to target cells will need to be characterized in prospective studies.

The roles of IGF-1 in immunity are only starting to emerge. Recently, it was discovered that Mycobacterium leprae (Batista-Silva et al., 2016) induces an increase in macrophage IGF-1 production, which then attenuates bacterial killing. Given the role of IGF-1 in modulating particle uptake by lung epithelial cells (Han et al., 2016), it is possible that excess IGF-1 continually instructs epithelial cells to ingest anti-inflammatory MVs, thus inhibiting the normal inflammatory process that is required to fight bacterial infections. Future experiments may investigate whether pathogens promote their own survival by hijacking communications between professional and non-professional phagocytes.

In sum, Han and colleagues convincingly show that macrophages secrete IGF-1 to control the phagocytic activity and inflammatory phenotype of non-professional phagocytes (Figure 1) (Han et al., 2016). The effect of IGF-1 in diminishing inflammation opens very exciting possibilities for investigating how this growth factor modulates the intracellular trafficking of professional and non-professional phagocytes in health and disease.

REFERENCES


Hippo Wades into Cancer Immunology

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The Hippo pathway limits organ size and suppresses tumors. Reporting in Cell, Moroishi et al. (2016), show that, paradoxically, Hippo pathway inactivation can repress tumor growth by modulating tumor immunogenicity. This could explain the rarity of pathway mutations in cancers and suggests Hippo pathway repression as a cancer immunotherapy modality.

The Hippo pathway was first discovered in Drosophila. It limits organ size by acting in a cell-autonomous, organ-intrinsic fashion. Based on striking tissue overgrowth upon disruption of Drosophila Hippo pathway genes, it was theorized to be a tumor suppressor pathway in humans. The first validation for this idea was provided by the discovery that the human ortholog of the Drosophila salvador gene (SAV1) is mutated in two human renal cancer cell lines (Tapon et al., 2002). Subsequently, this notion was strengthened by the discovery that the Drosophila ortholog of Neurofibromin 2 (NF2; also known as merlin), a bona fide human tumor suppressor gene, is an upstream member of the Hippo pathway (Hamaratoglu et al., 2006). Further confirmation was provided by murine studies, where overexpression of the key Hippo pathway oncoprotein YAP caused overgrowth and tumor formation in organs such as the liver and small intestine (Camargo et al., 2007; Dong et al., 2007). Likewise, mutating the key YAP-inhibitory kinases MST1/2 or LATS1/2 causes tumor formation in many organs. Although an overwhelming number of studies have proven the tumor suppressor capability of the Hippo pathway, some studies have argued for an opposing role. In a recent issue of Cell, Moroishi et al. (2016) provide a potential mechanism for how the Hippo pathway could actually promote cancer by showing that pathway inactivation represses the growth of transplanted murine tumors by enhancing tumor immunogenicity (Figure 1).

Although the vast majority of Hippo pathway studies have argued for its role as a tumor suppressor (Harvey et al., 2013), select studies have linked YAP hyperactivation to apoptosis and tumor suppression. These seemingly paradoxical...
results have been difficult to reconcile and have lacked clear mechanistic explanations. The study by Moroishi et al. (2016) now provides a potential mechanism for how Hippo pathway repression (and therefore YAP and TAZ hyperactivation) could limit tumor growth, by modulating the immunogenicity of tumors. The authors uncovered a role for the Hippo pathway in tumor immunity by using different syngeneic tumor models in mice harboring an intact immune system or, alternatively, with defined genetic deficiencies in various immune compartments. Tumor-cell-specific deletion of the key Hippo pathway kinases LATS1 and LATS2, which normally phosphorylate and inhibit the YAP and TAZ oncoproteins, resulted in enhanced anchorage independent proliferation in vitro, but substantially impeded growth of transplanted tumors in vivo. This unexpected phenotype was dependent on YAP, as well as its key cognate transcription factors, the TEADs (Moroishi et al., 2016).

