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Research Highlight

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A new perspective of mechanosensitive pannexin-1 channels in cancer metastasis: clues for the treatment of other stress-induced diseases

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Cancer metastasis is a process that cancer cells deviate from the primary site and spread to the other areas to form new colonies, which is the leading cause of death in cancer patients. During metastatic progression, circulating cancer cells lodge within the microvasculature of end organs, where most of them die from mechanical deformation. However, cancer cells can survive from mechanical deformation by unknown mechanisms. Recently, Furlow *et al.* [1] identified a mutation truncated form of pannexin-1 (Panx-1), $PANX1^{1-89}$, which was significantly enriched in highly metastatic cancer cells. $PANX1^{1-89}$ augmented Panx-1 channel-mediated adenosine triphosphate (ATP) release and enhanced the efficiency of metastasis by promoting metastatic breast cancer cells survival during physical deformation. Additionally, carbenoxolone (CBX), a Panx-1 inhibitor, was proved to reduce the efficiency of breast cancer metastasis. These results suggested that Panx-1 is one of the molecular bases for metastatic cell survival in microvasculature-induced biomechanical trauma [1].

In 2000, three members of pannexins, including Panx-1, Panx-2, and Panx-3, have been found to be new members of gap-junctions' family [2]. Panx-1 was ubiquitously expressed in human tissues. Subsequent studies further revealed that Panx-1 forms single-pass membrane channels that connect the intracellular and extracellular compartments rather than forming intercellular channels spanning the two plasma membranes, which is mainly different from classical gap junctions [3]. Physiologically, Panx-1 channels are mainly involved in the efflux of ATP and regulate cellular inflammasomes [4]. Many studies indicated that Panx-1 is related to epilepsy, neuropathic pain, painful musculoskeletal diseases, ischemia injury, myocardial fibrosis, overactivity of the human bladder, and cancers [5–13] (**Fig. 1**).

The beneficial or aggravating role of Panx-1 in cancer remains controversial. Lai *et al.* [5] reported that Panx-1 plays a tumor-suppressive role *in vitro* and *in vivo*. Reverse transcription polymerase chain reaction analysis revealed that C6 cells do not express Panx-1. However, stable expression of Panx-1 in C6 glioma cells significantly inhibits cell growth, proliferation, and motility *in vitro* [5]. Besides, Panx-1 is an important intratumor biomechanical environment regulator that accelerates the dynamic assembly of multicellular C6 glioma aggregates [6]. Panx-1 also significantly reduces the tumor size in athymic nude mice [5,6]. Derangere *et al.* [7] reported that caspase-1-dependent colon cancer cell pyroptosis is mainly induced through the interaction with Panx-1. These data supported that Panx-1 has a tumor-suppressor property, while some other studies indicated that Panx-1 promotes the development of cancer. Penuela *et al.* [8] found that Panx-1 is upregulated in B16 melanoma cells rather than in normal melanocytes. Furthermore, Panx-1-depleted B16 melanoma cells exhibit reduced cell migration and growth, resembling normal melanocytes. Knockdown of Panx-1 in mice also has the effect of reducing tumor size *in vivo* [8]. Moreover, Panx-1 is highly expressed in human platelets, and Panx-1 channels can promote the aggregation of platelets, which is a risk factor of cancer metastasis, by enhancing Ca^{2+} influx and ATP release [9]. How do these conflicts occur? Panx-1 is closely related to the development of tumor, but the exact mechanism of Panx-1 in cancer is still not clear. We speculate that Panx-1 may have protective or destructive properties in different types of tumors. In addition, the role of Panx-1 in cancer may also be dependent on tumor stage and severity. In Furlow's study, it was shown that Panx-1 enhances the high metastatic human breast cells to survive during metastasis process.

The activity of Panx-1 channels can be regulated by many factors, such as hypoxia, mechanical stress, osmotic pressure, intracellular calcium, and purinoceptor [3]. Panx-1 channels, as mechanosensitive channels, may contribute to the development of various stress-induced diseases. Nishida *et al.* [14] revealed that *Panx-1* mRNA is largely increased by mechanical stretch, which mediates ATP and uridine diphosphate release to induce the production of fibrogenic factors in rat cardiomyocytes, ultimately leading to cardiac fibrosis. Glaucoma is an ophthalmic disease characterized by pulsating or continuous rising intraocular pressure. The vitreal ATP release from pannexins is increased at continuous high pressures. Moreover, the pannexin channel

