



TAZ teases T cells with PD-L1

Ryan Kanai, John M. Lamar

Department of Molecular and Cellular Physiology, Albany Medical College, Albany, NY, USA

Correspondence to: John M. Lamar. Albany Medical College, 47 New Scotland Ave., Albany, NY 12208, USA. Email: lamarj@amc.edu.

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Metastatic cancer continues to be a devastating disease with few effective treatment options. One promising approach that has emerged recently is immunotherapy, and the immune checkpoint protein programmed death-ligand 1 (PD-L1) has garnered particular interest given its role in immune system evasion by cancer cells (1,2). Although it is clear that PD-L1 expression on cancer cells can promote immune suppression, it is not completely understood what causes PD-L1 upregulation on cancer cells. A recent publication in *Cancer Research* by Xiaolong Yang's lab (Janse van Rensburg *et al.* 2018) (3) sheds light on this by demonstrating that the Hippo pathway effectors Transcriptional Co-activator with PDZ-binding Motif (TAZ) and Yes-Associated Protein (YAP) both promote PD-L1 expression on cancer cells and that this leads to suppression of T-cell function.

YAP and TAZ are transcriptional co-activators with important roles in early embryonic development, organ formation and growth, and tissue regeneration and repair. They regulate these processes by driving the expression of a transcriptional program that enhances cell proliferation and survival and promotes stem cell maintenance (4-6). Over the past 15 years, YAP and TAZ have emerged as key players in cancer. They are significantly upregulated and/or have increased nuclear localization (i.e., activity) in many human cancers, and a wealth of experimental evidence shows that inappropriate YAP or TAZ activity promotes cancer development and drives tumor progression and metastasis (6-9). Although YAP and TAZ appear to enhance multiple pro-tumorigenic and pro-metastatic processes in

cancer cells (7-9), until recently, it was not known whether YAP or TAZ influence the ability of tumor cells to evade the immune system.

Janse van Rensburg and colleagues sought to address this question, and since YAP and TAZ are transcriptional co-activators, they first asked if any YAP/TAZ-regulated genes had established roles in modulating immune cell function. They used NanoString gene expression profiling to examine the impact of TAZ or YAP on immune-related gene expression in human breast epithelial cells. They identified 42 genes that were upregulated and 53 genes that were downregulated by either YAP or TAZ. PD-L1 was among the most strongly upregulated genes, and they confirmed that expression of TAZ or YAP can promote PD-L1 expression in these cells, whereas knockout or pharmacological inhibition of TAZ reduces it. Their work is one of several recent papers that show that YAP or TAZ activation promotes PD-L1 expression in multiple cancer types, including melanoma, lung adenocarcinoma, non-small cell lung cancer (NSCLC), and breast cancer (3,10-12).

PD-L1 is a type 1 transmembrane protein that is expressed on a variety of cells. Its main receptor, PD-1, is expressed on the surface of many immune cells, including T cells, B cells, and tumor-invading lymphocytes. Under normal conditions, the PD-L1/PD-1 pathway functions controls inflammation to avoid excessive tissue damage. When active T cells bind to their target antigen, it induces the release of numerous cytokines that promote an inflammatory response. This inflammatory response leads

to the expression of PD-L1 in the resident tissue, which in turn is bound by T cells through programmed cell death protein 1 (PD-1) receptor, resulting in immune tolerance and the protection of the native tissue. Some cancers upregulate PD-L1, which promotes immune tolerance and protects the cancer cells from cytotoxic CD8+ T cells. This, in turn, allows tumors to evade the immune system and enables them to become more aggressive. A better understanding of the molecular mechanisms controlling PD-L1 expression in tumor cells could lead to the development of more effective targeted immunotherapies.

Given this, Janse van Rensburg and colleagues sought to elucidate how YAP and TAZ promote PD-L1 expression. As transcriptional co-activators, TAZ and YAP can't directly bind DNA and must instead partner with other transcription factors to regulate gene expression. Although YAP and TAZ interact with numerous transcription factors, the TEA family (TEADs 1–4) has been shown to mediate many YAP/TAZ-dependent effects. Consistently, the authors found that TAZ-mediated PD-L1 expression is TEAD-dependent (3). They show that an activated TAZ mutant (TAZ-S89A) increased PD-L1 expression, but not if they mutated the TEAD interaction domain. This indicates that TAZ needs to bind TEADs in order to promote PD-L1 expression. Additionally, knockdown of TEADs 1, 3, and 4 reduces PD-L1 expression. They also found that TAZ-TEAD bind directly to the PD-L1 promoter, demonstrating that the regulation is direct. Consistently, other recent studies that described YAP-mediated PD-L1 expression also found that YAP partnered with TEADs and directly bound the PD-L1 promoter in melanoma cells (10), NSCLC cells (12), and lung cancer cells (11). Collectively, these studies suggest that PD-L1 is likely to be a YAP/TAZ-TEAD target gene in other cell types and that targeting YAP/TAZ-TEAD-mediated PD-L1 expression may be a viable treatment option for a variety of cancer types.

