetos et al., 2005; Li et al., 2005; Li et al., 2013; Mikolajewicz et al., 2018b; Pines et al., 2003; Wang et al., 2013; Xing et al., 2011), osmotic pressure (Pines et al., 2003; Romanello et al., 2005) and ultrasonic stimulation (Alvarenga et al., 2010; Hayton et al., 2005; Manaka et al., 2015). Osteocytes also release ATP in response to fluid shear (Genetos et al., 2007) and mechanical injury (Kringelbach et al., 2015). ATP release from mechanically-stimulated osteoclasts was implicated in mechanotransduction (Jørgensen et al., 2002) and similarly, macrophages have been shown to release ATP in response to osmotic pressure (Burow et al., 2015). The amount of ATP released depends on the degree of membrane deformation and/or damage experienced by cells. This includes small boluses of ATP release during normal activity, micro-damage induced ATP release from physical activity that prompts repair and bone adaptation, and overload-induced tissue damage and cell death that results in spillage of cellular contents, including ATP, that serves as a danger signal (Fig. 1).

Low-level mechanical stimulation is known to stimulate ATP release from bone cells. Osteoblasts (Brandao-Burch et al., 2012; Buckley et al., 2003; Genetos et al., 2005; Orriss et al., 2009; Romanello et al., 2001), osteocytes (Kringelbach et al., 2015) and osteoclasts (Brandao-Burch et al., 2012), were demonstrated *in vitro* to constitutively release low amounts of ATP, 1–25 amol/cell, to the extracellular environment (Table 1). For osteoblasts, the degree of ATP release was shown to depend on their proliferative and differentiation state (Brandao-Burch et al., 2012). ATP release from osteoblasts was shown to occur mainly through exocytosis of ATP-containing vesicles (Brandao-Burch et al., 2012; Genetos et al., 2005; Orriss et al., 2009; Romanello et al., 2005). In osteocytes, vesicular release in addition to hemichannels (i.e., pannexins, connexins) has been implicated in ATP release (Kringelbach et al., 2015; Seref-Ferlengez et al., 2016). When low-level physical forces, such as gentle perturbation of the media, are applied to osteoblastic cells, ATP release increases (Genetos et al., 2005; Kringelbach et al., 2015; Orriss et al., 2009; Romanello et al., 2005; Romanello et al., 2001). In several studies, the lack of membrane damage upon such stimulations was experimentally confirmed (Genetos et al., 2005; Romanello et al., 2001). Calcium-dependent vesicular release was strongly implicated in ATP release in these conditions (Genetos et al., 2005; Kringelbach et al., 2015; Orriss et al., 2009; Romanello et al., 2005). Thus, at low level of mechanical stimulation, bone cells release ATP mainly through vesicular exocytosis, in amounts proportional to the level of mechanical stimulation.

Physical forces that are large but not structurally damaging to the bone, such as those experienced during strenuous exercise, were shown to lead to micro-damage of the cells in the form of membrane tears, also called plasma membrane disruptions (PMD) (Mikolajewicz et al., 2018b; Terasaki et al., 1997; Yu et al., 2018). These PMDs do not lead to cell death and are repairable via Ca^{2+}/PLC/PKC-dependent vesicular exocytosis which occurs within 60s of stimulus (Lopez-Ayon et al., 2014; Mikolajewicz et al., 2018b; Terasaki et al., 1997; Yu et al., 2018). ATP is spilled through the PMDs in amounts proportional to the damage (Mikolajewicz et al., 2018b; Rumney et al., 2012), however, cell repair, via vesicular exocytosis and membrane tension forces, limits the spillage of ATP, so that overall ATP release depends both on the degree of damage and the cell capacity for repair (Hagan et al., 2020; Mikolajewicz et al., 2019; Mikolajewicz et al., 2018b). The amounts of ATP released through PMDs were estimated to lead to a dose-dependent release of 21 $\pm$ 11 to 422 $\pm$ 97 amol ATP/cell, approaching 1/3 of total ATP content in the cell (Mikolajewicz et al., 2018b). Thus, at intermediate ranges of force, ATP released is proportional to the stimulus applied but inversely proportional to the cell capacity for repair.

Physical forces beyond the load-bearing capacity of the skeleton can occur in traumatic situations, or in high-intensity environments, as seen in athletes and military personnel. These forces result in tissue damage and bone fractures, which are associated with cellular destruction and spillage of cellular contents into the extracellular environment. ATP is present in the cell in mM concentrations (Ataullakhanov and Vitvitsky, 2002), therefore large amounts of ATP are released into the surrounding tissues, proportional to the number of irreversibly damaged cells. (Kringelbach et al., 2014). The amount of ATP release due to high forces can be estimated to be between 50 and 500 amol ATP/cell (Table 1) to complete release of ATP content – 2.6–9.5 fmol ATP/cell (Mikolajewicz et al., 2018a). Extracellular ATP has been implicated in fracture healing

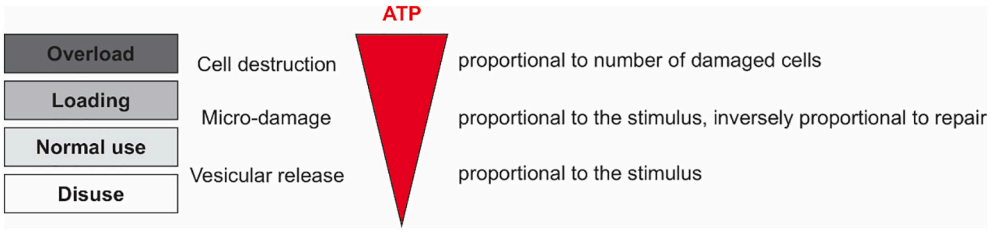

Fig. 1. ATP release reflects the cell damaging capacity of physical forces. During normal use, low forces acting on bone result in vesicular release of ATP. With increase in forces during loading, such as exercise, bone cells undergo micro-damage in the form of reversible plasma membrane tears and spill intracellular ATP. In this case, amount of released ATP also depends on the cell ability to repair, which limits the spillage. Overload to the skeleton leading to tissue damage, results in the release of total cellular ATP content in amounts proportional to the number of destroyed cells.

