Reviewer's report

Title: Symbiotic energy metabolism based on lactate shuttle can sustain prostate cancer progression

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Reviewer: Pierre Sonveaux

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In this study, Sanità et al report that in prostate cancer stromal fibroblasts preferentially express MCT4 and tumor cells MCT1. The treatment of cultured fibroblasts with conditioned medium from tumor cells increased their production of lactate, HIF-1a and (to be confirmed) MCT4 expression. In turn, the supernatant of conditioned fibroblasts promoted tumor cell proliferation in vitro, and preconditioned fibroblasts promoted prostate cancer growth in vivo more efficiently than naïve ones. This is an interesting study, but it is not totally novel as the same authors reported a bunch of similar findings in a previous publication (Fiaschi et al. Cancer Res 2012;72:5130-40).

Major Essential Revision:

1 – Figure 1. A ‘glycolytic metabolism’ or ‘aerobic glycolysis’ refers to a high rate of glucose conversion to lactate, and is therefore measured by the ratio of lactate production divided by glucose consumption. Glucose consumption data and ratios are missing in Figure 1 and Figure 4A.

2 – Was there a correlation between MCT1 expression and in vitro lactate uptake in PCa cells? siRNA should be used to demonstrate this.

3 - It is unclear if the MCT4 and HIF-1 responses in WI-38 cells depend on nutrient starvation in CM (whereas in the control condition they have full nutrient supply) or to the production of stimulatory factor(s) by PC3 cells. This is made even more confusing in the experiment showing that the supernatant of CM-incubated WI-38 cells promotes tumor cell proliferation, as this second experiment is stated to have been done in the presence of low glucose (P16 line 359 and P27 line 664: 0.6 g/L glucose). So WI-38 cells incubated in the absence of glucose, glutamine and/or other nutrients start to produce lactate? Lisanti further reported that the ability of fibroblasts to release lactate depend on their stimulation by tumor cell-derived ROS, which is apparently not the case in your experiment. Does an antioxidant added to CM prevent the glycolytic switch of CM-treated WI-38 cells?

4 – Figure 5. MCT1 has also been reported to be expressed in cell mitochondria (see several recent reviews by Halestrap). To attribute the in vivo growth-promoting effect to the lactate released by fibroblasts would further require blocking lactate release by the latter in vivo (siMCT4). Also, MCTs conveys other monocarboxylates than lactate: does lactate supplied in the
absence of (conditioned) fibroblasts promote LNCaP tumor growth in vivo? (see protocol used in De Saedeleer CJ et al., PLoS ONE 2012;7:e46571).

Minor Essential Revisions

1 – The title does not reflect the observations. No ‘symbiotic’ (win-win) relationship was described experimentally, just a metabolic relationship.

2 – The introduction should quote and detail the paper of Sonveaux et al. (JCI 2008, your reference #30) reporting for the first time a metabolic symbiosis in cancer, as well as the several reports of Michael Lisanti’s group regarding the ‘enslavement’ of fibroblasts by oxidative tumor cells.

3 – Was lactate used as a sodium salt in in vitro experiments? What is the possible molecular explanation for its toxicity in the presence of high glucose?

4 – In figure 3B, MCT4 upregulation by the PC3-conditioned medium is not evident. Quantification is needed and/or all blots should be shown in supplementary figures.

5 – There are many grammatical errors throughout the manuscript.

Discretionary Revisions:

1– There can be no speculative assertions in the results section. (P14 line 320) That heterogeneous MCT4 expression in cultured LNCaP tumor cells could be the result of local hypoxia is speculative.

2 – Data with metformin that suppressed the growth-promoting effect of lactate on PC3 and LNCaP cells should be shown, as lactate in addition to its metabolic use also has signaling properties that could promote tumor cell growth (see De Saedeleer CJ et al., PLoS ONE 2012;7:e46571 and Dhup S et al., Curr Pharm Des 2012;18:1319-30).

3 – Figure 6. Based on Végran et al. Cancer Res 2011;71:2550-60 (see also correspondence in Cancer Res 2012;72(7)), is it possible to state from the human patient pictures that MCT4 is also expressed in tumor blood vessels?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I have received financial support from organizations involved in the development
of new therapeutics targeting tumor cell metabolism. In this context, together with other Inventors, I have filed a patent application related to these new therapeutics.