OUTLOOK

Transcriptional activation of macropinocytosis by the Hippo pathway following nutrient limitation

Sharanya Sivanand¹ and Matthew G. Vander Heiden^{1,2}

¹Koch Institute for Integrative Cancer Research at Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA;

²Dana-Farber Cancer Institute, Boston, Massachusetts 02115, USA

Cancer cells must adapt metabolism to thrive despite nutrient limitations in the tumor microenvironment. In this issue of *Genes & Development*, King and colleagues (pp. 1345–1358) report a role for transcriptional regulators of the Hippo pathway to facilitate protein scavenging and support proliferation under some nutrient-deprived conditions.

A subset of cancer cells engages in macropinocytosis to take up bulk extracellular material as a source of nutrients. Macropinocytosis appears to be particularly advantageous for tumor cells when nutrients are scarce, and cancer cells equipped with the ability to engage in protein scavenging can proliferate even when deprived of select individual amino acids (Finicle et al. 2018).

Scavenging exogenous protein can be an important source of amino acids for some cancers, including pancreatic cancer, and is attributed in part to oncogenic activation of Kras signaling (Finicle et al. 2018). Trafficking of V-ATPase to the plasma membrane downstream from oncogenic Ras is one mechanism to promote macropinocytosis (Ramirez et al. 2019); however, because Ras is not required for macropinocytosis, additional cooperative mechanisms must exist (Palm et al. 2015). Activation of PI3K downstream from Kras enhances the extent to which cancer cells can engage in macropinocytosis (Araki et al. 1996). This suggests that other means of activating PI3K, as well as the metabolic context, might also determine whether cells use this process to scavenge nutrients (Michalopoulou et al. 2020). Of note, the complete pathway for how intracellular nutrient sensing influences nutrient scavenging remains unclear; furthermore, given the bidirectional feedback between nutrient availability and transcriptional responses to support growth, how each factor affects macropinocytosis is an area of ongoing investigation. King et al. (2020) have uncovered new insight into this by identifying a role for the Hippo pathway in promot-

ing macropinocytosis in response to leucine limitation. Specifically, the investigators identified a role for the transcriptional coactivators Yap and Taz in activating the TEAD family of transcription factors, which promote transcriptional activation of the Axl receptor tyrosine kinase that in turn activates PI3K/Akt and stimulates macropinocytosis (Fig. 1).

To identify regulators of macropinocytosis, the investigators used a panel of cell lines adapted to grow in the absence of leucine and performed chromatin accessibility studies in combination with RNA sequencing analysis to assess genome-wide changes in transcription factor occupancy and transcript levels. These studies revealed a role for the TEAD family of transcription factors as a mediator of the adaptive response to amino acid limitation. Given the known association between the Hippo pathway transcriptional coactivators Yap and Taz and the TEAD transcription factors, and the up-regulation of target genes associated with Yap activation, King et al. (2020) further investigated the role of these factors in macropinocytosis. Consistent with a role for the Hippo pathway in adaptation to leucine depletion, the investigators found enhanced nuclear enrichment of Yap/Taz, which are otherwise retained in the cytoplasm when repressed, suggesting that leucine availability affects shuttling of these factors in and out of the nucleus. While the exact link between leucine sensing and control of Yap/Taz nuclear localization is not understood, these findings suggest a cross-talk between metabolic inputs and Hippo signaling.

King et al. (2020) also found up-regulation of the Yap/Taz transcriptional target Axl, which encodes a receptor tyrosine kinase that can activate the PI3K/Akt pathway, which in turn can promote macropinocytosis (Araki et al. 1996). To mechanistically test the link between Hippo pathway activation of Axl and PI3K/Akt signaling-mediated increases in macropinocytosis, the investigators used an orthogonal approach to activate Axl kinase with

[Keywords: Yap; cancer metabolism; macropinocytosis]

Corresponding author: mvh@mit.edu

Article is online at <http://www.genesdev.org/cgi/doi/10.1101/gad.343632.120>.

© 2020 Sivanand and Vander Heiden This article is distributed exclusively by Cold Spring Harbor Laboratory Press for the first six months after the full-issue publication date (see <http://genesdev.cshlp.org/site/misc/terms.xhtml>). After six months, it is available under a Creative Commons License [Attribution-NonCommercial 4.0 International], as described at <http://creativecommons.org/licenses/by-nc/4.0/>.

Prior work has also linked elevated Yap/Taz activity with epithelial–mesenchymal transition (EMT) (Cordeonsi et al. 2011), which can play a role in the capacity of cancer cells to disseminate, colonize, and proliferate in distant sites (Aiello et al. 2018). While induction of EMT is not sufficient to increase macropinocytosis, the investigators hypothesize that the response to amino acid limitation could be differentially regulated based on where cells fall within the EMT spectrum, potentially supporting a more invasive phenotype. In fact, they found cells adapted to grow in the absence of leucine are more invasive, and cells at the leading edge of the tumor display elevated Yap nuclear localization, correlating with elevated macropinocytosis.