Table 1
Estimated ATP release from bone cells. Given are examples of studies measuring ATP release from mechanically-stimulated bone cells, in which sufficient information was given to recalculate the values to the common scale.

Study	Cells	Stimulus	Cell damage	ATP release (mol/cell)
Unstimulated release				
(Romanello et al., 2001)	Osteoblast	None	No	4.2E-18
(Genetos et al., 2005)	Osteoblast	None	No	2.5E-17
(Romanello et al., 2005)	Osteoblast	None	n/d	1.0E-18
Low stimulation				
(Genetos et al., 2005)	Osteoblast	LFF	no	2.3E-16
(Wang et al., 2013)	Osteoblast	TFF	No	3.2E-17
(Romanello et al., 2005)	Osteoblast	Hypotonic	n/d	4.9E-18
(Kringelbach et al., 2015)	Osteocyte	LFF low	n/d	1.7E-18
(Mikolajewicz et al., 2018b)	Osteoblast	TFF low	Low	2.1E-17
High stimulation				
(Kringelbach et al., 2015)	Osteocyte	LFF high	n/d	5.1E-17
(Mikolajewicz et al., 2018b)	Osteoblast	TFF high	High	4.2E-16
(Mikolajewicz et al., 2018b)	Osteoblast	Poke	Yes	7.0E-17

(Hayton et al., 2005; Leung et al., 1989; Manaka et al., 2015). ATP in large amounts also serves as a danger signal, or danger-associated molecular pattern (DAMP) molecule, to the neighboring cells (Burnstock and Verkhratsky, 2012), resulting in pain and inflammation (Inoue, 2022). Thus, high levels of extracellular ATP reflect the damaging capacity of physical forces.

Overall, ATP release through different mechanisms engaged at different levels of mechanical stimulation allows to establish a signal that is proportionally and strongly increasing with an increase in the stimulus. Importantly, ATP release exhibits large increases in amplitude when significant physiologically damaging thresholds are reached, such as when force increases in size to damage a cell membrane and when it further increases to irreversibly destroy the cells.

3. ATP diffusion and transformation to ADP indicates the proximity to the damaging event

When ATP is released from mechanically-stimulated or damaged cells, the contents of vesicles in case of vesicular release, or cytoplasm in case of membrane injury are also released into the extracellular environment. Generally, the intracellular ATP concentration is 10 times higher than that of ADP, and 100 times higher than the concentrations of AMP or adenosine (Ataullakhanov and Vitvitsky, 2002). Therefore, initially ATP is the most abundant extracellular mediator that diffuses through the environment delivering information about the mechanical event to neighboring cells that did not directly experience the mechanical forces. As ATP diffuses, it is gradually degraded by ectonucleotidases, resulting in the simultaneous reduction of ATP-mediated signaling and production of other bio-active purines, mainly ADP and adenosine. Thus, spatiotemporal distance from the site of mechanical stimulation coincides with changes in the composition of signaling mediators (Fig. 2). We propose that the combination of ATP and ADP-mediated signals communicate information about force proximity and magnitude to neighboring cells.

The fate of extracellular ATP is determined by the type and activity of the ATP degrading enzymes. In osteoblast cultures, the half-life of ATP has been measured to be between 5 and 20 min (Mikolajewicz et al., 2019; Orriss et al., 2009; Wang et al., 2013). The key families of enzymes that degrade ATP include ecto-nucleoside triphosphate diphosphohydrolases (NTPDases) that convert ATP to ADP and ADP to AMP; ecto-nucleotide pyrophosphatase/phosphodiesterases (NPPs) that convert ATP to AMP, and ecto-5′-nucleotidase (eN) that degrades AMP to adenosine (Giuliani et al., 2020; Zimmermann et al., 2012) (Table 2). Two other enzymes that degrade nucleotides are alkaline phosphatase (ALP) and tartrate-resistant acid phosphatase (TRAP), highly expressed by osteoblasts and osteoclasts, respectively (Zimmermann et al., 2012). Several studies have examined the expression of purine nucleotide-degrading enzymes on bone cells. Osteoblasts express NTPDase 1–6 (Orriss et al., 2015; Yegutkin, 2008), NPP1–3 (Orriss et al., 2015; Vaingankar et al., 2004), and eN (Orriss et al., 2015; Takedachi et al., 2012), as well as ALP that was strongly implicated in ATP degradation (Mikolajewicz et al., 2019). Osteoclasts express NTPDase 1 and 3 (Hajjawi et al., 2014; Shih et al., 2019), NPP1 and 3 (Hajjawi et al., 2014), and eN (Shih et al., 2019). In osteocytes, few studies have examined ATP-degrading enzymes, however, osteocytes do degrade extracellular ATP and other nucleotides (Gibson and Fullmer, 1966), and express at least NPP1 (Hajjawi et al., 2014) and TRAP (Dallas et al., 2013; Solberg et al., 2014). Overall, the profile of nucleotides will depend on the affinity and efficacy of the specific nucleotidases present on cells neighboring the site experiencing mechanical forces. The cell composition at different sites can be complex and is not limited to bone cells, but also can include other tissues, such as bone marrow and vasculature. More studies are needed to characterize the extracellular metabolism of purine nucleotides and ligand availability for P2 receptor signaling in the complex in situ environment.

