Journal of Cell Signaling
ISSN: 2576-1471

Maruta, J Cell Signal 2018, 3:1
DOI: 10.4172/2576-1471.1000177

Commentary Open Access

PAK Family Kinases Come of Age: Celebrating 40 Years of Discovery

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Received date: December 26, 2017; **Accepted date:** January 06, 2018; **Published date:** January 11, 2018

Introduction

Since our team at NIH found the very first member of PAK family kinases (called "myosin I heavy chain kinase") in a soil amoeba in 1977 [1], this family of RAC/CDC42-dependent Ser/Thr kinases kept expanding their territory during the last four decades. Among this unique family, however, PAK1 has been most extensively studied so far, mainly because it is essential for malignant transformation of mammalian cells, but non-essential for normal cell growth [2], and shortens the heathy lifespan of small animals such as *C. elegans* [3], and is involved even in PDGF/MSH-dependent melanogenesis [4]. For this reason, a variety of PAK1-blockers/inhibitors have been developed or identified since the turn of this century, and some of them such as propolis and 15K could be potentially useful for therapy of solid tumors, promoting the longevity by suppressing a variety of other PAK1-dependent diseases/disorders such as AD (Alzheimer's disease), hypertension and diabetes (type 2), and even for the cosmetic treatment of hyper-pigmentation (so-called "skin-whitening"). Thus, the potential market value of these PAK1-blockers would be huge in both pharmaceutical and cosmetic industries. In this commentary, I shall briefly highlight the uniqueness of PAK1-blockers useful for signaling therapy causing no serious side effect, in contrast to conventional anti-cancer drugs such as DNA/ RNA/ microtubule poisons which clearly cause serious side effects such as hair-loss, suppression of immune system and loss of appetite. Rather surprisingly, these PAK1-blockers such as propolis and 15K promote hair growth and boost even our immune system [5,6] easing the damaging side effects caused by conventional anti-cancer drugs.

PAK Family Kinases

So far six distinct members of PAK family kinases have been identified in mammals including *Homo sapiens*. PAK1, PAK2 and PAK3 belong to the group 1 whose kinase activity depends on RAC or CDC42, while PAK4, PAK5, and PAK6 belong to the group 2 whose kinase activity depends solely on CDC42 [7]. Mainly PAK1 and PAK4 are involved in malignant (anchorage-independent) growth of cancers and melanogenesis as well [2,4,8]. Huge difference between PAK1 and PAK4 in their physiological function is that PAK4-deficiency causes embryonic death of mice mainly due to a heat failure [9], while PAK1-deficiency extends the healthy lifespan of small animals such as *C. elegans* [3], instead of the embryonic death. Thus, PAK4-blockers such as PF3758309 [10] could potentially causes a serious side effect(s), but none of PAK1-blockers is expected to cause any side effect, but contrary the latter (such as propolis and 15K) indeed promote the longevity.

Signalling Pathways Essential for PAK1 Activation

In living cells, PAK1 requires a variety of signal transducers (in addition to RAC/CDC42) for its full activation [2]. An SH3 docking protein called PIX is one of them. PIX binds the Pro-rich motif of 18 amino acids called PAK18 (residues 186-204) on PAK1 through its SH3 domain for the activation of PAK1 (Figure 1). Thus, a cell-permeable peptide called WR-PAK18 could block the activation of PAK1 selectively in cancer cells, blocking their growth and metastasis, but without affecting the normal cell growth [11].

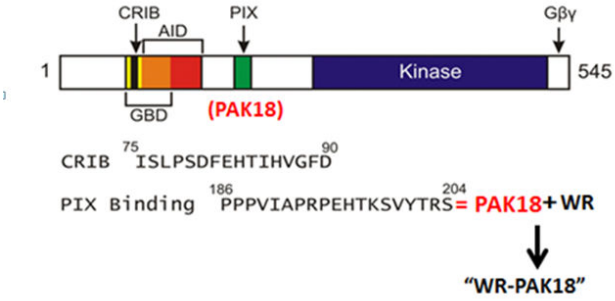

Figure 1: WR-PAK18: Blocking the PAK1-PIX interaction

At least three distinct Tyr-kinases, ETK, FYN, and JAK-2 are also essential for the activation of PAK1 in cancer cells (Figure 2). Thus, ETK inhibitor (AG879 or GL-2003), FYN-inhibitors (PP1, PP2 or PP12), and JAK-2-inhibitors (Cucurbitacins or AG490) could be useful as PAK1-blockers for cancer therapy and promotion of longevity [12]. In addition, another Ser/Thr kinase called CK2 (casein kinase 2) is also essential for the activation of PAK1 [13]. Thus, a CK2-inhibitor called CX-4945 could be potentially useful as both cancer therapeutic and elixir [14]. Interestingly, CX-4945 is a COOH-bearing PAK1-blocker, and its cell-permeability is rather poor, due to its negative charge. Thus, its cell-permeabity could be robustly boosted by its esterization with the water-soluble 1,2,3-triazolyl alcohol through Click Chemistry (CC) in the future [15]. Since both these Tyr-kinases and CK2 selectively activate PAK1, without affecting any other members of PAK family kinases, their specific inhibitors could serve as "PAK1-specific" blockers.

