Lactate jump-starts mTORC1 in cancer cells

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The mTOR kinase (mammalian Target of Rapamycin) is a major regulatory hub that senses and integrates nutrient, energy and growth factor inputs to promote cell growth. In this issue of EMBO Reports, Byun and colleagues report that high intracellular levels of lactate activate mTORC1 in KRAS transformed cells independently of a growth factor input [1]. This suggests a mechanism for how mTORC1 can be co-opted to support oncogenic growth and proliferation.

Lactate production is increased in many tumors as a consequence of the Warburg effect, where cancer cells generate ATP preferentially via glycolysis despite the availability of oxygen. Lactate is the metabolic end product of glycolysis and is often dismissed as an unwanted byproduct that is discarded from the cell. However, recent studies have revealed an active role for lactate in cancer metabolism. There are several scenarios where tumor cells utilise lactate as a carbon source. For example, in the case of metabolic symbiosis, lactate generated in the inner, hypoxic core of a tumor is utilised by cells in the periphery of the tumor where oxygen levels are sufficient to support the back conversion of lactate to pyruvate for mitochondrial respiration. In the so-called reverse Warburg effect, non-transformed stromal cells are stimulated by tumor cells to produce lactate which is then taken up and utilised by tumor cells (reviewed in 2). There are also tumors where circulating lactate is taken up as a metabolic fuel [3].

In this issue, Byun and colleagues report another interesting aspect of lactate in oncogenic growth. Starting from KRAS transformed MEF cells, they observed KRAS-MEK induced overexpression of COUP-TFII (chicken ovalbumin upstream promoter transcription factor). COUP-TFII upregulates LDHA (lactate dehydrogenase), the enzyme catalyzing the terminal step of glycolysis which converts pyruvate to lactate. Thus far, these observations

follow the well-established sequence of events in cancer where oncogenic transformation is accompanied by a global metabolic shift to aerobic glycolysis with a concomitant increase in lactate production. The novel and striking finding reported by Byun et al. is that lactate is an activator of mTORC1 (mTOR Complex 1). mTORC1 positively regulates translation and various other anabolic pathways to support cell growth and proliferation. Evidence for a direct role of lactate in mTORC1 activation is the observation that exogenous lactate rescues mTORC1 signaling upon knockdown of COUP-TFII or LDHA. The mechanism described for lactate-mediated mTORC1 activation involves perturbation of negative regulation upstream of mTORC1. The small G-protein Rheb, in its GTP-bound form, activates mTORC1 on the surface of the lysosome (Fig. 1). The GTPase activating complex TSC (composed of the TSC1 and TSC2 proteins) negatively regulates Rheb-GTP and thus inactivates mTORC1 signaling. Byun et al. observed that high levels of exogenous lactate (20mM) disrupt the binding of TSC to Rheb-GTP thereby preserving Rheb-GTP levels. Exogenous lactate also inhibits translocation of TSC (visualized by TSC2) to the lysosomal surface where it would normally encounter and inhibit Rheb-GTP. Thus, lactate sustains constitutively high levels of active Rheb and, in turn, constitutively active mTORC1. Although surprising, this is consistent with a recent report showing that autophagy, which is suppressed by mTORC1, can be inhibited by lactate [4]. Lactate administration has also been shown to activate mTORC1 in muscle of adult mice [5].

What are the implications of this study? Lactate overproduction is seemingly more frequent in cancers than mTORC1 hyperactivation. Presumably, there is a threshold for the concentration of intracellular lactate required for mTORC1 activation. Intracellular lactate is exported from cells by the ubiquitous MCT1 (monocarboxylate transporter) and by the hypoxia-induced MCT4 isoform whose expression is frequently induced in tumors. Thus, depending on the levels of MCT1 and MCT4 expression, tumors differ in their lactate exporting capacity and thereby in their ability to accumulate intracellular lactate to levels required for mTORC1 activation. Few data are available on intracellular lactate concentrations in tumors to confirm this assumption. Nevertheless, as an MCT1 inhibitor (AZD3965) is currently in

clinical trials for cancer [6], it would be of interest to ascertain if high intracellular lactate levels may have the undesired effect of stimulating mTORC1 in patient tumors.

Conversely, mTORC1 activation is encountered in cancers where none of its negative regulators (TSC and PTEN) are mutated. These negative regulators are upstream of Rheb. In these cases, it is possible that mTORC1 is activated by lactate blocking TSC action. Again, this can be addressed by determining the intracellular lactate concentration in tumors.

Are there normal physiological conditions where lactate could serve as an mTORC1 activator? Upon stimulation, T-cells go through a short phase of rapid proliferation. As in cancer, this rapid proliferation is characterized by a shift to aerobic glycolysis to generate ATP and biosynthetic precursors for formation of new cells. The increase in glycolysis could also serve to produce lactate to sustain mTORC1 activation. Indeed, T-cell activation is exquisitely sensitive to rapamycin (IC50 ~0.05nM, substantially below that required in other cells) [7], suggesting that maintaining mTORC1 activity is critically important in T-cell activation. However, it should be noted that T-cell proliferation is blocked by MCT1 inhibition (which should result in even higher intracellular lactate levels and mTORC1 activation) [8].