ATP released in response to mechanical stimulation diffuses through the extracellular environment (Jørgensen et al., 2002; Mikolajewicz et al., 2019; Mikolajewicz et al., 2018b). The distance covered by ATP will depend on the amount released, and thus the severity and extent of the mechanical stimulus. In addition, diffusion distance also depends on the geometry of the injury (Mikolajewicz et al., 2019) and the constraints of the environment, as diffusion through bone tissue is slower than through fluids of the lacuna-canalicular network, bone marrow, or vasculature (Fernández-Seara et al., 2002). As ATP is actively degraded, ADP, AMP and adenosine are gradually generated and diffuse through the environment with their characteristic diffusion coefficients, thereby achieving faster diffusion due to lower molecular weight. Overall, cells that are near the site of mechanical stimulation will mainly receive ATP as the mechanotransductive signal (Fig. 2). If the magnitude of stimulation is low, ATP diffusion will quickly dissipate the signal, and ADP

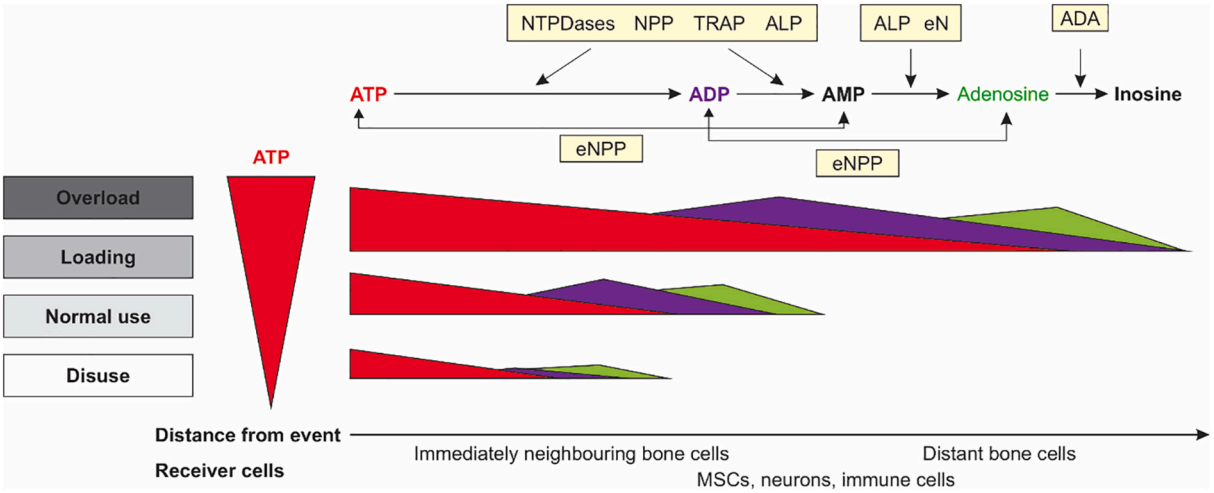

Fig. 2. Proximity and strength of mechanical stimulus is encoded by variable purine compositions due to ATP diffusion and degradation. ATP released during mechanical stimulation diffuses into the environment, where it is degraded by ectonucleotidases into ADP and adenosine, which in turn continue to diffuse and undergo degradation. Depending on the distance from the source and on the magnitude of mechanical stimulation, receiver cells, including immediately neighboring and distant bone cells, as well as mesenchymal stem cells (MSCs), neurons and immune cells, will receive different combination of purinergic mediators.

Table 2
Expression of ectonucleotidases degrading ATP and ADP in bone cells. The list of ectonucleotidases is based on (Zimmermann et al., 2012). Symbols indicate the following: +++: highly expressed; ++ moderately expressed; + expressed; - not expressed; ↓ (down arrow) expressed then decreased.

Family name	Protein name	Substrates	Osteoblasts	Osteoclasts	Osteocytes
Ecto-nucleoside triphosphate diphosphohydrolase	NTPDase1 (CD39)	ATP, ADP	+ (Orriss et al., 2015)	+ (Hajjawi et al., 2014; Shih et al., 2019)	+ (Hajjawi et al., 2014)
	NTPDase2	ATP, less ADP	+ (Orriss et al., 2015)	− (Hajjawi et al., 2014)	
	NTPDase3	ATP, ADP	+ (Orriss et al., 2015)	+ (Hajjawi et al., 2014)	
	NTPDase4	Less ATP, ADP	+++ (Orriss et al., 2015; Yegutkin, 2008)		
	NTPDase5	ADP	+++ (Orriss et al., 2015; Yegutkin, 2008)		
Ecto-5′-nucleotidase	eN (CD73)	AMP	++ (Orriss et al., 2015; Takedachi et al., 2012)	++ (Shih et al., 2019)	++ (Gibson and Fullmer, 1966)
Ecto-nucleotide pyrophosphatase/ phosphodiesterase	NPP1	ATP, ADP	+++ (Orriss et al., 2015; Vaingankar et al., 2004)	+ (Hajjawi et al., 2014)	
	NPP2	ATP, ADP	+ (Orriss et al., 2015)	− (Hajjawi et al., 2014)	
	NPP3	ATP, ADP	++ (Orriss et al., 2015)	+↓ (Hajjawi et al., 2014)	
Alkaline phosphatase	TNAP	ATP, ADP, AMP	++ (Orriss et al., 2015)		
TRAP	TRAP	ATP, ADP	++ (Solberg et al., 2014)	+++ (Kaunitz and Yamaguchi, 2008; Oddie et al., 2000)	++ (Dallas et al., 2013; Solberg et al., 2014)

produced from ATP degradation will not be sufficiently high to stimulate an ADP-dependent P2 response, as ATP is an order of magnitude more potent in inducing cellular responses compared to ADP (Mikolajewicz et al., 2019). However, in cases of injury (Fig. 2), ATP diffusion and degradation will produce enough ADP to contribute to downstream signaling in neighboring cells at intermediate distances from the site of severe injury.

