Lactate-Induced IL-8 Pathway in Endothelial Cells—Response

Frédérique Végran, Emmanuel Seront, Pierre Sonveaux, and Olivier Feron

In a recent publication (1), we have documented the capacity of lactate to enter endothelial cells via the monocarboxylate transporter MCT1 and to signal by stimulating an autocrine proangiogenic NF-κB/interleukin-8 (IL-8) pathway. In this mechanistic study, the reason why we used human umbilical vein endothelial cells (HUVEC) in our in vivo experiments with human xenografts was that there is no clear-cut IL-8 homolog in mouse. We therefore preferred working with endothelial cells of human nature (i.e., HUVEC) that we injected together with human tumor cells in Matrigel plugs to study the lactate-driven interplay between these cells.

We read with interest the letter of Pinheiro and colleagues about their failure to detect significant MCT1 expression in human tumor-associated endothelial cells. First, we would like to stress that in HUVECs and other tested endothelial cells, the metabolic use of lactate could only be marginally documented contrary to what we and others have reported in tumor cells (2, 3) and oxidative muscle fibres or brain cells (4). One central message of our article (1) was that lactate may however still represent a signaling molecule in these largely glycolytic cells and thus, this also infers that MCT1 does not need to be highly expressed in endothelial cells to support the observed proangiogenic effects. A faint expression of MCT1 can notably be observed in some endothelial structures from the work of Pinheiro and colleagues. Second, a limited sensitivity of their antibody may also account for the lack of clear MCT1 expression in endothelial cells of tumor blood vessels (vs. strong staining of clustered tumor cells). Furthermore, discrimination between the plasma membrane and cytosolic locations of MCT1 in sparse tumor-associated endothelial cells is compli-

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Figure 1. Representative MCT1 immunostaining in human bladder cancer where significant vascular staining is observed using peroxidase (A and B) or DyLight 488–conjugated (green fluorescent; C, D) secondary antibodies. D, vascular costaining using CD31 antibodies and Alexa 568–conjugated (red fluorescent) secondary antibody. Arrowheads indicate MCT1 expression in red blood cells trapped inside blood vessels.
successfully verified using tumor cells and endothelial cells transfected or not with short hairpin RNA or siRNA directed against MCT1. We used this antibody on fresh sections of paraffin-embedded human bladder cancers available in our laboratory at the time of this letter. Figure 1 shows MCT1 staining of blood vessels in these human tumors using peroxidase (Fig. 1A and B) or DyLight 488–conjugated (Fig. 1C, green staining) secondary antibodies. In another experiments, we costained tumor sections with an anti-CD31 antibody (red staining, Alexa 568 secondary antibody) and could thereby validate the vascular nature of the MCT1 staining (Fig. 1D). Interestingly, MCT1-expressing red blood cells could also be observed within some blood vessels. Although a more thorough study would be necessary to determine possible differences of endothelial MCT1 staining according to the tumor stage and angiogenic status of the tumors, we believe that this piece of evidence indisputably supports the expression of MCT1 in blood vessels of human tumors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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