Interestingly, TAZ/TEAD-dependent PD-L1 expression does not appear to be conserved in mice. Janse van Rensburg and colleagues found that TAZ did not promote PD-L1 expression in several murine cell lines. They also found that a luciferase reporter construct driven by the mouse Pd-11 promoter was not induced by TAZ-S89A-TEAD4, suggesting that the TAZ-TEAD complex does not bind the mouse Pd-11 promoter. YAP activation was also unable to promote mouse PD-L1 expression. Although research of the PD-1/PD-L1 pathway using mouse tumor cells suggests that PD-L1 promotes immune evasion in mice (13), these findings show that PD-L1 expression is

regulated differently at the transcriptional level in humans and mice. It is currently not known whether YAP and TAZ promote immune evasion of mouse cancer cells, but when Janse van Rensburg and colleagues used the same NanoString gene expression profiling approach to identify immune-related TAZ target genes in mouse cancer cells, they identified 83 genes that were regulated by TAZ. However, only 14 of those 83 genes overlapped with the TAZ target genes identified in human cells. It would be interesting to see if any of these TAZ target genes can repress T-cell function to promote immune suppression. There are also other studies that show that YAP activation can influence tumor progression by influencing the function of other immune cells. For example, in a mouse model of prostate cancer, YAP activation led to recruitment of myeloid-derived suppressor cells (14). Another study found that YAP activation in mouse liver tumor-initiating cells recruited pro-tumorigenic macrophages (15). Perhaps some of the TAZ-regulated genes the authors identified in mouse cells play a role in these processes.

Janse van Rensburg and colleagues also tested whether TAZ-mediated upregulation of PD-L1 on cancer cells could influence T-cell function. This was examined by co-culturing Jurkat T cells with cancer cells overexpressing TAZ-S89A. They demonstrated that TAZ activation was sufficient to promote T cell apoptosis, and that this effect was blocked by administration of a PD-L1 blocking antibody. YAP-mediated PD-L1 expression on melanoma cells also suppresses T-cell function (10). These findings provide the rationale to test the functional significance of YAP/TAZ-mediated PD-L1 expression using *in vivo* cancer models. The obvious question is whether preventing YAP/TAZ-mediated PD-L1 expression can promote T-cell reactivation to drive an anticancer immune response. However, PD-1 is also expressed on other immune cells including monocytes, T cells, B cells, dendritic cells, and tumor-infiltrating lymphocytes (16), and these cell types also play important roles during cancer development and progression. It would also be interesting to investigate if the upregulation of PD-L1 caused by YAP/TAZ activation can influence the behavior of any of these cell types. Given the importance of immunosuppression during both primary tumor development and the metastatic cascade, it would be worthwhile to test the importance of this pathway for tumor initiation as well as during metastasis. Unfortunately, the fact that TAZ does not appear to regulate PD-L1 expression in murine cells indicates that syngeneic or transgenic mouse models of cancer cannot be used for such

experiments. Xenotransplants of human cancer cells into humanized mice would be one potential means to study this. It should also be possible to generate mouse cancer cells with the human PD-L1 promoter driving expression of either the mouse or human PD-L1 gene. Importantly, human PD-L1 can be recognized and bound by mouse PD-1 receptors (17). In the absence of definitive mouse model experiments, a more thorough investigation of how strongly PD-L1 expression and YAP/TAZ activation are correlated in human cancers would provide additional rationale for targeting this pathway. So far, studies show that the expression or activation of YAP correlates strongly with PD-L1 expression in clinical melanoma (10) and NSCLC samples (12), but it has not been explored in other cancer types. No studies to date have tested if TAZ expression or nuclear localization is correlated with PD-L1 expression.