Thus, ATP and its degradation products provide spatiotemporal information about the degree of injury and the proximity of the receiver cell to the site of injury. In addition, the cellular composition of the environment through which purines diffuse has the potential to alter the signal arriving at distant neighbors, such as neurons and immune cells.

4. P2 receptors form a complex signal integration network

When ATP and ADP reach the receiver cell, they act on the purinergic P2 receptor family. There are 7 ligand-gated P2X receptors ($P2X_{1–7}$) and 8 G-protein coupled P2Y receptors ($P2Y_{1,2,4,6,11–14}$). While P2X receptors are sensitive to ATP only, P2Y receptors exhibit a range of subtype-specific sensitivities to different purines and pyrimidines, including ATP, ADP, UTP, UDP, and UDP-glucose (Illes et al., 2021; Jacobson et al., 2020; von Kügelgen, 2021). P2Y receptors are further divided into two subgroups based on their sequence alignment and pharmacology. $P2Y_1$-like receptors comprising $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, and $P2Y_{11}$, couple to G_q resulting in the activation of phospholipase C (PLC) (Jacobson, 2013). The $P2Y_{11}$ receptor also couples to G_s, resulting in activation of cAMP. $P2Y_{12}$-like receptors that include $P2Y_{12}$, $P2Y_{13}$, and $P2Y_{14}$ couple to G_i, leading to inhibition of cAMP (Jacobson, 2013). Bone cells have been shown to express all 15 P2 receptors by osteoblasts and osteoclasts of different origins and/or at different stages of their differentiation (Orriss et al., 2010; Reyes et al., 2011).

The affinity for ATP varies widely among purinergic receptors, covering eight orders of magnitude of ATP concentrations (Grol et al., 2013; Xing et al., 2016). Of interest, most P2 receptors are tuned to exhibit maximal sensitivity to changes in [ATP] over a concentration range of 10 nM – 100 μM [ATP], after which there is a single low-affinity receptor $P2X_7$ that is sensitive to changes in ATP in the mM range (Fig. 3). Importantly, many P2 receptors interact, either by directly forming heterodimers (Brown et al., 2002; Nakata et al., 2005; Palygin et al., 2010), or indirectly through downstream signaling (Mikolajewicz