Aiello NM, Maddipati R, Norgard RJ, Balli D, Li J, Yuan S, Yamazoe T, Black T, Sahmoud A, Furth EE, et al. 2018. EMT subtype influences epithelial plasticity and mode of cell migration. *Dev Cell* **45**: 681–695.e4. doi:10.1016/j.devcel.2018.05.027

Araki N, Johnson MT, Swanson JA. 1996. A role for phosphoinositide 3-kinase in the completion of macropinocytosis and phagocytosis by macrophages. *J Cell Biol* **135**: 1249–1260. doi:10.1083/jcb.135.5.1249

Cordenonsi M, Zanconato F, Azzolin L, Forcato M, Rosato A, Frasson C, Inui M, Montagner M, Parenti AR, Poletti A, et al. 2011. The hippo transducer TAZ confers cancer stem cell-related traits on breast cancer cells. *Cell* **147**: 759–772. doi:10.1016/j.cell.2011.09.048

Finicle BT, Jayashankar V, Edinger AL. 2018. Nutrient scavenging in cancer. *Nat Rev Cancer* **18**: 619–633. doi:10.1038/s41568-018-0048-x

Han Y. 2019. Analysis of the role of the Hippo pathway in cancer. *J Transl Med* **17**: 116. doi:10.1186/s12967-019-1869-4

Kim SM, Nguyen TT, Ravi A, Kubiniok P, Finicle BT, Jayashankar V, Malacrida L, Hou J, Robertson J, Gao D, et al. 2018. PTEN deficiency and AMPK activation promote nutrient scavenging and anabolism in prostate cancer cells. *Cancer Discov* **8**: 866–883. doi:10.1158/2159-8290.CD-17-1215

- King B, Araki J, Palm W, Thompson CB. 2020. Yap/Taz promote the scavenging of extracellular nutrients through macropinocytosis. *Genes Dev* doi:10.1101/gad.340661.120
- Michalopoulou E, Auciello FR, Bulusu V, Strachan D, Campbell AD, Tait-Mulder J, Karim SA, Morton JP, Sansom OJ, Kammphorst JJ. 2020. Macropinocytosis renders a subset of pancreatic tumor cells resistant to mTOR inhibition. *Cell Rep* **30**: 2729–2742.e4. doi: 10.1016/j.celrep.2020.01.080
- Palm W, Park Y, Wright K, Pavlova NN, Tuveson DA, Thompson CB. 2015. The Utilization of Extracellular Proteins as Nutrients Is Suppressed by mTORC1. *Cell* **162**: 259–270. doi:10.1016/j.cell.2015.06.017
- Ramirez C, Hauser AD, Vucic EA, Bar-Sagi D. 2019. Plasma membrane V-ATPase controls oncogenic RAS-induced macropinocytosis. *Nature* **576**: 477–481. doi:10.1038/s41586-019-1831-x
- Sullivan MR, Danai L V, Lewis CA, Chan SH, Gui DY, Kunchok T, Dennstedt EA, Vander Heiden MG, Muir A. 2019. Quantification of microenvironmental metabolites in murine cancers reveals determinants of tumor nutrient availability. *Elife* **8**: e44235. doi:10.7554/eLife.44235

Transcriptional activation of macropinocytosis by the Hippo pathway following nutrient limitation

Sharanya Sivanand and Matthew G. Vander Heiden

Genes Dev. 2020, **34**:

Access the most recent version at doi:[10.1101/gad.343632.120](https://doi.org/10.1101/gad.343632.120)

Related Content **Yap/Taz promote the scavenging of extracellular nutrients through macropinocytosis**

Bryan King, Jingwen Araki, Wilhelm Palm, et al.
Genes Dev. October , 2020 34: 1345-1358

References This article cites 11 articles, 3 of which can be accessed free at:
<http://genesdev.cshlp.org/content/34/19-20/1253.full.html#ref-list-1>

Articles cited in:
<http://genesdev.cshlp.org/content/34/19-20/1253.full.html#related-urls>

Creative Commons License

This article is distributed exclusively by Cold Spring Harbor Laboratory Press for the first six months after the full-issue publication date (see <http://genesdev.cshlp.org/site/misc/terms.xhtml>). After six months, it is available under a Creative Commons License (Attribution-NonCommercial 4.0 International), as described at <http://creativecommons.org/licenses/by-nc/4.0/>.

Email Alerting Service

Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article or [click here](#).