The apparent difference between the in vitro and in vivo findings led Moroishi and colleagues to speculate that the host immune system responded more vigorously to LATS1/2-deficient tumor cells. Supporting this notion, they showed that Hippo pathway repression modulated tumor immunogenicity by enhancing the content of nucleic acid released in extracellular vesicles (EV) by tumor cells. Recognition of nucleic acids derived from EV by host immune cells involved endosomal Toll-like receptors and their key downstream adaptor proteins MyD88 and TRIF. This resulted in potent tumor inhibition, which invoked type I interferon (IFN) receptors. Type I IFNs are a family of immune-stimulatory cytokines with pleiotropic effects on a variety of innate and adaptive immune cells, including NK cells, dendritic cells, and T cells (Parker et al., 2016). Thus, it is possible that EV-mediated induction of type I IFN enhanced tumor immunity not only during the induction phase in lymphoid tissues, but also by directly acting on immune cells within the tumor microenvironment.

The experiments by Moroishi et al. (2016) imply that enhanced activation of dendritic cells by EV-induced type I IFN and consequently, the induction of tumor-specific CD8 T cells was the dominant driver of tumor control. For instance, the growth of LATS1/2-deficient tumor cells was not suppressed in Rag1−/− mice, which lack T and B cells. Furthermore, inoculation with LATS1/2-deficient tumor cells or immunization with irradiated LATS1/2-deficient tumor cells induced effector responses capable of controlling the growth of LATS1/2-competent tumor cells expressing an identical model antigen, ovalbumin. Such results are consistent with the idea that induction of systemic CD8 T cell immunity and the resulting infiltration of tumor lesions by CD8 T cells and other immune cells mediated the elimination of transplanted tumors.

In recent years, immunotherapy aimed at reinvigorating the function of cancer-specific T cells has revolutionized the treatment of select cancers. In particular, targeting immune checkpoint regulators such as CTLA-4, as well as PD-1 and its ligand PD-L1, has delivered durable responses and hence drastically extended the lifespan of many cancer patients (Postow et al., 2015). Now a rush has ensued to develop combination therapies that enhance and extend the benefits of targeting the CTLA-4 and PD-1/PD-L1 pathways. Many of these efforts center on other immune checkpoint regulators, such as TIM-3 and LAG-3 (Melero et al., 2015). The present study suggests an alternative therapeutic mechanism; i.e., making tumors more immunogenic by suppressing the Hippo pathway. It will thus be important to test Moroishi and colleagues’ findings in human cancer cells by assessing their response to pharmacological LATS1/2 inhibition or YAP/TAZ activation. Along the same lines, future studies will have to elucidate the molecular pathways that link Hippo inactivation to increased nucleic acid deposition into extracellular vesicles, thereby providing additional avenues for therapeutic modulation of tumor immunogenicity.

Any therapeutic disruption of the Hippo pathway as a cancer therapy should be performed with extreme care, given that it is essential for multiple different biological processes and because of its established role in suppression of tissue growth and cancer. Such an approach could be especially problematic in those cancers that have a high prevalence of mutations in Hippo pathway genes and that cause YAP hyperactivation, like mesothelioma, uveal melanoma, epithelioid hemangioidothelioma, and mucinous tubular and spindle cell carcinoma of the kidney (Harvey et al., 2013; Mehra et al., 2016). Intriguingly, Hippo pathway mutations are relatively infrequent in most common cancers (Harvey et al., 2013). Several theories have arisen to describe this observation, and the present study provides another potential explanation (Moroishi et al., 2016). Although reduced LATS1/2 activity and subsequent YAP hyperactivity...
could provide a proliferative and survival advantage to a tumor cell, this could be counterbalanced by provocation of the immune system. Clearly, further studies are required to dissect the impact of tumor promoting, versus tumor suppressing, functions of the Hippo pathway before it can be rationally targeted to treat cancers.

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