Cell Research

www.nature.com/cr
www.cell-research.com

RESEARCH HIGHLIGHT

A new STAT3 function: pH regulation

Yuxin Wang[1] and George R. Stark[1]

Cell Research (2018) 28:1045; https://doi.org/10.1038/s41422-018-0098-3

In a recent paper published in *Cell Research*, Liu et al. describe a novel function of STAT3, a classical oncogene, on lysosomes to regulate pH by interacting with the vacuolar H^+-ATPase. This finding suggests a new anti-cancer strategy by limiting this function.

Each of the seven members of the Signal Transducer and Activator of Transcription (STAT) family of transcription factors is phosphorylated on a single conserved tyrosine residue in response to a wide variety of cytokines, including the interferons and cytokines that activate the common gp130 receptor.[1] However, STAT3 is the only family member whose expression is required for normal development. Moreover, in many different tumors, STAT3 is an oncogene whose activation through tyrosine phosphorylation is maintained indefinitely, in contrast to the rapid downregulation of STAT3 phosphorylation in normal tissues that have been exposed to pro-inflammatory signals.

In addition to their primary function as inducible transcription factors, STATs 1, 2, and 3 can also activate transcription without tyrosine phosphorylation.[2,3] The STAT1, 2, and 3 genes are driven by the corresponding activated, tyrosine-phosphorylated STATs, leading to substantial increases of U-STATs, which lack tyrosine phosphorylation and accumulate in cells at late times, when the initial tyrosine phosphorylation of the STATs has been greatly diminished by potent negative regulatory mechanisms. In the case of U-STAT3, a set of genes is expressed that are distinct from those driven by phosphorylated STAT3, in part because U-STAT3 forms a transcriptionally active complex with NFκB.[2]

Increased levels of STAT3 can also facilitate non-canonical functions of this protein that are independent of transcriptional activation. During the last ten years, work from several laboratories has shown that STAT3 is present in mitochondria and has important functions there that are independent of its phosphorylation on tyrosine 705, but depend on phosphorylation of serine 727.[4] Phosphorylation of serine 727 aids but is not essential for transcriptional activation by phosphorylated STAT3. Examples of key observations are from Gough et al.[5] who showed that mitochondrial STAT3 supports transformation in response to oncogenic RAS mutations in myeloproliferative neoplasms, and from Meier et al.[6] who showed that mitochondrial STAT3 regulates the activity of the electron transport chain and thus the production of reactive oxygen species in cancer cells. Now, from the current paper by Liu et al.,[7] we learn that STAT3 has important functions in lysosomes that also do not involve the activation of transcription.

pH reversal is a recently described phenomenon in carcinogenesis in which the cytosol becomes more alkaline (from pH 7.2 to 7.5) and the extracellular space becomes more acidic (from pH 7.4 to below 7.0).[8] pH reversal has been linked to cancer cell survival, largely due to its inhibitory effect on apoptosis, as well as to increased glycolysis, which reinforces metabolic adaptation, tumor cell survival, invasion, immune evasion and drug resistance.[8,9] Although the importance of pH reversal in cancer cells is established, little has been known until now about how this process develops and is maintained. Exciting new research from the Danish Cancer Society's Research Center sheds new light on this phenomenon. Marja Jäättelä's group found that the classic oncoprotein STAT3 is on lysosomes, which are small but abundant intracellular organelles.[7] An important function of lysosomes is to serve as cellular proton pools that are the main regulators of intracellular pH. The portion of STAT3 that is located on lysosomes helps to maintain a more alkaline cytosolic pH in cancer cells, even when the external pH becomes acidic. A huge protein complex, the vacuolar H^+-ATPase, resides on lysosomal limiting membranes and pumps protons into lysosomes by utilizing the energy provided by ATP, thus making the lysosomal lumen acidic.[10] Liu et al. found that STAT3 associates with the vacuolar H^+-ATPase and stimulates it to pump protons, thus altering the cytosolic pH of the cancer cell.

This novel finding reveals that STAT3 exerts its oncogenic effects in the nucleus, in mitochondria, and also on lysosomes, and also reveals that, once cancer cells experience acute cytosolic acidification, more STAT3 will be excluded from the nucleus and recruited to lysosomes in an effort to restore cytosolic pH, thus establishing a positive feedback loop. These results suggest that inhibiting STAT3 in the nucleus might promote its functions in mitochondria and on lysosomes, and thus might actually help the cancer cell to survive. The new information suggests a potential strategy of targeting the function of STAT3 on lysosomes to limit cancer cell growth and progression, but also indicates that efforts to limit the oncogenic properties of STAT3 must account for the various ways in which this highly versatile protein aids cancer cell functions and survival.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

REFERENCES

1. Stark, G. R. & Darnell, J. E. Jr. *Immunity* **36**, 503–514 (2012).
2. Yang, J. et al. *Genes Dev.* **21**, 1396–1408 (2007).
3. Cheon, H. et al. *EMBO J.* **32**, 2751–2763 (2013).
4. Rincon, M. & Pereira, F. V. *Int. J. Mol. Sci.* **19**, pii: E1656 (2018).
5. Gough, D. J., Marie, I. J., Lobry, C., Aifantis, I. & Levy, D. E. *Blood* **124**, 2252–2261 (2014).
6. Meier, J. A. et al. *Sci. Signal.* **10**, pii: eaag2588 (2017).
7. Liu, B. et al. *Cell Res.* **28**, 996–1012 (2018).
8. Webb, B. A., Chimenti, M., Jacobson, M. P. & Barber, D. L. *Nat. Rev. Cancer* **11**, 671–677 (2011).
9. Damaghi, M., Wojtkowiak, J. W. & Gillies, R. *J. Front Physiol.* **4**, 370 (2013).
10. Whitton, B., Okamoto, H., Packham, G. & Crabb, S. *J. Cancer Med.* **7**, 3800–3811 (2018).

[1]Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, USA
Correspondence: George R. Stark (STARKG@ccf.org)

Published online: 10 October 2018