mankind' [10]. Therefore, many studies on carbohydrates and vitamins were awarded at the early years of the prize, when society had relatively insufficient knowledge and availability of food and medicine. The CVD epidemic due to a drastic lifestyle change refocused research efforts to target cholesterols as an anti-CVD strategy. The post-genomic era has also seen several advances in the research of proteins, including metabolic enzymes and membrane channels [4]. While the prize-winning studies were performed in diverse animal models, we now know that the biochemistry of metabolism has been highly conserved across species during evolution [11].

Metabolism has evolved a complex network of signaling pathways that is rewired to meet considerably different metabolic requirements of unhealthy cells to normal cells [12,13]. Targeting the metabolic dependencies of abnormal cells will be a promising therapy in clinical settings [14]. Moreover, the discovery of novel metabolites, along with technological and conceptual advances in metabolomics and isotope tracing, will illuminate the mechanisms underlying metabolic diseases [15]. Although metabolic research has not been awarded the prize in the past 15 years, I believe that in the future, the Nobel Prize will reward scientists in the field of metabolism who address a true unmet medical need for new treatments for serious metabolic diseases, such as diabetes and inborn errors of metabolism.

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Spotlight

Firing Up Glycolysis: BCG Vaccination Effects on Type 1 Diabetes Mellitus

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In addition to the impact of Bacillus Calmette–Guerin (BCG) vaccination on antimicrobial host defence, a novel study reveals beneficial effects on glycaemic control in patients with long-standing type 1 diabetes mellitus (T1DM). These effects are ascribed to an accelerated glucose consumption in immune cells due to increased glycolysis and reduced oxidative phosphorylation.

BCG is one of the oldest vaccines in use, and still the only one available for the prevention of TB. Interestingly, however, aside from the effect on its target infection, a growing body of evidence also points to heterologous protective 'nonspecific effects' (NSE) of BCG against other infections [1]. Broad immunological effects have been proposed to mediate the nonspecific protective effects of BCG, including activation of a heterologous T cell response [2] and/or epigenetic and functional reprogramming of innate immune cells, such as monocytes and macrophages, a process called 'trained immunity' [3]. Interestingly, induction of trained immunity is accompanied by robust changes in the cellular metabolism of myeloid cells, including a strong increase in glycolysis [4].

In addition to the impact of BCG vaccination on antimicrobial host defences, an increasing number of studies also report effects on allergic and autoimmune disease. An interesting novel study published in June 2018 in *NPJ Vaccines* by Kühtreiber *et al*. adds to this body of evidence by revealing potent effects of BCG vaccination on glycaemic control of patients with T1DM and an average disease duration of 19 years [5]. The authors undertook the difficult but important task of performing a prospective long-term trial assessing the effects of BCG vaccination on the regulation of glucose metabolism. Although no improvements in diabetes-associated parameters were observed directly after vaccination with BCG, a robust reduction in HbA_{1c} levels of almost 10% after 3 years and up to 18% 4 years after receiving the BCG vaccine was reported. No effects were observed on β cell regeneration

and endogenous insulin production, which was probably not unexpected, given that the autoimmune process usually destroys most β cells during the first years following a diagnosis of T1DM [6]. In addition, no effects were seen on systemic insulin sensitivity levels. Instead, using various readouts from isolated peripheral blood lymphocytes, an increase in glycolysis with a reduction of oxidative phosphorylation accelerated glucose utilisation, a process proposed to contribute to a reduction in systemic plasma glucose levels. The resulting improvements in HbA_{1c} levels were persistent, with lower levels reported up to 8 years after the initial BCG vaccination.

BCG vaccination as a potential therapeutic strategy against diabetes has been tested previously. During the early 1990s, several studies reported the protective effects of BCG vaccination in the non-obese diabetic (NOD) animal model, which develops diabetes as a result of insulitis due to leukocyte infiltration of pancreatic islets [7,8]. A single intravenous injection of live BCG led to suppression of insulitis and prevented the development of diabetes [7]. Follow-up experiments identified BCG-induced prevention of the autoimmune response due to the generation of suppressor macrophages, subsequently blocking β cell loss [8]. In contrast to these earlier studies, which reported the beneficial effects of BCG vaccination on the prevention of diabetes, the current study reported the efficacy of BCG vaccination in patients with long-standing T1DM, with a potential mechanism of action beyond the destruction of β cell function. Therefore, it is likely that different mechanisms of action exist depending on the timing of BCG vaccination. During the initial phase of the disease the effects of BCG primarily limit β cell destruction and years after the onset of disease BCG vaccination may act mainly through shifts in cellular metabolism to reduce HbA_{1c} levels. However, not all studies have reported beneficial effects: BCG vaccination in children at the time of onset of T1DM did not reduce in HbA_{1c} levels during 2 years of follow-up [9]. Nevertheless, protective effects of BCG vaccination have also been reported in other autoimmune diseases, such as multiple sclerosis [10].

The observations reported by Kühtreiber *et al*. open new avenues for the development of therapeutic approaches for patients with T1DM. Moreover, if the reprogramming of cellular metabolism and stimulation of glycolysis are indeed the main mechanisms through which BCG vaccination exerts its effects on glycaemic control, one may also envision beneficial effects in T2DM. Indeed, redirecting glucose metabolism away from oxidative phosphorylation towards the energetically less efficient glycolytic route is also the mechanism of action of metformin [11], one of the most effective and commonly used drugs for T2DM. However, this hypothesis needs to be supported by additional studies in humans to strengthen the clinical observations reported by Kühtreiber and colleagues, as well as to investigate in more detail the mechanisms to explain this phenomenon.

In line with this, one of the most important consequences of this study is probably the need for further research in this area. The first challenge will be to validate these observations in a larger independent study, and to assess whether these effects would benefit only T1DM or may also be beneficial for patients with T2DM. Second, these studies should elucidate pathophysiological questions arising from the study by Kühtreiber *et al*., such as why the effects on HbA_{1c} were observed only 3 years after the initial BCG vaccination, and whether there are any potential impacts of BCG vaccination on tissues other than immune cells. Third, and crucial for the development of a therapeutic strategy, more studies need to be done to decipher the molecular mechanisms mediating these effects of BCG. While the epigenetic reprogramming of regulatory T cells is an intriguing observation made by the authors, future studies should assess whether similar processes take place in cells and tissues expected to have a higher impact on glucose homeostasis, such as hepatocytes, adipose, and muscle cells. Using hyperinsulinaemia euglycemic clamps, one should be able to reveal the potential effects of BCG on insulin-mediated glucose uptake in muscle and adipose tissue. Muscles represent the preferred deposition site of diet-ingested glucose [12] and account for ~60–70% of whole-body insulin-mediated glucose uptake [13]. While direct glucose uptake into the liver is not insulin dependent, 30% of whole-body insulin-mediated glucose disposal is dependent on the liver through the insulin-dependent regulation of key metabolic processes [13]. Thus, it is reasonable to consider that effects of BCG beyond glucose utilization in immune cells are needed to be able to obtain an 18% reduction in HbA_{1c} levels.

In conclusion, the study by Kühtreiber and colleagues [5] opens the door towards new strategies for the treatment of diabetes by using BCG vaccination, with the shift in cellular metabolism towards glycolysis as an important mediator. This study should now be followed up by larger clinical trials, as well as by mechanistic studies to decipher the pathways responsible for the effects; only then will the promise of BCG vaccination as an immunomodulatory agent be fulfilled.

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