Journal Club

BRINGING WARBURG TO LYMPHOCYTES

Standing in a coffee line at a Keystone Symposia meeting (*circa* 2000), I overheard two postdocs discussing a talk just given by Craig Thompson: "Who cares about glucose?" remarked one; "Metabolism is boring," declared the other. A few others around them grinned in agreement. What Craig talked about at that meeting included a study that was later published in *Immunity* (Frauwirth *et al.*, 2002), which in many ways laid a foundation for the field of cellular immunometabolism as we know it today.

For decades, our knowledge of the core metabolic pathways was based on classical studies of skeletal muscle, heart and liver — tissues that are made up mostly from post-mitotic cells. A big revelation that came from studies of tumours, and later lymphocytes, was that metabolism in proliferating cells follows a different set of rules. Another surprising discovery was that basic metabolic pathways, such as glycolysis and oxidative phosphorylation, can be regulated by signalling pathways activated by growth factors and cytokines (reviewed by Krauss *et al.*, 2001).

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Thus, earlier studies from the Thompson group had shown that glucose uptake in mammalian cells depends on growth factors. The 2002 study by Frauwirth *et al.* showed that glycolysis in activated T cells is regulated by T cell receptor and CD28 signalling, in part through the phosphoinositide 3-kinase-dependent expression of glucose transporter 1. Glucose uptake was necessary for T cell proliferation and could be inhibited by ligation of the co-inhibitory receptor cytotoxic T lymphocyte antigen 4. Most importantly, the paper showed that proliferating T cells do not use most of their glucose for maximal ATP production through oxidative phosphorylation: the last glycolytic product, pyruvate, was converted into lactate in the cytosol and dumped by T cells into their environment, rather than entering the tricarboxylic acid cycle to feed into mitochondrial oxidative phosphorylation. In other words, Frauwirth *et al.* discovered that activated T cells use Warburg metabolism, which was previously thought to be unique to cancer cells. This finding was subsequently generalized to all proliferating cells (reviewed by Vander Heiden *et al.*, 2009) and led to the realization that different cellular activities require distinct metabolic support programmes.

The field of cellular immunometabolism has made big strides over the past decade, becoming one of the hottest areas of research in immunology. Like many major scientific paradigms, it had humble beginnings, which many of us could not appreciate waiting in that coffee line 15 years ago.

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ORIGINAL RESEARCH PAPER Frauwirth, K. A. *et al.* The CD28 signaling pathway regulates glucose metabolism. *Immunity* **16**, 769–777 (2002)
FURTHER READING Krauss, S., Brand, M. D. & Buttgereit, F. Signaling takes a breath – new quantitative perspectives on bioenergetics and signal transduction. *Immunity* **15**, 497–502 (2001) | Vander Heiden, M. G., Cantley, L. C. & Thompson, C. B. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* **324**, 1029–1033 (2009)