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INVITED COMMENTARY

Intracellular lactate flux: a new regulator of the allogenic immune response*

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During the past decade, long-term graft- and patient-survival rates have not improved significantly, despite the reduced incidence of acute rejections. This is partly because of the toxicities of immunosuppressive drugs and patients' deaths from cardiovascular events, which can be associated with the cardiovascular risk factors related to immunosuppressive drugs [1]. Among these drugs, calcineurin inhibitors (CNIs) are strongly associated with renal toxicity and the development of cardiovascular risk factors, including hypertension, diabetes, and dyslipidemia; thus, there is a need for a toxicity-free CNI-free regimen [2]. However, very few molecules have emerged that can totally or partially replace CNIs. Most evaluated molecules have targeted or regulate T-cell activation, especially signal 1 or 2 activation of T cells, as well as the third signal involved in the expansion of activated T cells.

It has recently been shown that other mechanisms are implicated in the development or differentiation of T lymphocytes. These modify nutrients or precursors that are not only involved in the expansion phase of activated lymphocytes, such as inositol monophosphate dehydrogenase, but are also able to modulate T-cell activation or to switch their phenotype from activated T cells to regulatory cells. For example, tryptophan metabolism induced by IDO-expressing dendritic cells is associated with inducing regulator T cells [3]. Adenosine metabolism, induced by the CD73 ecto-enzyme, also participates in the development of regulatory cells [4]. However, the mechanisms that make these metabolites effective are still not completely understood, although they do affect the phenotype of T cells, which leads to the development of regulatory T cells. For adenosine, the binding of the small molecule induces some signaling in the cell through the A2A adenosine receptor [5]. Their role in organ transplantation has yet to be demonstrated, but this finding opens up a new area of transplantation research.

Other compounds may also be of interest. Påhlman *et al.* [6] demonstrated that inhibition of lactate transport in lymphocytes favored tolerance in rats. The lactate transporters are a group of proton-linked monocarboxylate transporters of at least eight members but only four have been functionally characterized (MCT-1, MCT-2, MCT-3, MCT-4) that have been cloned independently by two research groups [7]. MCT-1 is wildly expressed in vivo in several tissues such as kidney, gut, hematopoietic cells, brain, gut, muscles, and lymphocytes [8,9]. MCT-1 can favor the release of lactate accumulated in cells following glycolysis. Without MCT-1, lactates and pyruvates will be accumulated in the cytoplasm of cells and the normal aerobic glycolysis can't be processed because of the intracellular accumulation of lactate and protons. Overexpression of MCT-1 in Chinese hamster ovary cells or in chronically stimulated skeletal muscles increases

lactate exflux and maintain both glycolysis and function of cells indicating that MCT-1 is a critical lactate-transport protein across membranes [10,11]. Activity patterns may also be important for establishing the capacity of lactate transport in muscle. When muscle activity is reduced by hind-limb unweighting or denervation, lactate transport is decreased. On the other hand, after chronic muscle stimulation and exercise training, lactate transport is increased. In endothelial cells. MCT-1 promotes angiogenesis by increasing the lactate activation of HIF1a, which is implicated in the secretion of proangiogenic factors (vascular endothelial growth factor and fibroblast growth factor) and also increases cell survival by activating the NFκB pathway [12]. MCT-1, but not MCT-2, MCT-3, or MCT-4, is significantly expressed in activated lymphoid cells but not in resting cells probably because activation of T cells required an important production of energy for their multiplication and activation. MCT-1 expression at the plasma membrane is stabilized by CD147 [13]. Interestingly, Murray *et al.* have identified several compounds that inhibit MCT-1 with a high affinity, but not other members of this family [14]. These compounds are able to inhibit lymphocyte proliferation which correlates with lactate accumulation but do not induce cell death. They demonstrated that two inhibitors are efficient at preventing graft rejection. However, they are also associated with side effects, such as testis toxicity, probably because of the expression of MCT-related molecules or MCT-1 in testis cells. By introducing several modifications to the core of the pyrollopyrimidine of their initial compounds, researchers have now selected molecules that have a similar ability to impair lymphocytic activation and induce graft tolerance in rat heart transplant models in both combinations of low or high responders. The effect was maintained after the withdrawal of the molecule suggesting that some of this compound induce tolerance. Tis tested in a situation of second transplantation without any immunosuppressive treatment. The mechanism by which these compounds may induce tolerance in rodents is still unknown.

Surprisingly, these molecules have a slightly lower affinity to MCT-1 but are less lipophilic and have a better bioavailability than the initial compound. After a short period of administration in a small-animal model, a good safety profile has been observed, though extended analyses are needed to demonstrate the absence of other side effects in big animals and humans. In addition, since MCT1 is expressed in the brush border of tubular epithelial cells, and because MCT1 is overexpressed in hypoxic conditions, particular attention has to be done in other transplantation such kidney transplantation in which ischemia-reperfusion may stimulate the expression of MCT-1 and for which inhibition of MCT-1 may lead to important lesion because these cells need a lot of energy for their different functions.

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