Journal of Carcinogenesis & Mutagenesis

Fujiwara et al., J Carcinogene Mutagene 2013, 4:1
DOI: 10.4172/2157-2518.1000e110

Editorial Open Access

DREF, a Concertmaster for Hippo Pathway and JNK Pathway in *Drosophila*

Shunsuke Fujiwara, Hideki Yoshida and Masamitsu Yamaguchi*

Department of Applied Biology, Insect Biomedical Research Center, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto, 606-8585, Japan

Hippo Pathway and its Cross-talk with JNK Pathway

Coordination of positive and negative regulation for cell proliferation is essential to achieve organ formation with proper size. During normal development and regeneration of organs such as after surgical excision, the organs reach at each proper size with cell proliferation and its arrest at proper timing. Studies, in the past decade, have defined a kinase cascade as a key signal transduction pathway to interpret this mechanism. The Hippo pathway was firstly identified in *Drosophila* as a tumor-suppressive signal cascade and plays a crucial role in controlling organ size [1-7]. Interestingly, its core kinases cassette is conserved evolutionally among metazoans, consisting of four proteins, Hippo (Hpo), Salvador (Sav), Mob (Mats) and Warts (Wts) in *Drosophila* [1-10] (Figure 1), and MST1/2, WW45, Mob1/2 and Lats1/2 in mammals, respectively [11-17]. The Ste20-like kinase, Hpo is activated by phosphorylation [18], then the activated Hpo phosphorylates Wts, Sav, and Mats [7,19]. Sav binds to both Hpo and Wts to facilitate its reaction by serving as a scaffold [7]. Mats functions as a co-factor of Wts [10]. Then the activated Wts phosphorylates and inactivates the transcriptional co-activator Yorkie (Yki) [20]. Consequently, the inactivated Yki is retained in cytoplasm, resulting in reduced transcription of its target genes such as *cyclin E* that promotes cell-proliferation and *dIAP1* that inhibits cell death [20]. Loss-of-function mutations in *hpo*, *wts*, *sav*, or *mats* induce up-regulation of Yki activity, increase expression of *cyclin E* and *dIAP1*, and exhibit tumor-like overgrowth [21-26]. Similarly in mammals, MST1/2 binds to WW45 to phosphorylate and activate the complex of Mob1/2 and LATS1/2. In addition mammalian homologue of Yki, YAP and TAZ also function as transcriptional co-activators and promote cell proliferation [13,27-32].

Many of the Hpo pathway-related genes were identified by genetic screen in *Drosophila* [33]. Imaginal discs of *Drosophila* with *hpo* mutation exhibit severe tumor-like phenotypes that form dark and folded eye or head, resembling the hide of "hippopotamus" [6]. In particular, the interommatidial cells of eye disc with each mutation in core kinase genes become resistant to apoptotic signals and survive as extra cells [3-8,10]. The mutant cells proliferate rapidly than normal cells without major change in cell size. These findings suggest the Hpo pathway is essential for growth and size control of organs or tissues.

With searching of the Hpo pathway components, several upstream inputs have been clarified. Multiple and apparently complex upstream modulators of Hpo pathway have been identified. The *expanded* (*ex*) and *merlin* (*mer*) have been initially identified as upstream components of Hpo pathway (Figure 1). Both Ex and Mer are FERM domain-containing protein and defined as tumor suppressors. Mutations of either gene alone exhibit weaker phenotype than that of the core component mutations. However double mutation of *ex* and *mer* results in severe tumor-like phenotype [34]. These observations suggest that their function is at least partially redundant. They physically interact each other and colocalize in cells and tissues [35]. Another factor called Kibra also forms a complex with Ex and Mer, and functions upstream of Hpo signal [36] (Figure 1). The Ex-Mer-Kibra complex localizes to apical domain of epithelial cells, binds to Hpo and Sav, and promotes Wts phosphorylation [34]. Currently, Crumbs (Crb) has joined the Hpo pathway as an adhesion receptor on the sub-apical membrane [37-39]. Crb is a determinant of epithelial apical-basal polarity in *Drosophila* embryos, and related to growth control in imaginal discs. Crb directly binds to Ex and appears to regulate the Hpo pathway activity through Ex localization [37,38]. Interestingly, Ex is lost from the membranes of wild type cells that border *crb* mutant cells. These observations suggest that Crb functions as a receptor to recognize cell-cell contact through Crb-Crb interaction [37]. And the cell-cell contact recognition via Crb-Crb binding appears as an input to regulate growth by influencing Hpo pathway activity (Figure 1). Mammalian homologues of Crb share conserved amino acids with the intracellular domain of *Drosophila* Crb, which is also reported to function in apical-basal polarity [40].