There is already significant interest in targeting the PD-1/PD-L1 axis in cancer. Several PD-1 and PD-L1 therapies have been developed, including the anti-PD-1 antibodies Pembrolizumab and Nivolumab, and the anti-PD-L1 antibodies Atezolizumab, Avelumab, and Durvalumab, and many of these drugs have been or are currently in clinical trials (16,18,19). To date, the response rates to these drugs have been quite good, but there are populations of patients that do not respond (16,18,19). Therefore, the discovery of biomarkers that can help identify cancers that would respond well to PD-1/PD-L1 treatments is crucial. If YAP/TAZ activation is found to promote PD-L1 expression on a significant percentage of human cancers, it may be possible to use YAP and TAZ as such biomarkers. Another issue is the toxicities and side effects associated with targeting PD-L1 or PD-1. Most side effects are minor, such as rashes, diarrhea, fatigue, decreased appetite, and asthenia, but in some rare cases, more severe side effects such as nephritis and renal dysfunction, pleural effusion and inflammation, hypercalcemia, encephalitis, colitis, hepatitis, and disorders related to immune dysfunction have also occurred (16-18). Strategies that inhibit PD-L1 expression specifically on the tumor cells may help avoid these treatment-related adverse effects. The papers by Janse van Rensburg *et al.* and others suggest that it may be possible to inhibit PD-L1 expression specifically on cancer cells by preventing YAP/TAZ activation.

As mentioned above, YAP and TAZ are often aberrantly active in human cancer, and evidence suggests that this drives cancer development and progression. This had led to

significant interest in YAP and TAZ as therapeutic targets, and several recent reviews discuss this thoroughly (7,20-22). This enthusiasm began following a study that revealed that Verteporfin and other porphyrin family members block YAP-TEAD interaction and inhibit YAP-mediated tumor growth (23). Since this study, several others have found that Verteporfin can disrupt YAP/TAZ-TEAD interaction and function and inhibit tumor formation and growth in several cancer types [reviewed in (7)]. Knock down and knockout studies also show that YAP and TAZ are essential for tumor growth and cancer progression in *in vivo* models [reviewed in (7-9)]. However, none of these *in vivo* studies investigated if YAP or TAZ influences immunosuppression. Plus, most of these studies used either immunocompromised mice or transgenic mouse models of cancer, which, as discussed above, cannot be used to assess the impact of YAP/TAZ on PD-L1-mediated immune suppression.

There is also reason to believe that directly targeting YAP and TAZ may cause adverse side effects due to their established roles in tissue repair and stem cell maintenance. An alternative strategy may be to inhibit YAP/TAZ-mediated PD-L1 expression by targeting YAP/TAZ regulatory pathways in cancer cells. The main YAP/TAZ regulatory pathway is the Hippo pathway, a serine/threonine kinase cascade that leads to phosphorylation and repression of YAP and TAZ. Inactivating mutations in this pathway can promote cancer, and numerous pathways with established roles in cancer can activate YAP and TAZ by repressing the Hippo pathway (6-8). This suggests that altering the Hippo pathway or upstream regulatory pathways would influence PD-L1 expression in cancer cells. Consistently, this paper by the Yang lab shows that knockdown of either of the two sets of Hippo pathway kinases, Large Tumor Suppressor Homolog 1 and 2 (LATS1/2) or Mammalian Sterile 20-like Kinase 1 and 2 (MST1/2), resulted in increased expression of PD-L1. Conversely, overexpression of LATS decreased PD-L1 expression (3). Furthermore, manipulation of upstream regulators of the Hippo-YAP/TAZ pathway also altered PD-L1 expression. They found that treatments that typically activate the Hippo pathway, such as the protein kinase A activator Forskolin, glucagon, phosphatidylinositol 4,5-bisphosphate 3-kinase inhibition, 3-phosphoinositide-dependent protein kinase 1 (PDK1) inhibition, serum starvation, and Raf inhibition all reduced PD-L1 expression, whereas treatments that repress the Hippo pathway, like 12-O-tetradecanoylphorbol-13-acetate (TPA), epidermal growth factor, insulin, and S1P increased PD-L1 expression. This suggests that identifying and targeting

pathways upstream of YAP and TAZ that are dysfunctional in cancer cells may be one way to inhibit PD-L1 expression specifically on cancer cells.

In summary, the work by the Yang lab nicely demonstrates that both YAP and TAZ promote PD-L1 expression on human breast and lung cancer cells. TAZ is recruited directly to the human PD-L1 promoter by TEADs, and this TAZ-TEAD-dependent induction of PD-L1 promotes T-cell apoptosis. Their findings, in combination with other recent publications (3,10-12), have revealed a novel mechanism of PD-L1 upregulation, and suggest that YAP and TAZ activation in cancer cells may help these cells evade the immune system. This work paves the way for future studies aimed at testing the importance of this pathway in immune suppression, and reveals another potentially important role for the Hippo-YAP/TAZ pathway during cancer progression.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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