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Parathyroid hormone reprograms osteoblast metabolism

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A seminal event in the evolution of life on Earth was the emergence of the eukaryotes, which acquired compartmentalized intracellular structures that enabled their metabolic processes to produce energy with great efficiency and flexibility. When the tricarboxylic acid (TCA) cycle and oxidative phosphorylation are fully engaged and pyruvate generated in glycolysis is shunted to the mitochondria for oxidation to CO_2, a single molecule of glucose can be utilized to fuel the synthesis of 36 molecules of ATP for use in cellular processes. In some instances, however, cells forego this energetic-haul and switch their metabolic program to a more rapid but less efficient mode of ATP production known as aerobic glycolysis or the Warburg effect. In this process, one molecule of glucose is used to generate 2 ATP in glycolysis and the resulting pyruvate is converted to lactate or shuttled to other biosynthetic pathways. A high rate of glucose consumption, which is used clinically to identify rapidly dividing malignant cells, is then required to maintain cellular ATP levels[1, 2].

Studies conducted more than 50 years ago demonstrated that bone cells present in metaphyseal bone slices and then isolated calvarial osteoblast cultures are highly glycolytic using glucose at a rate nearly equivalent to hepatocytes but at much lower rates of oxygen consumption[3–5]. It was proposed that 80% of the glucose consumed by osteoblasts was converted to lactate and this together with citrate, another intermediate in the metabolism of glucose, would facilitate the process of bone turnover and also contribute to the overall solubility of mineral ions in the extracellular milieu[3, 6–8]. This intriguing idea linking osteoblast bioenergetics and bone function was largely forgotten by the field despite more recent work suggesting that products of incomplete glucose metabolism impact bone biomineralization[9, 10].

Over the last decade and a half, a renewed interest in the metabolic requirements of bone cells has been motivated by studies from two related perspectives. First, from a cellular biology perspective, the energetic costs of cellular proliferation and differentiation have

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gained greater appreciation. In particular, protein synthesis, a major function of osteoblasts as they prepare and deposit an abundant extracellular matrix, is among the most energetically costly cellular process[11, 12]. The osteoblast's ability to acquire the macromolecules necessary for these biosynthetic pathways are directly related to its ability to form bone[13]. Second, from an integrative physiology perspective, it was recognized that the functions of important metabolic hormones are linked to bone homeostasis. In 2000, Ducy et al[14], reported that leptin altered bone mass through a hypothalamic relay and later work led to the recognition that leptin's central effect on the osteoblast also contributes to the hormone's influence on insulin secretion[15]. Additionally, insulin signaling in the osteoblast was found to be required for normal glycemic control in mice, as insulin induces the production and bioavailability of osteocalcin, which stimulates pancreatic insulin secretion in a feed-forward endocrine loop[16–18]. Its reasonable to predict that such interactions evolved due to the energetic costs of bone formation[19].

To better understand the bioenergetic requirements of osteoblasts, determine how cellular metabolism influence osteoblast differentiation and function, and more clearly define the role of bone in whole-body metabolism, investigators have refocused their attention on the cellular mechanisms for energy acquisition and consumption. Osteoblasts express transporters necessary for the cellular acquisition of glucose and genetic ablation of specific glucose transporters impedes osteoblast and bone development in mouse models while also impairing normal glucose metabolism[20, 21]. Further, reexaminations of osteoblast bioenergetics demonstrated that in actively proliferating cells, ATP is produced by glycolysis. As osteoblasts mature oxidative phosphorylation, in conjunction with the accumulation of abundant high-transmembrane-potential mitochondria, assumes a more central role; once mineralization is complete, osteoblasts revert back to glycolytic pathways[22, 23]. These findings indicate that osteoblasts adjust their bioenergetic machinery in association with altered energy requirements during their life span. Recent works from the Long laboratory have demonstrated that osteoblast metabolism is also coupled to the engagement of key osteoblast developmental signaling pathways[24]. For example, signals downstream of WNT-LRP5 converge on mTORC2 and AKT pathways to facilitate glycolysis during early osteoblast differentiation[25]. In addition, hypoxia and Hif-1 generated signals induce glycolysis during osteoblast differentiation by enhancing the expression of glycolytic enzymes, including pyruvate dehydrogenase kinase 1, lactate dehydrogenase A, and hexokinase II[26].

