Editorial

Regulation of tumor immune evasion by the Hippo effector TAZ

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Representing one of the world's leading causes of death, cancer accounted for 22% of the recorded fatalities in the United States in 2015 (1). Cancer arises from a complex interplay of genetic and epigenetic alterations that can result in dysregulation of signalling networks (2). One such network is the Hippo pathway, which has been demonstrated to act, among other processes, in the control of proliferation and organ size (3). The mammalian Hippo pathway core cassette consists of upstream kinases (MST1 and MST2) and downstream kinases (LATS1 and LATS2). The interaction between the upstream and downstream kinases is assisted by the scaffold protein SAV. Active Hippo signalling leads to the MST-dependent phosphorylation of LATS and its coactivator MOB1. Key effectors of the Hippo signalling pathway are the paralogues YAP and TAZ, both of which can act as potent oncogenes (4). TAZ has been shown to promote anchorage-independent growth and tumorigenesis in breast cancer cells (5) while enhancing proliferation and transformation in lung cancer cells (6). The activity of both YAP and TAZ is negatively regulated by the phosphorylated Hippo core cassette (7), highlighting the role of the Hippo pathway in tumor suppression.

In recent years, it has become obvious that a complex crosstalk exists between the cancer microenvironment and the immune system (8). Interactions between cancer and immune cells reduce immune responses, lead to enhanced tumor growth, induce immune cell apoptosis, and ultimately promote cancer immune evasion. The transmembrane protein programmed death-ligand 1 (PD-L1) and its receptor PD-1 have emerged as key elements in tumor-induced immunosuppression (9). PD-L1 is frequently found on the plasma membrane of cancer cells and can bind to T-cell expressed PD-1, resulting in T cell apoptosis. This interaction allows tumor cells to escape the immune system.

Previous studies suggest that the Hippo pathway is involved in the cancer-induced immune response (10,11). However, the transcriptional targets of YAP and TAZ in the context of immunoevasion are poorly understood. A genetic screen by Janse van Rensburg *et al.* identifies a range of candidate immune targets of YAP/TAZ (12). While 35 genes were shown to be regulated by TAZ alone, 12 genes were regulated by YAP only; 24 genes were regulated by both YAP and TAZ. Given its role in cancer immune evasion, the authors chose to further study PD-L1. Overexpression of YAP or TAZ lead to elevated protein levels of PD-L1, as did depletion of components of the Hippo core cassette. Overexpression of LATS2 had the opposite effect. PD-L1 protein expression was also induced by overexpression of TAZ in lung cancer cells. The study further showed that TAZ and PD-L1 are co-expressed in several breast and lung cancers in the TCGA dataset. In some cancer cell lines, depletion of TAZ lead to a decrease in PD-L1 protein expression, which was rescued by restoring TAZ expression. TAZ-dependent regulation of PD-L1 required transcriptional activators from the TEAD family. Expression of a mutant form of TAZ incapable of TEAD binding or knockdown of TEAD1/3/4 resulted in a reduced expression of PD-L1. Co-expression of TEAD-binding mutant TAZ and TEAD1–4 produced an increase in PD-L1 promoter activity. A deletion scan of the PD-L1

promoter identified a putative TEAD-response element. Importantly, TAZ overexpression in lung and breast cancer cell lines impaired Jurkat T cell function via PD-L1-mediated induction of apoptosis. Blocking of PD-L1 suppressed apoptosis of T cells that had been elicited by TAZ overexpression in lung cancer cells. T cells showed diminished IL-2 production when co-cultured with TAZ-overexpressing lung cancer cells. This phenotype was rescued by a PD-L1-specific antibody.

Intriguingly, PD-L1 regulation by TAZ is not conserved between mice and humans. PD-L1 expression did not respond to TAZ in mouse cell lines, and the authors did not identify a TEAD response element in the mouse PD-L1 promoter. This highlights that care needs to be taken when using model organisms, at least in the context of immunoresponse studies of cancer.

The Hippo pathway and its effector TAZ play a crucial role in cancer immune evasion (9). The report by Janse van Rensburg *et al.* (12) has provided important novel insights into the molecular mechanisms which allow tumor cells to escape immune surveillance, thereby promoting cancer progression. The data presented indicates that through its effector TAZ, the Hippo pathway integrates input from a number of upstream signalling pathways. Unravelling the particular cellular (and individual) contexts in which this is relevant to cancer will establish criteria that will help design patient-based treatment approaches. A profound understanding of the interplay between cancer and the immune system is paramount to the development and improvement of cancer therapies, especially in the context of immunotherapy (8). Janse van Rensburg *et al.* (12) made a significant contribution to the current knowledge about species-specific regulation of immune-related genes, underlining the importance to choose appropriate model systems when studying tumor immunology. More extensive research on immune targets that are differently regulated between species will be needed to ensure the success of further studies in this field.

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Footnote

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