

VIEWPOINT

YAP-Hippo signalling downstream of leukemia inhibitory factor receptor: implications for breast cancer

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Abstract

The proto-oncogenes YAP and TAZ have previously gained much attention as downstream effectors of Hippo tumour suppressor signalling. While the regulation of YAP/TAZ by MST/LATS kinases is reasonably well understood, the nature of factors functioning upstream of MST/LATS is yet to be elucidated in detail. A recent paper by Ma and co-workers defines a novel role for leukemia inhibitory factor receptor (LIFR) signalling upstream of the Hippo-YAP pathway in breast cancer metastasis. Moreover, a whole genome *in vivo* RNA interference screen by Lippmann and colleagues identified LIFR as a breast tumour suppressor. Here, we discuss the implications of these studies for breast cancer research and treatment.

Background

Hippo signalling is a tumour suppressor cascade highly conserved from yeast to man [1]. In mammals, Hippo signalling is deregulated in various cancers; hence, mammalian Hippo signalling has gained much attention over the past years [2]. In a nutshell, the canonical Hippo pathway functions as follows: activated MST1/2 kinases (mammalian Ste20-like serine/threonine kinase 1/2) phosphorylate hMOB1 (human Mps one binder 1) and LATS1/2 (large tumour suppressor serine/threonine kinase 1/2), resulting in the formation of an active hMOB1-LATS complex that phosphorylates the proto-oncogenes YAP (Yes-associated protein) and TAZ (transcriptional co-activator with PDZ-binding motif), which finally leads to the accumulation of inactive cytoplasmic YAP/TAZ [3].

YAP is overexpressed in various human cancers [4,5], supporting a role for it as a proto-oncogene. In breast

cancer, however, gain or loss of YAP expression has been reported [6-9], suggesting that YAP might have oncogenic and tumour suppressive functions dependent on the breast cancer subtype. TAZ is overexpressed in breast cancer [10,11], but a recent report [12] suggests also a tumour suppressive role for TAZ. Therefore, the roles of YAP/TAZ-Hippo signalling in breast cancer are debatable. Considering that metastases at distant sites, and not the primary breast tumour, are the main cause of death, we must further consider YAP/TAZ functions in metastasis, as highlighted by a recent report by Ma and colleagues [13].

The articles

To uncover novel factors involved in the initiation/progression of tumours, Lippman and colleagues [12] screened *in vivo* the entire human genome by RNA interference, thereby identifying LIFR as a novel tumour suppressor. Silencing of LIFR was sufficient to transform normal mammary cells, and reciprocally, LIFR overexpression in breast cancer cells suppressed tumour growth [12], suggesting that LIFR is a clinically important breast tumour suppressor. However, Iorns and colleagues [12] did not define how LIFR functions as a tumour suppressor.

In parallel, Ma and co-workers discovered a role for LIFR as a novel breast cancer metastasis suppressor [13]. In full agreement with Iorns and colleagues [12], they also found that LIFR is downregulated in breast cancer [13], but controversially reported that LIFR silencing did not affect primary tumour growth [13]. However, overexpression of LIFR in metastatic breast cancer cell lines dramatically reduced metastases formation [13]. Furthermore, Ma and colleagues investigated the mechanisms downstream of LIFR. Based on a recent report [14] linking LIF (the ligand for LIFR) to the regulation of YAP, they examined the role of LIFR in YAP-Hippo signalling. Unlike in embryonic stem cells [14], addition of LIF resulted in increased YAP phosphorylation in breast cancer cell lines, thereby resulting in the inactivation of YAP [13]. Since phosphorylation of MST/LATS was

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increased upon LIFR overexpression [13], it is possible that the effect on YAP is driven by canonical Hippo signalling. Moreover, they provided evidence suggesting that LIFR signals to MST/LATS via Scribble [13], an adaptor that can link MST/LATS/YAP/TAZ complexes [11].

The viewpoint

Two recent reports highlight LIFR as a novel player in breast cancer. The work by Iorns and colleagues [12] defines LIFR as a breast tumour suppressor, while Ma and co-workers [13] define LIFR as a breast cancer metastasis suppressor. Current evidence strongly suggests that LIFR functions by inhibiting YAP [13]. This novel role for YAP in breast cancer metastasis is supported by a recent paper from the Hynes laboratory [15], but the involvement of canonical Hippo signalling is not so evident. They show that LIFR overexpression correlates with increased LATS1 phosphorylation, while YAP(S112A) drives metastases despite LIFR overexpression [13]. This suggests that LIFR triggers YAP phosphorylation by activating LATS1. However, given that YAP phosphorylation appears to be independent of LATS1/2 in other cancer settings [16], it will be important to confirm the identity of the kinase(s) targeting YAP in these settings before we can make final conclusions.

Considering that TAZ-Hippo signalling is already implicated in breast cancer [10,11], it is likely that LIFR also functions upstream of TAZ. In particular, it will be interesting to determine whether the recently reported role for TAZ in breast cancer metastasis [17] is controlled by LIFR. However, Iorns and colleagues identified TAZ (WWTR1) as a potential breast tumour suppressor in their screen [12]. At first glance, these observations do not seem to make sense, but as already speculated for YAP [4,6-9], TAZ might have oncogenic and tumour suppressive functions dependent on the breast cancer subtype or progression stage, a phenomenon already reported for other factors in different cancer types [18]. Since increased YAP/TAZ levels correlate with taxol resistance [7,19], YAP/TAZ have been considered as targets/biomarkers in breast cancer. Based on the work by the Ma and Lippman laboratories [12,13], however, LIFR activation appears to be the more attractive clinical target for the treatment of breast cancer, since the roles of YAP/TAZ-Hippo signalling in breast cancer subtypes are yet to be defined in more detail.

Abbreviations

LIF, leukemia inhibitory factor; LIFR, leukemia inhibitory factor receptor.

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