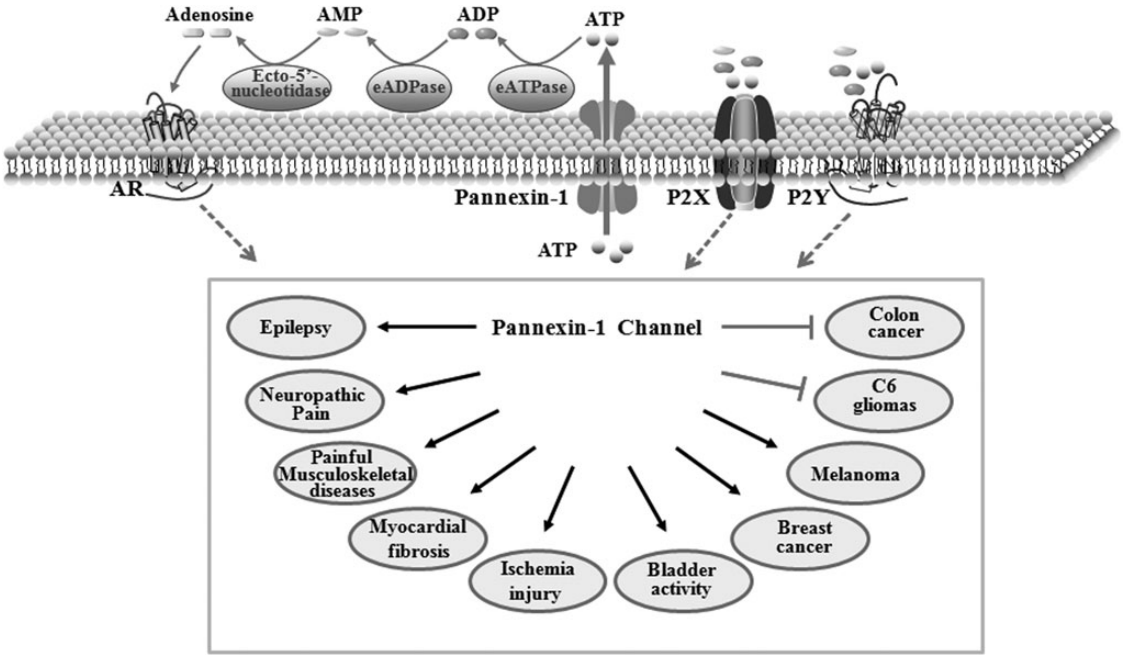

Figure 1. The role of Panx-1 channels in multiple diseases Activation of Panx-1 channels promotes the release of ATP from cells. ATP and its metabolic products ADP and AMP bound to P2X and P2Y receptors, or adenosine bound to adenosine receptor (AR) may mediate most effects of Panx-1 channels in multiple diseases.

release of ATP may be related to high pressure that induces ganglion cell death in acute glaucoma [15]. Apart from tumor, vascular stress-related diseases also include hypertension, pulmonary hypertension, intracranial hypertension, glaucoma, cardiac hypertrophy, and angiogenesis. The expression of Panx-1 or the activity of Panx-1 channels may also change in some vascular stress-related diseases. For example, the permeability of Panx-1 channels is significantly increased in cerebral hypoxic ischemia injury, even though there is no change of Panx-1 expression [16]. The next question is whether mutations of Panx-1 exist in these diseases? Furlow *et al.* [1] identified a mutation encoding a truncated form of the Panx-1 channel, $PANX1^{1-89}$, as recurrently enriched in highly metastatic breast cancer cells. $PANX1^{1-89}$ functions to permit metastatic cell survival during traumatic deformation in the microvasculature by augmenting ATP release from mechanosensitive Panx-1 channels activated by membrane stretch.

Physiologically, Panx-1 channels are mainly involved in the efflux of ATP, which is an important signaling molecule that participates in cell survival, adhesion, proliferation, differentiation, and migration. Rapaport and Fontaine [17] have already reported that ATP and adenosine monophosphate (AMP) have an inhibitory effect on CT26 colon adenocarcinoma cell growth. The chemotherapy is mainly based on promoting ATP release and then inducing tumor cells apoptosis [18]. However, the roles of ATP in cancer cell death or survival are controversial. Furlow *et al.* [1] found that ATP release from Panx-1 channels activated P2Y-purinergic receptors then promoted cancer cell survival. Moreover, metastasis cell viability was markedly reduced after exposure to the ATP hydrolase [19]. Then, how to explain these conflicts? Perhaps, the ATP maintained a comparative balance by the negative feedback on the Panx-1 channels, not by inducing cell death under some pathological conditions [19]. As some researchers showed that differential expression of ATP receptors (P2X receptor or P2Y receptor) or activating different ATP receptors may lead to contradictory effects on cancer cells (proliferation or apoptosis) [20,21]. Recently, Song *et al.* [22] reported that high level of ATP activates the antiapoptotic signaling, but not proapoptotic molecules in the lung tumor microenvironment. Furthermore, adenosine was one type of the metabolic products of ATP. Ohta *et al.* [23] showed that in adenosine-rich tumor microenvironment, the function of T cells may be seriously impaired, which induces inefficiency of antitumor T cells to promote tumor cell survival. Besides Panx-1-released ATP, its products, such as adenosine diphosphate (ADP), AMP, or adenosine, may also play vital roles in the progression of tumor and other diseases.

To date, a series of Panx-1 inhibitors has been found [24–28] (**Supplementary Table S1**). These inhibitors are useful for regulating the functions of Panx-1 channels, and they may be used as therapeutic drugs for those Panx-1 over-activation-induced diseases. Probenecid, a well-established drug for the treatment of gout, has been shown to specifically attenuate Panx-1 channel-induced ATP release [24]. CBX, a direct and powerful Panx-1 channel inhibitor, is a drug for gastric ulcer [25]. Although these two inhibitors possess the superiority to clinically used drugs, the lower potency of probenecid and the non-selective features of CBX make these two inhibitors insufficient to be effective drugs for treating Panx-1 over-activation-induced diseases. The specific molecular targeting Panx-1 channels need further research. Thus, by using structural modification or molecular screening to discover some specific and powerful inhibitors or inducers of Panx-1 channels will be an important field of Panx-1 study.

In conclusion, Furlow *et al.* [1] identified a novel mechanism for tumor metastasis. The overactive Panx-1 promotes breast cancer cell survival in the context of mechanical deformation. Panx-1 inhibitors can be used to treat highly metastasis cancer. Mechanosensitive Panx-1 channels will be a new target for the prevention of metastasis and stress-induced diseases. The use of specific and powerful inhibitors Panx-1 channels for the treatment of metastasis and stress-induced diseases still need to be further explored.

Supplementary Data

Supplementary data is available at *ABBS* online.

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