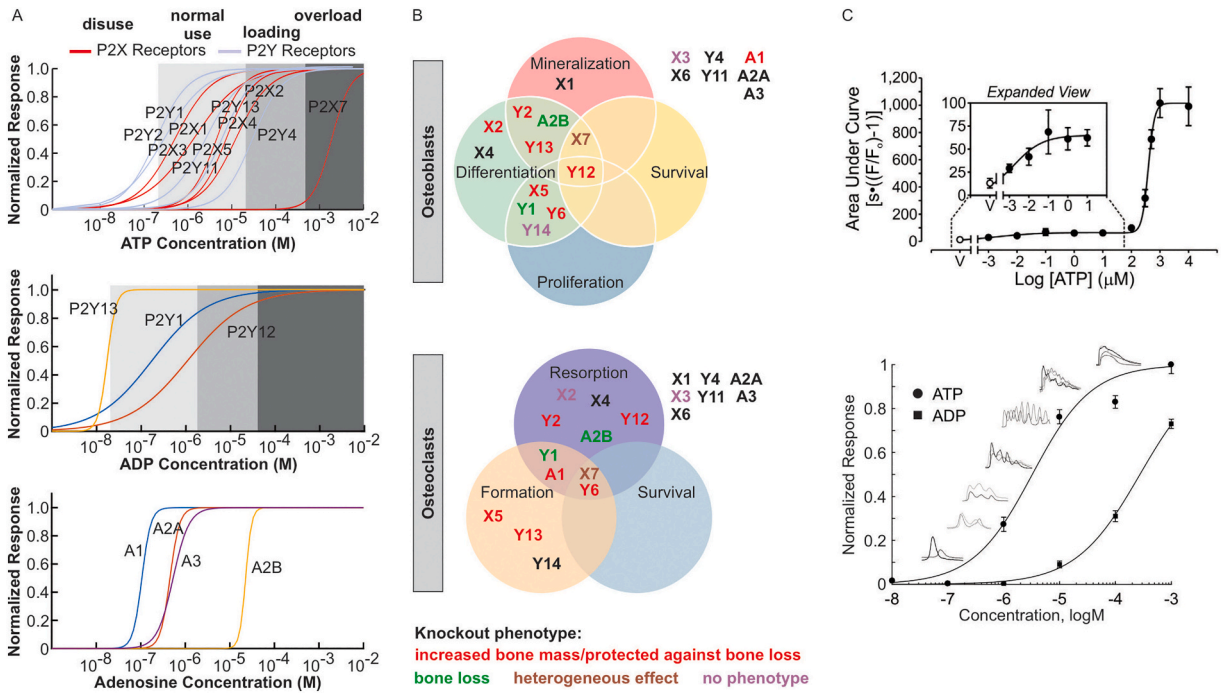

Fig. 3. Complex signals generated by purinergic receptors. A) Concentration dependence curves for ATP-sensitive P2X and P2Y receptors (*top*, reproduced with modifications with permission from Xing et al. (2016)), ADP-sensitive P2Y receptors (*middle*, plotted based on data from (Dsouza and Komarova, 2021; Ennion et al., 2004; Léon et al., 1997)) and adenosine sensitive P1 receptors (*bottom*, plotted based on data from (Fredholm, 2007)). Shaded areas represent approximate ranges of ATP (*top*) and ADP (*middle*) concentrations released during different levels of mechanical stimulation. B) Venn diagram depicting the role of purinergic receptors in osteoblast (*top*) and osteoclast (*bottom*) formation, activity and survival identified in knock-out studies (Biver et al., 2013; Chessell et al., 2005; Gartland et al., 2003; Ke et al., 2003; Kim et al., 2017; Orriss et al., 2011a; Su et al., 2012; Wang et al., 2012; Wang et al., 2014). C) Examples of complex signaling features generated by P2 receptors. (Top) Area under the curve of calcium responses of osteoblasts to increasing concentration of ATP (Reproduced with permission: Grol et al. (2013) (Bottom) ATP and ADP dose dependence of the amplitude of osteoblast calcium responses. Inserts: prevalent patterns of calcium responses (adapted with permission from Mikolajewicz et al. (2019) and Mikolajewicz et al. (2021)).

et al., 2021). One of the most prominent P2 downstream signals is a transient elevation of $[Ca^{2+}]_i$, which has a complex [ATP] dependence (Grol et al., 2013; Mikolajewicz et al., 2021). The amplitude of $[Ca^{2+}]_i$ elevation has a non-monotonic dependence on [ATP], which was attributed to the interactions between high affinity and intermediate or low-affinity receptors (Mikolajewicz et al., 2021; Xing et al., 2016). In addition, the duration of $[Ca^{2+}]_i$ elevation exhibits a sigmoidal [ATP] dependence, due to $P2X_7$ activation (Grol et al., 2013; Xing et al., 2016). Consequently, there are two ranges of [ATP] where P2 stimulation results in pronounced increases in the cumulative amount of $[Ca^{2+}]_i$ during the signaling event (i.e., the area under the calcium response): first at low [ATP], which can be considered a sensitivity threshold, and second at high [ATP] corresponding to tissue damage – an injury threshold (Grol et al., 2013; Xing et al., 2016). Moreover, P2-mediated responses to intermediate 0.1–10 μM [ATP] exhibit highly oscillatory dynamics, that changes with an increase in [ATP] (Mikolajewicz et al., 2021). Cyclic AMP (cAMP) is another prominent secondary messenger downstream of P2Y receptors, however, it has been less studied in the context of bone cell mechanotransduction. Thus, different P2 receptors interact to form complex concentration dependencies that *i*) are sensitive to a wide range of [ATP] and *ii*) modulate the downstream signaling signature and response.

Given that P2 receptors function in a complex network rather than individually, it is difficult to decipher specific roles and identify distinct attributes of each P2 receptor (Table 3). Moreover, almost every mouse model harboring a P2 receptor knockout demonstrates an altered bone phenotype (Orriss et al., 2011a). We have mapped the findings from knockout studies to specific aspects of osteoblast and osteoclast function (Fig. 3). Overall, it is evident that ATP is stimulatory for both osteoclast and osteoblast formation and function but is not strongly implicated in bone cell survival. When individual receptors are deleted, such as $P2Y_2$ (Orriss et al., 2017; Orriss et al., 2007), the phenotype of bone gain is commonly observed, suggesting that osteoclast regulation by ATP is critical for mechanotransductive bone adaptation. This highlights the importance of studies of osteoclast regulation by mechanical forces. While osteoclasts are generally not considered to be the main targets/responders to loading, these cells are recognized as drivers of bone loss in response to unloading. Of interest, ADP receptors, $P2Y_1$, $P2Y_{12}$, and $P2Y_{13}$, have been more strongly implicated in bone formation, compared to ATP receptors, even though these receptors were shown to be important for both osteoclasts and osteoblasts (Biver et al., 2013; Orriss et al., 2011b; Su et al., 2012; Wang et al., 2012; Wang et al., 2014). $P2Y_1$ knockout (Orriss et al., 2011b) and $P2Y_{13}$ (Wang et al., 2012) resulted in bone loss, and in some studies, a similar phenotype was observed after treating mice with $P2Y_{12}$-targeting drug clopidogrel (Syberg et al., 2012); however, conflicting results were seen in other studies, likely due to the combination of osteoclast- and osteoblast-mediated changes (Mediero et al., 2016; Su et al., 2012). Nevertheless, these findings suggest that ADP-sensitive P2 receptors, all having EC_{50} in the intermediate range of ATP/ADP values (Fig. 3), play a role in bone adaptation. Finally, the low-affinity ATP receptor $P2X_7$ has an important role in bone repair and has been referred to as the repair receptor (Jørgensen, 2018). Mice deficient in $P2X_7$ had a significant delay in callus remodeling following osteotomy (Li et al., 2009). In humans, a study conducted on military personnel and elite athletes showed that loss of function single nucleotide polymorphism (SNP) in $P2X_7$ was associated with stress fractures, while gain of function SNP in $P2X_7$ was associated with reduced fracture occurrence (Varley et al., 2016). $P2X_7$ also plays a critical role in inflammation where it promotes pro-inflammatory factors, such as IL-6 and TNF (Di Virgilio et al., 2017), and in pain responses, where it acts as a positive mediator of pain (Hansen et al., 2011; Hughes et al., 2007).

Table 3
Roles of purinergic receptors in bone cells. Given are examples of demonstrated roles of purinergic receptors in the differentiation, function and survival of osteoblasts and osteoclasts, as well as the bone phenotype in knockout animals where available.