Moreover, Planar Cell Polarity (PCP) appears to be involved in the Hpo pathway function. Fat (Ft) is a large transmembrane cadherin-like protein involving determination of PCP. Ft is reported to be the most upstream activator of the Hpo pathway [34,41-44]. Ft ligand, Dachsous (Ds) is another cadherin-like protein and Ft-interactant, Four-jointed (Fj) are also shown to be involved in the Hpo signaling. Ds and Fj are expressed in complementary gradient manner in imaginal discs [45,46]. Juxtaposition of cells that express different levels of Fj and Ds induces expression of the Hpo pathway target genes and cell proliferation in *Drosophila* wing discs. Moreover, uniform expression level of Fj and Ds inhibits cell proliferation [47,48]. Although the link between PCP and Hpo pathway appears to be complex, these findings suggest that the Hpo pathway activity is driven by partially redundant multiple inputs involving cell-cell contact and/or cell polarity (Figure 1).

One of the key mechanisms to control organ size is a so-called "contact inhibition". In confluent cells, activation of Mer can be observed, which has been reported to require contact inhibition [49]. Also in mammals, cytoplasmic location and inactivation of YAP is induced by high cell density in the Hpo pathway-dependent manner. In addition, inhibition of YAP activity restores contact inhibition in human cells by disruption of WW45, a human homolog of Sav [50]. Moreover, in mammalian cells, the Hpo pathway components are required for contact inhibition of proliferation via cell contact through

***Corresponding author:** Masamitsu Yamaguchi, Department of Applied Biology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto, 606-8585, Japan, E-mail: myamaguc@kit.ac.jp

Received December 25, 2012; **Accepted** December 26, 2012; **Published** January 08, 2013

Citation: Fujiwara S, Yoshida H, Yamaguchi M (2013) DREF, a Concertmaster for Hippo Pathway and JNK Pathway in *Drosophila*. J Carcinogene Mutagene 4: e110. doi:10.4172/2157-2518.1000e110

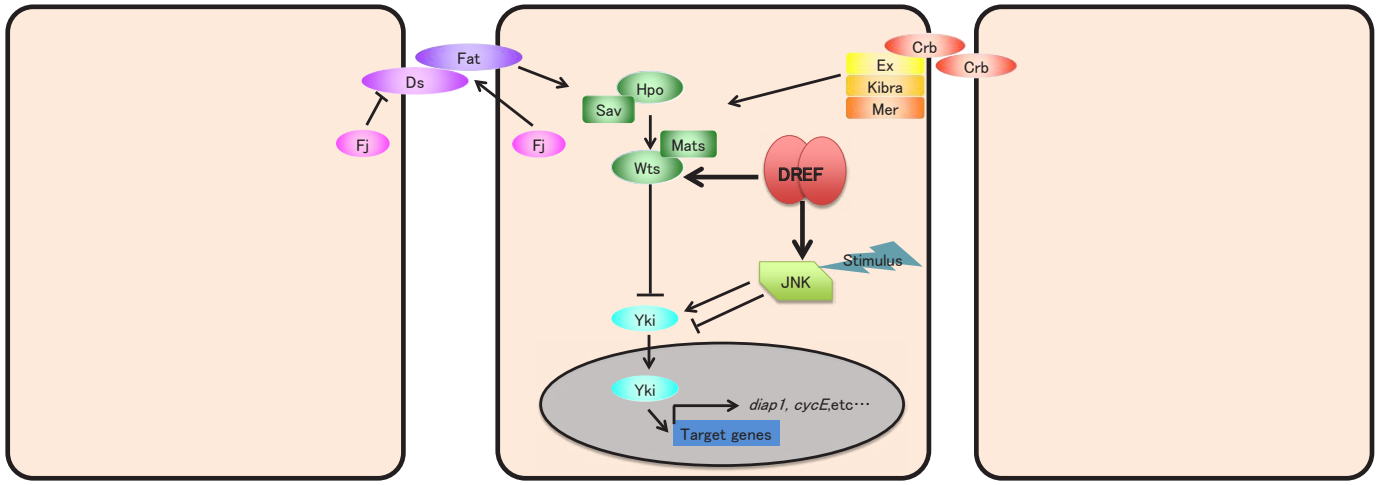

Figure 1: DREF that regulates both *wts* and *bsk* genes appears to play a key role in coordination of Hippo and JNK pathway in *Drosophila*.