Lactate is receiving belated recognition as being more than an unwanted end-product of glycolysis. It is also a source of metabolic fuel and a signaling molecule in its own right [9]. The central finding of this study, namely that lactate activates mTORC1, has important implications for cancer biology and beyond.

Conflict of interest statement

The authors declare no conflict of interest.

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References

1. Byun JK, Park M, Yun JW *et al* (2019) *EMBO Rep.* (this issue)
2. Morrot A, da Fonseca LM, Salustiano EJ *et al* (2018) *Front. Oncol.* 8: 81
3. Faubert B, Li KY, Cai L *et al* (2017) *Cell* 171: 358-371
4. Im JH, Kang KW, Kim SY *et al* (2018) J*. Exp. Clin. Res* 37: 295
5. Cerda-Kohler H, Henriquez-Olguin C, Casas M *et al* (2018) *Physiol. Rep.* 6: e13800
6. Park SJ, Smith CP, Wilbur RR *et al* (2018) *Am. J. Cancer Res.* 8: 1967-1976
7. Kuo CJ, Chung J, Fiorentino DF *et al* (1992) *Nature* 358: 70-73
8. Murray CM, Hutchinson R, Bantick JR *et al* (2005) *Nat. Chem. Biol.* 1: 371-376
9. Sun S, Li H, Chen J *et al* (2017) *Physiology 32:* 453-463

Figure legends

Figure 1: High intracellular levels of lactate activates mTORC1 by relieving TSC repression of Rheb.

Left panel: Under normal physiological conditions mTORC1 is tightly regulated. mTORC1 is activated by Rheb. Rheb itself is negatively regulated by TSC. TSC is in turn repressed by intracellular cues that sense when conditions are favorable for cell growth. Right panel: Highly glycolytic conditions generate large amounts of lactate. When intracellular lactate levels exceed a certain threshold, it prevents TSC from interacting with Rheb leading to constitutive mTORC1 activity.

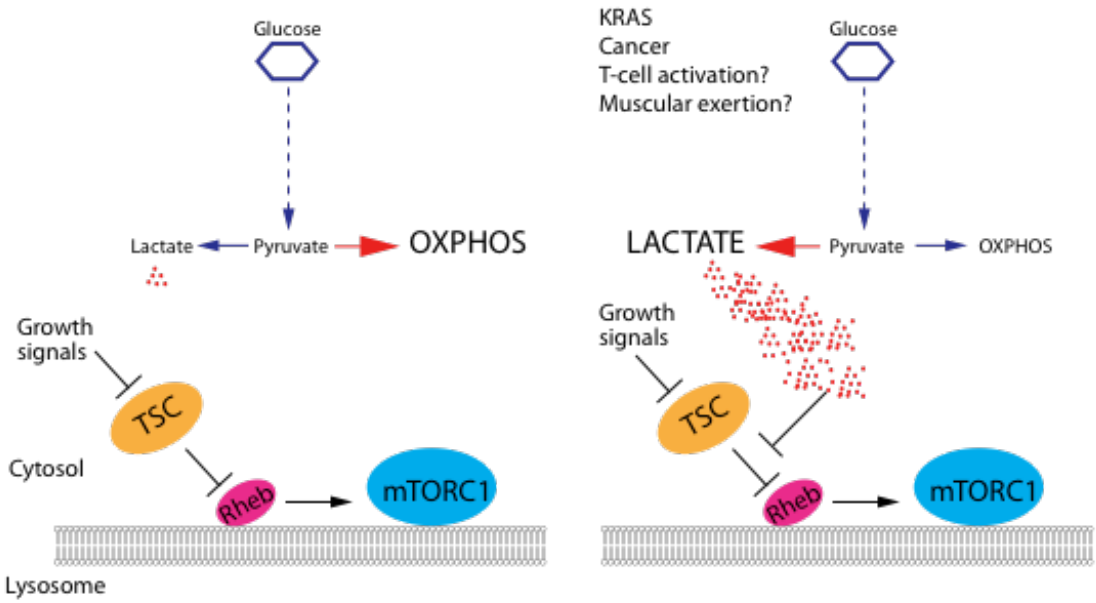

Figure 1 High intracellular levels of lactate activates mTORC1 by relieving TSC repression of Rheb.

Left panel, under normal physiological conditions mTORC1 is tightly regulated. mTORC1 is activated by Rheb. Rheb itself is negatively regulated by TSC. TSC is in turn repressed by intracellular cues that sense when conditions are favorable for cell growth. Right panel, highly glycolytic conditions generate large amounts of lactate. When intracellular lactate levels exceed a certain threshold, it prevents TSC from interacting with Rheb leading to constitutive mTORC1 activity.