Type	Agonists	Osteoclasts	Osteoblasts	Knockout phenotype
X1	ATP		↓ mineralization (Orriss et al., 2012)	
X2	ATP	↑ resorption (Morrison et al., 1998)	Transiently expressed during differentiation (Orriss et al., 2006)	
X3	ATP		Expressed (Orriss et al., 2012; Zippel et al., 2012)	
X4	ATP	↑ resorption (Naemsch et al., 1999)	↑ mature osteoblasts (Orriss et al., 2012)	
X5	ATP	↑ maturation/ fusion (Kim et al., 2017)	↑ proliferation (Nakamura et al., 2000; Orriss et al., 2006), ↑ response to PDGF, IGF-1 (Kim et al., 2017)	Protected from inflammation related bone loss (Kim et al., 2017)
X6	ATP		Adipogenic lineage commitment (Zippel et al., 2012)	
X7	ATP	↑ maturation/ fusion (Agrawal et al., 2010), ↑↓ resorption (Gartland et al., 2003; Hazama et al., 2009; Wang et al., 2018) ↑↓ survival (Miyazaki et al., 2012; Penolazzi et al., 2005)	↑ differentiation (Noronha-Matos et al., 2014; Sun et al., 2013), ↑↓ mineralization (Noronha-Matos et al., 2014; Orriss et al., 2012; Panupinthu et al., 2007; Sun et al., 2013), ↑↓ survival (Adinolfi et al., 2012; Young et al., 2018)	Pfizer model (Ke et al., 2003): ↓ BMD, ↑ trabecular resorption, ↓ periosteal formation GSK model (Chessell et al., 2005; Gartland et al., 2003): ↑ cortical thickness,
Y1	ADP > ATP	↑ formation, ↑ resorption (Hoebertz et al., 2001)	↑ proliferation (Alvarenga et al., 2010; Rodrigues-Ribeiro et al., 2015), ↑ response to systemic factors (Bowler et al., 1999; Buckley et al., 2001)	↓ BMD, ↓ trabecular number (Orriss et al., 2011a)
Y2	ATP = UTP	↑ resorption (Orriss et al., 2017)	↑ proliferation (Katz et al., 2011), ↑ Runx2 (Costessi et al., 2005), ↓ mineralization (Hoebertz et al., 2002)	↑ BMD (Orriss et al., 2011b; Orriss et al., 2017)
Y4	UTP > ATP	No effect (Jørgensen et al., 2002)	Interaction with P2Y2 (Orriss et al., 2006)	
Y6	UDP> > ATP	↑ formation, ↑ resorption (Orriss et al., 2011a), ↑ survival (Korcok et al., 2005)	↑ proliferation (Alvarenga et al., 2010), ↑↓ differentiation (Ayala-Peña et al., 2013; Orriss et al., 2006)	↑ BMD (Orriss et al., 2011a)
Y11	ATP		Adipogenic lineage commitment (Zippel et al., 2012)	
Y12	ADP> > ATP	↑ adhesion, ↑ resorption (Su et al., 2012)	↑ proliferation (Syberg et al., 2012) ↑↓ differentiation (Mediero et al., 2016; Syberg et al., 2012) ↑ survival (Syberg et al., 2012)	Protected from bone loss related to arthritis, tumor growth and ovariectomy (Su et al., 2012)
Y13	ADP > ATP	↑ formation, ↓ RANKL/OPG by osteoblasts (Wang et al., 2012)	Lineage commitment (Biver et al., 2013), ↑ differentiation (Biver et al., 2013; Wang et al., 2012; Wang et al., 2013)	Age-dependent ↓ bone turnover (Biver et al., 2013; Wang et al., 2012; Wang et al., 2014) ↑ osteogenic response to loading (Wang et al., 2014)
A1	Adenosine	↑ differentiation (He and Cronstein, 2012; He et al., 2013; Kara, Chitu, et al., 2010)	May favor MSC-adipocyte differentiation (Gharibi et al., 2012)	↑ BMD (Kara, Doty, et al., 2010)
A2A	Adenosine	↓ differentiation (Mediero et al., 2012b)	↑ viability (Vincenzi et al., 2013), ↑ proliferation (Katebi et al., 2009)	
A2B	Adenosine	↓ differentiation (He and Cronstein, 2012)	↑ differentiation (Takedachi et al., 2012; Trincavelli et al., 2014)	↓ BMD (Carroll et al., 2012), ↓ Tb.N, ↓ bone formation rate (Corciulo et al., 2016)
A3	Adenosine	↓ differentiation (Rath-Wolfson et al., 2006)	↑ proliferation (Costa et al., 2011)	

Overall, we suggest that P2 receptors present on an individual cell interact at multiple levels to generate a concerted signal that integrates the information regarding ATP- and ADP- concentrations in the environment.

5. Termination of ATP-induced signals by adenosine

Extracellularly, adenosine is primarily formed as a result of ecto-5′-nucleotidase (eN) action on adenine nucleotides (Colgan et al., 2006; Fredholm, 2014; Strazzulla and Cronstein, 2016), and secondarily to reactions catalyzed by NTPDase1, NPP-1 and ALP (Strazzulla and Cronstein, 2016). Adenosine is also produced intracellularly from AMP by soluble cytosolic 5′ nucleotidase (Cyto-5′NT) or used by adenosine kinase (ADK) to form AMP (Fredholm, 2014), which then is involved in energy metabolism (Ataullakhanov and Vitvitsky, 2002). In addition, adenosine participates in homocysteine metabolism, where it can be produced together with L-homocysteine from S-adenosyl-L-homocysteine (SAH) by SAH hydrolase (Lee et al., 2001). Adenosine is degraded to inosine by adenosine deaminases (ADA) both intracellularly and extracellularly. Adenosine, as well as inosine, can be directly released from or taken up by the cells through equilibrative nucleoside transporters (ENTs), which strive to achieve equal intra-and extra-cellular nucleoside concentrations (Strazzulla and Cronstein, 2016; Young et al., 2008). Thus, adenosine in the extracellular environment can reflect both the degradation of extracellular purines as well as the state of cellular

metabolism (Fig. 4A).