E-cadherin or α/β-catenin [51-54]. Taken together, these findings suggest that the Hpo pathway tightly links with cell contact inhibition, which induces proliferation arrest in order to control organ size.

Recent studies highlight another aspect of the Hpo pathway function. The Hippo pathway has been linked to regulation of organ regeneration. Yki activation in Intestinal Stem Cell (ISC) can be observed in response to damage and results in increasing of ISC proliferation in *Drosophila* [55]. Also in mice, YAP is related to intestine regeneration program after damage [56]. In *Drosophila*, intestine cells can be damaged by toxin or pathogens. In this damage-induced system, JNK and JAK/STAT pathways are known to be related to damage response and ISC proliferation. Damage signal is transmitted largely by JNK, and JAK/STAT induces ISC proliferation [57,58]. Currently, linkage between Yki and JNK, JAK/STAT pathways has been identified, in which JNK-dependent Yki activation in differentiated intestinal cells can be observed and induces expression of Upd, a JAK/STAT pathway ligand [59-61]. In *Drosophila* wing discs, cells that undergo apoptosis stimulate the nearby cells to proliferate. This phenomenon is called "compensatory cell proliferation" and is important to overcome tissue damage [62]. Also in this process, activation of Yki through the JNK pathway can be observed, and direct activation of JNK also induces Yki activation in surviving and nearby cells [63] (Figure 1).

Interaction between the Hpo pathway and JNK pathway is also shown in several other studies. In order to prevent diseases such as cancer, elimination of abnormal cells plays a central role in homeostatic mechanisms. Clones of cells mutant for the tumor suppressor gene *scribble* (*scrib*) are eliminated from *Drosophila* imaginal discs as "loser" by the mechanism called "cell competition" [64]. When all cells in imaginal discs are mutant for *scrib,* they induce hyperactivation of Yki that drives overgrowth into large neoplastic masses. However, this elimination of abnormal cells can be observed in imaginal discs containing both normal and *scrib* mutant cells [65-69]. Under these conditions, inhibition of Yki activation arises through JNK-dependent mechanisms in the *scrib* mutant cells to prevent overproliferation and induce apoptosis. These lines of striking evidence indicate that the Hpo pathway components play a crucial role in tumor suppression, and JNK tightly links with the Hpo pathway to control organ and tissue homeostasis (Figure 1).

DRE/DREF System Plays a Key Role in Transcriptional Regulation of Hpo Pathway- and JNK Pathway-Related Genes

Currently it is reported that *Drosophila* DRE (DNA Replication-Related Element) / DREF (DRE-Binding Factor) transcriptional regulatory system is essential for regulating the *wts* gene, a Hpo pathway core component and the *basket* (*bsk*) gene, a *Drosophila* JNK [70,71] (Figure 1). DRE/DREF system is known to closely relate to regulation of a number of cell proliferation-related genes [72]. However since many other genes have been identified as targets of the DRE/DREF system, it is now emerging that the DRE/DREF transcriptional regulatory system induces expression of genes that have a wide variety of functions [72]. Interestingly, Wts and Bsk are similar in function by which prevent inappropriate cell proliferation. Wts is a core component of the Hpo pathway, which functions as a tumor suppressor. And JNK serves a protective function for genome and promotes apoptosis just like *p53*, which is also known as a target of DRE/DREF [73]. In addition, as described above the Hpo pathway and the JNK pathway cooperate in tissue growth and regeneration. Thus DREF that regulates both *wts* and *bsk* genes appears to play a key role in coordination of these two signal transduction systems. In addition, genome database search revealed human DREF (hDREF)-binding consensus sequences in 5'-flanking region of the human *lats1* and both *jnk1* and *2* genes. Transcription of these genes may therefore also be regulated by the DRE/DREF system in human, as is the case of *Drosophila*. These findings suggest that DRE/DREF system is a key regulator to achieve fine-tuning of tissue and organ growth and homeostasis in both *Drosophila* and human.

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