Signal Transducers Down-Stream of PAK1

There are several distinct direct substrates (transducers) of PAK1. An oncogenic Ser/Thr kinase called c-RAF is one of them, and phosphorylation at its Ser 338 by PAK1 is essential for the activation of oncogenic RAF-MEK-ERK signaling cascade [7]. Activation of oncogenic COX-2 gene also requires PAK1 [15]. Interestingly, a racemic old pain-killer called ketorolac was recently found to block PAK1 by inactivating RAC/CDC42 through R-form, while COX-2 is directly inhibited by S-form [15].

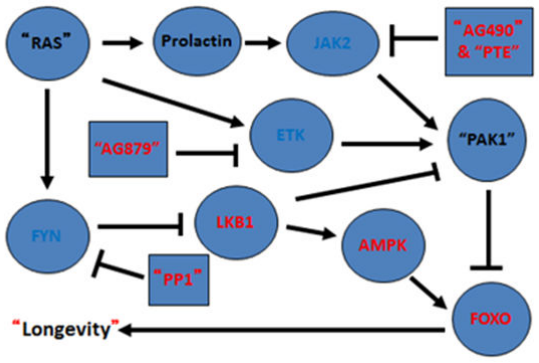

Figure 2: Tyr-kinases essential for RAS-induced PAK-1 activation

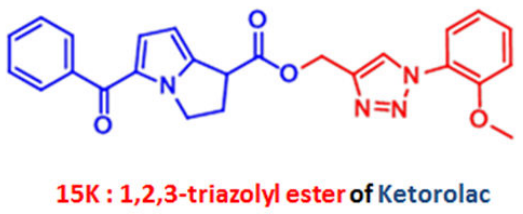

Figure 3: 15K, a Triazolyl ester of COOH-bearing "Ketorolac"

However, ketorolac is a COOH-bearing PAK1-blocker, and its cell-permeability is very poor. Thus, we have managed to boost its cell-permeability 500 times by coupling the water-soluble 1,2,3-triazolyl alcohol through CC [15], producing a very potent PAK1-blocking ester called 15K with IC50 ranging 5-25 nM depending on cancer cell lines (Figure 3). We recently confirmed that 15K extends the healthy lifespan of *C. elegans* at 50 nM, and boosts the heat-endurance (survival after prolonged heat-shock) of this worm several times even at 10 nM (Figure 4), strongly suggesting that 15K could be a potent elixir (longevity-promoter) as well as cancer therapeutic [12, 16].

Direct Inhibition of PAK1

Several compounds that directly inhibit PAK1 have been developed. Among them is IPA-3 that allosterically binds PAK1, instead of binding its ATP-binding pocket [16]. A series of FRAXs developed by Afraxis are potent ATP-antagonists relatively specific for the group 1 of PAK1 family [12]. However, both IPA-3 and FRAXs are water-insoluble and poorly cell-permeable, so far being unsuitable for clinical application. However, a natural compound called FRA (Frondoside A) derived from a sea cucumber is a water-soluble sulfated saponin, and was recently found to inhibit PAK1 directly and rather selectively [17]. Its IC50 against A549 cancer cells is around 500 nM, and highly cell-permeable. Thus, FRA could be a good candidate for clinical trials of cancer therapy when its mass supply is established.

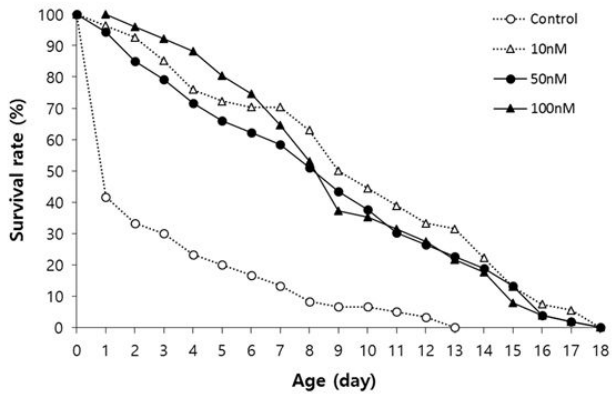

Figure 4: 15K boosts heat-endurance of *C. elegans*

Conclusion

Since the oncogenic/ageing/melanogenic kinase PAK1 contribute to a wide variety of diseases/disorders, in contract to "Gleevec", an ABL/PDGFR/KIT inhibitor which is useful for therapy of only less than 0.1% of all human cancers such as CML and GIST, it is most likely that PAK1-blockers could be among the most promising "signaling therapeutics" useful for the treatment of major solid tumors as well as many other PAK1-dependent diseases/ disorders, eventually promoting the longevity, instead of causing nasty side effects. Thus, vigourous promotion or marketing/development of PAK1-blockers such as propolis and 15K would be highly desirable for the welfare of both mankind and all other animals on this planet in the near future. Since the current increasing "global-warming" is posing the heat-induced premature death (or shorter lifespan) of all animals living in either land or water, the unique property of PAK1-blockers boosting their heat-endurance would be worth highlighting.

Acknowledgement

The author is very grateful to both Drs. Sang-Kyu Park and Mok-Ryeon Ahn in Korea for their valuable contribution to our recent *in vivo* (*C. elegans*) or *in ovo* (chicken egg) studies with 15K, respectively.

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