At resting state extracellular adenosine levels are generally in the nanomolar range with reports ranging from 1.4 to 2000 nM in human plasma (Ramakers et al., 2008), with a similarly wide range 0.8–2100 nM in the intracerebral extracellular space (Ballarin et al., 1991; Fredholm, 2014; van der Mierden et al., 2018). Measuring endogenous adenosine concentrations can be technically difficult (Lofgren et al., 2018; Ramakers et al., 2008), and it was suggested that true physiological levels are likely at the lower side of the measured spectrum, at 10–30 nM (Lofgren et al., 2018). In pathological states following tissue damage adenosine was shown to rise well above 1 μM (10–1000-fold from basal levels under hypoxia) (Fredholm, 2014; Yegutkin, 2021). The characteristics of adenosine-processing enzymes suggest that at physiological concentrations adenosine is mostly used in cellular metabolism since ADK requires low concentrations of adenosine (Michaelis constant (K_m) for ADK is ~40 nM (Spychala et al., 1996)). However, when adenosine levels increase, another adenosine processing enzyme, ADA becomes strongly involved, since it is activated at higher concentration of adenosine (K_m for ADA is more than 40 μM (Spychala, 2000; Yegutkin, 2021), at least three orders of magnitude higher than that for ADK). Though local variations in adenosine levels were extensively studied in the brain and cardiovascular system, much less is known about the bone microenvironment.

Adenosine activates a family of G protein-coupled receptors known as P1 receptors or adenosine receptors (AR) (Ralevic and Burnstock, 1998). Four P1 receptors are currently recognized, A_1, A_{2A}, A_{2B}, and A_3. A_1 and A_3 act by inhibiting cyclic AMP (cAMP) production and decreasing protein kinase A activity, whereas both A2 receptors stimulate cAMP (Eisenstein et al., 2020; Sheth et al., 2014). Similar to P2 receptors, P1 receptors cover a significant range of concentrations. A_1 and A_3 are activated by adenosine at low concentrations – 0.18 - 0.53 μM (Fredholm, 2007; Fredholm et al., 2001). A_{2A} has a slightly lower affinity and is activated by 0.56–0.95 μM adenosine, while A_{2B} is only activated at very high adenosine levels, 16.2–64.1 μM adenosine (Fredholm, 2007; Fredholm et al., 2001). In bone, all four ARs were found to be expressed on mature osteoclast and osteoblasts as well as their precursors (Ham and Evans, 2012; Mediero and Cronstein, 2013; Strazzulla and Cronstein, 2016). A_1 was reported to strongly stimulate osteoclastogenesis (He et al., 2013; Kara et al., 2010a; Kara et al., 2010b), while its role in osteoblast formation is less clear, even though it was shown to promote the osteogenic commitment of mesenchymal stem cells (D'Alimonte et al., 2013). A3 was reported to inhibit osteoclastogenesis (Rath-Wolfson et al., 2006) and stimulate osteoblast differentiation (Costa et al., 2011; Evans et al., 2006). A_{2A} was shown to inhibit osteoclast differentiation and function (Mediero et al., 2012a; Mediero et al., 2012b), and to promote bone regeneration (Mediero et al., 2015). This receptor is also well established in vasculature as a modulator of vascular tone and blood flow (Khayat and Nayeem, 2017; Tabrizchi and Bedi, 2001), therefore its angiogenic properties can also promote bone formation and help in the early stages of fracture healing (Wang et al., 2021). The low-affinity A_{2B} receptor has been implicated as the strong promoter of osteoblast differentiation (Carroll et al., 2012; Trincavelli et al., 2014). AR knockout animal models have been studied in A1 and A2B, where opposite phenotypes, bone gain and bone loss respectively, were found (Fig. 3). Thus, the adenosine receptors have a dynamic range of functions within the bone microenvironment and have diverse roles in bone homeostasis.

It is somewhat difficult to conceptualize the action of AR on bone cells. A_1, A_{2A}, and A_3 receptors are activated in the same range of adenosine concentrations but produce distinct and contrary signals. A_1 and A_3 inhibit cAMP production, but A_{2A} stimulates cAMP. Although A_1 and A_3 both inhibit cAMP, A_1 stimulates while A_3 inhibits osteoclast differentiation. One potential explanation could be in the context of adenosine stimulation. Adenosine increases in the extracellular environment can occur due to two distinct processes – degradation of extracellular ATP or changes in cellular metabolism. Furthermore, in the context of cellular metabolism, adenosine levels can rise due to problems with bioenergetics or due to alterations in homocysteine metabolism, both of which are regulated independently. Thus, it is possible that these P1 receptors respond to adenosine in a context-dependent manner, allowing for cells to distinguish between mechanotransductive and bioenergetic mechanisms of adenosine elevation. For example, if adenosine increases due to the degradation of extracellular ATP, then activation of P1 receptors will be accompanied by activation of P2 receptors. In contrast, if adenosine increases intracellularly due to deficiency in bioenergetics, then simultaneously other changes in the

