Trained immunity: A key player of “metabolic memory” in diabetes

In the 2000s, researchers surprisingly observed that the beneficial effects of intensively controlled blood glucose levels at the early phase of diabetes on diabetic complications persisted for the subsequent long term. These effects continued even after post-clinical trials, when the blood glucose levels did not differ between the intensive and conventional therapy groups. The effect called “metabolic memory” (alternatively “legacy effect”) in patients with both type 1 and type 2 diabetes is now widely accepted, encouraging diabetologists to intensively treat patients in the early diabetes phase. However, the mechanisms underlying “metabolic memory” are not well understood.

Edgar et al.1 showed that hyperglycemia-induced “trained immunity” in hematopoietic stem cells (HSCs) and macrophages directly progresses to atherosclerosis. Bone marrow-derived macrophages (BMDMs) from diabetic mice which were grown in the normoglycemic condition persisted the pro-inflammatory changes, increased adhesion to the endothelium, and enhanced modified low-density lipoprotein uptake and foam cell formation. Epigenetic reprogramming at the level of histone H3 methylation has been proposed as the molecular mechanisms underlying “metabolic memory.” These observations confirm the persistence of trained innate immunity (Figure 1).

The research group further implicated transcription factors, purine-rich box 1 (PU.1), CCCTC-binding factor (CTCF), and notably, transcription factor Runx-related transcription factor 1 (RUNX1), as mediators of trained immunity by the open chromatin analyses. Pharmacological RUNX1-specific inhibitor, Ro5-3355, inhibited the high glucose-induced trained phenotype. In monocytes and macrophages, RUNX1 cooperates with PU.1 to regulate macrophage colony-stimulating factor receptor. RUNX1 is required for the generation and maintenance of HSCs, and the differentiation. Furthermore, in patients with type 2 diabetes, atherosclerotic plaque macrophages and peripheral leukocytes were enriched for RUNX1 targets. These results suggest the pivotal role of RUNX1 for trained immunity and atherosclerosis.

Cellular metabolism is a critical media-tor of trained immunity-dependent epigenetic reprogramming of innate immune cells and their stem cells. Intracellular cascades that lead to the upregulation of different metabolic pathways, such as glycolysis, tricarboxylic acid cycle, and fatty acid metabolism trigger trained immunity. In this study, they observed that high glucose shifted to a glycolytic phenotype in primary human monocytes and mouse BMDMs, which promoted pro-inflammatory M1-associated gene expression and suppressed M2-associated gene expression. Decrease in glycolysis by dichloroacetate (a mitochondrial pyruvate dehydrogenase kinase inhibitor) restored these pro-inflammatory changes. Thus, high glucose induced cellular pro-inflammatory characteristics by altering glycolysis. BMDMs and HSCs of diabetic mice retained these pro-inflammatory characteristics. These observations confirm the persistence of trained innate immunity through aerobic glycolysis. The induction of aerobic glycolysis through the protein kinase B–mechanistic target of rapamycin (mTOR)–hypoxia inducible factor-1α (HIF-1α) pathway formed the metabolic basis of the trained immunity. β-Glucan–trained monocytes showed elevated aerobic glycolysis with a reduced vasal respiration rate, increased glucose consumption, lactate production, and higher intracellular ration of nicotinamide adenine dinucleotide (NAD+) to its reduced form NADH. A Western diet has also been reported to induce trained immunity by epigenetic reprogramming in bone marrow progenitor cells. Atherosclerosis-prone Ldlr−/− mice kept on a Western-type diet for 4 weeks showed profound pro-inflammatory transcriptional and epigenetic reprogramming in circulating monocytes and bone marrow myeloid progenitor cells.

The observations made by Edgar et al.1 suggest that hyperglycemia–induced trained immunity is a possible key player of “metabolic memory” in
patients with diabetes. Increased aerobic glycolysis plays an important role in inducing trained immunity in diabetes. As described above, β-glucan and a Western diet are other inducers of trained immunity. Importantly, increased glycolysis is a characteristic of β-glucan-induced trained immunity. Additionally, inhibition of the Akt-mTOR-HIF-1α pathway, which mediates glycolysis, abrogates β-glucan-induced trained immunity. Enhance cholesterol synthesis is also critical for β-glucan-induced trained immunity. Fluvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, inhibits trained immunity. Although diabetes alone affects chromatin accessibility, the effects of interleukin-1β (IL-1β) in cells primed by diabetes were even more pronounced, suggesting that there are additional stimuli that induce trained immunity. The involvement of the IL-1β pathway in trained immunity is consistent with other inducers. The inhibition of IL-1β inhibited β-glucan-induced trained immunity.

Regulating trained immunity can be novel therapeutic strategies for different diseases. Depending on conditions, it could be beneficial to induce trained immunity or to reduce trained immunity. The bacillus Calmette-Guérin (BCG) vaccine, which is known to induce trained immunity, reduces neonatal mortality in low-weight African children at birth. Furthermore, BCG not only protects patients from secondary infections with Candida albicans, Schistosoma mansoni and Mycobacterium tuberculosis, but also prevents malignancies, such as bladder cancer, melanoma, leukemia and lymphoma through the induction of trained immunity in monocytes and macrophages. The results of Edgar et al. showed that the suppression of trained immunity can reduce atherosclerosis in patients with diabetes. Evidence suggests that trained immunity can be reduced in patients with diabetes by maintaining good glycemic control and avoiding a second stimulus, such as chronic inflammation or a Western diet. This can subsequently prevent atherosclerosis. Furthermore, decreasing trained immunity by several candidates, such as the inhibition of Akt/mTOR/HIF-1α, cholesterol synthesis pathways or RUNX1, might be a novel therapeutic approach to regulate trained immunity and prevent atherosclerosis in patients with diabetes.

There are several questions about trained immunity in diabetes. Trained immunity is generally reversible and lasts for a shorter duration than adaptive immunological memory. However, a recent study presented the transgenerational effects of trained immunity. We need to better understand how long diabetes-induced trained immunity lasts. Additionally, it is not clear whether good glycemic control overrides high glucose-induced trained immunity or how long it takes to override trained immunity. However, emerging evidence suggests that trained immunity can partially explain “metabolic memory” in patients with diabetes that might subsequently be a new therapeutic target.

Figure 1 | Proposed mechanism of the involvement of trained immunity in metabolic memory under the diabetic condition. High glucose-induced trained immunity is a possible key player of “metabolic memory” in patients with diabetes. Increased aerobic glycolysis plays an important role in inducing trained immunity in diabetes. Pro-inflammatory priming more increased trained immunity. β-Glucan, Western diet and enhanced cholesterol synthesis are other inducers of trained immunity. Edgar et al. showed that trained immunized bone marrow-derived macrophages (BMDM) in diabetic mice promoted atherosclerosis. HSC, hematopoietic stem cell.
DISCLOSURE
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