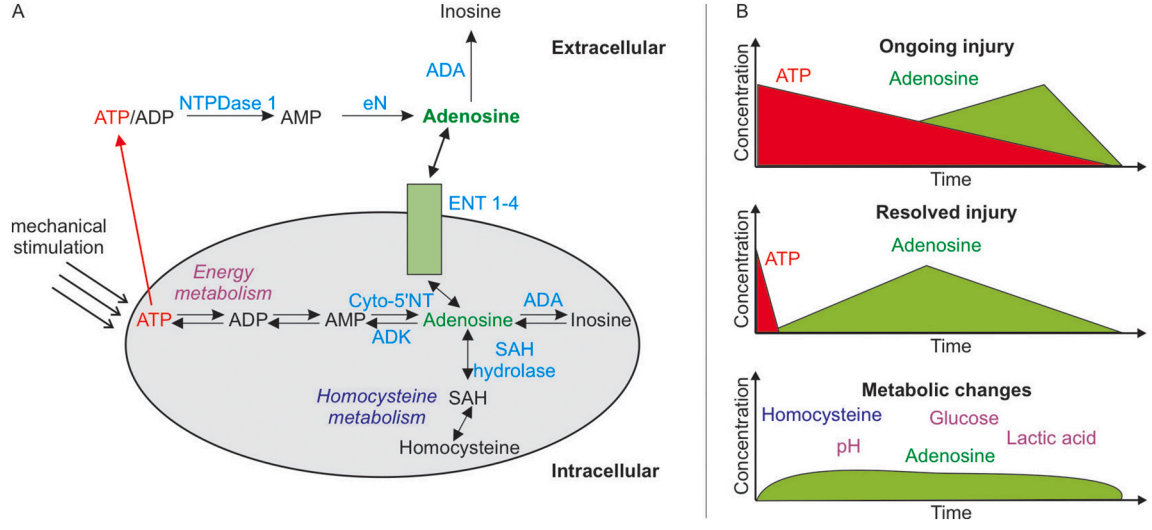

Fig. 4. Adenosine signaling may differentiate between different mechanical and metabolic stressors. A) Extracellular adenosine can be produced through degradation of extracellular ATP, or through release of intracellular adenosine that is formed in the pathways of energy metabolism or homocysteine metabolism. ADK; Adenosine kinase, ADA; Adenosine deaminase, Cyto 5′-NT; cytosolic 5′ nucleotidase, eN; Ecto-5′-nucleotidase, SAH; S-adenosyl-homocysteine. B) Adenosine profile as well as the presence of other metabolites reflect distinct states. Top: illustrated in the case of ongoing injury characterized by continuous presence of both ATP and adenosine. Middle: in the case of resolved injury, ATP signal stops, while adenosine produced from previously present ATP remains to signal the start of resolution phase. Bottom: the profile of adenosine released due to metabolic stresses likely has lower but more persistent profile compared to bolus production following mechanical stimulation.

microenvironment will occur, such as changes in pH, oxygen, glucose, or lactate (Ataullakhanov and Vitvitsky, 2002; Tiedemann et al., 2020). Homocysteine regulation will be similarly linked to unique alterations in the respective metabolites. In this regard, adenosine receptors are known for the complexity of the regulatory layers, including the formation of homo-and heterodimers with other receptors; allosteric regulation, as well as biased agonism (Vecchio et al., 2018). A_{2A} receptor was recently shown to be strongly regulated by cations (Ye et al., 2018), and P1 and P2 receptors were shown to exhibit functional crosstalk (Morales et al., 2000). In the context of injury, adenosine was suggested to act as a termination signal with anti-inflammatory and pain-relieving capacities in some cases, while serving as a pro-inflammatory mediator in others (Antonioli et al., 2019; Blackburn et al., 2009; Jung et al., 2022). It is possible that these differences are related to the presence of ATP- and ADP-mediated signals: While the injury is ongoing, the simultaneous presence of ATP and adenosine are indicative of a serious and continuous problem that has lasted for a sufficient time for adenosine accumulation. In contrast, when the injury is terminated and ATP is no longer released in the environment, ADP and then adenosine become the last injury-related signals in the environment, and therefore signal the beginning of the resolution of inflammation, pain, and active healing.

6. Conclusions

We present a conceptual model of concerted action of purinergic receptors providing information to the receiver cells regarding the degree of and proximity to the site experiencing physical forces. We suggest that ATP released in response to a variety of physical forces is proportional to their cell-damaging capacity. We propose that mechanically-stimulated ATP release acts as a signal to the neighboring non-wounded cells. The amplitude of ATP allows cells to distinguish between small non-damaging forces and large detrimental forces. The total amount of ATP release reflects the magnitude of the force, while the stimulated cell's ability to repair limits further ATP release. The presence of an ADP component in the signal suggests proximity to the site where the large forces were applied, which is a positive signal to stimulate mechanoadaptation. Adenosine may indicate a serious ongoing issue when it occurs together with ATP, or it can serve as a termination signal if ATP is no longer present. Importantly, the properties of P2 and P1 receptors indicate that responses are not dichotomous, but rather graded, so that the information conveyed is complex and nuanced. The difficulty with interpreting knockout studies confirms that this system should be approached holistically, rather than as a sum of components. While we focused on the role of ATP-mediated signals in bone, this purinergic system is prevalent across a variety of cellular systems such as the brain, skeletal muscle, bladder, liver, and lungs, as well as other organs where mechanical forces are important in the regulation and maintenance of tissue health. The conceptual model presented in this manuscript consolidates the knowledge regarding the individual components of the purinergic system into a conceptual framework of choreographed responses to physical forces, intended to inform novel hypotheses for future studies.

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CRediT authorship contribution statement

Chrisanne Dsouza: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Mahmoud S. Moussa:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Nicholas Mikolajewicz:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Svetlana V. Komarova:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors of the manuscript "Extracellular ATP and its derivatives provide spatiotemporal guidance for bone adaptation to wide spectrum of physical forces", Chrisanne Dsouza, Mahmoud S Moussa, Nicholas Mikolajewicz, and Svetlana V Komarova, state that they have no actual or potential conflicts of interest with regard to the submitted publication.

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