In this issue of the *JBMR*, Esen and colleagues[27] continue this productive line of investigation by studying the influence of anabolic parathyroid hormone treatment (PTH) stimulation on osteoblast bioenergetics. Teriparatide, a peptide corresponding to amino acids 1–34 of human parathyroid hormone (PTH), has been used in the clinic to increase bone mass and reduce fracture risk for more than a decade[28], but the molecular mechanisms that lead to an increase in bone formation are still poorly understood. Building on historical data[3, 29, 30], this new work demonstrates that PTH exposure increases both the rate of glucose uptake and oxygen consumption in osteoblasts. Surprisingly, however, entry of glycolytic metabolites into the TCA cycle is suppressed. Instead, PTH induced the production of lactate, presumably via an increase in the abundance of Ldha, as genetic knockdown of this enzyme abolished the hormone's effect on glucose consumption. To

demonstrate the importance of this phenomenon to PTH-induced anabolism in vivo, mice were administered dichloroacetate, an antagonist of pyruvate dehydrogenase kinase that represses lactate formation by favoring the entry of pyruvate into the TCA cycle. Consistent with Esen's in vitro results, dichloroacetate dramatically reduced the ability of PTH to increase bone volume.

Intriguingly, the impact of PTH on glucose utilization by the osteoblast appears to occur via an indirect mechanism. While increased glucose consumption was dependent on the generation of cyclic AMP, one of the earliest responses to PTH, Esen reasoned that the delayed metabolic response (observed 6 to 48 hours after stimulation) was due to the involvement of a second factor. Consistent with this idea, Igf1, which is induced by PTH and is required for its anabolic actions in bone[31–33], was sufficient to and required for PTH to reprogram osteoblastic metabolism. Mechanistically, the engagement of Igf1 signaling triggered the activation of the mTORC2 complex, which the Long laboratory previously reported to be involved in skeletal growth and to induce aerobic glycolysis[25, 34]. Activation of Wnt signaling, also required for PTH-induced anabolism[35, 36], appears not to be involved.

The finding that aerobic glycolysis is necessary for the full bone-anabolic effects of PTH prompts important new questions about the nature of osteoblast metabolism. First, PTH's ability to suppress the entry and progress of glycolytic metabolites through the TCA cycle suggests that osteoblasts do not obtain the full energetic benefit of the glucose they consume. Further, if a large portion of the pyruvate generated by glycolysis is converted to and secreted as lactate, glucose-derived carbon cannot be used in biosynthetic pathways. It has been suggest that the pyruvate and lactate might serve to scavenge and offer protection against cytotoxic oxidants[37], but early radiotracer studies demonstrated carbon molecules from ^{14}C-labelled glucose could be found in bone collagen and the amino acids necessary for it to be produced[38]. In this context, determining what portion of consumed glucose ultimately ends up as lactate and whether PTH instructs the osteoblast to shuttle glucose metabolites towards biosynthetic pathways, such as amino acid synthesis, would be of great value.

A second, equally important question pertains to the effects of PTH on other metabolic substrates. As indicated above, Esen demonstrates that PTH suppresses the oxidation of glucose in the TCA cycle, while concomitantly inducing a seemingly paradoxical increase in the oxygen consumption rate. The most plausible explanation for these data is that PTH favors the oxidation of another substrate to generate ATP. Recent studies from the Long laboratory[39] and our own[40] have identified glutamine and fatty acids, respectively, as potential energy sources utilized by osteoblasts. Fatty acid oxidation, in particular, is sensitive to cyclic AMP/PKA signaling[41, 42], which is activated by PTH, and in our hands, pharmacological inhibition of β-oxidation impairs osteoblast differentiation in vitro[40]. Whether glutamine metabolism is responsive to the activation of similar signaling pathways is less clear but deserving of further study.

Finally, Esen's work begs the question of how the utilization of glucose by osteoblasts in response to PTH contributes to the overall glycemic control of an organism. Recent studies

suggest that the osteoblast directly contribute to the clearance of circulating glucose in mouse models[20, 21], while bone turnover, an established response to PTH, may contribute to the bio-activation of endocrine osteocalcin[17]. Moreover, a recent small randomized controlled trial suggested that intermittent PTH (1–84) administration reduced fasting plasma glucose levels in postmenopausal osteoporotic non-diabetic women[43]. However, this effect may have been mediated by alterations in serum osteocalcin levels rather than PTH-induced glucose uptake, as a separate study in postmenopausal women with primary hyperparathyroidism indicated that fasting plasma glucose was related to bone mineral density but not the levels of PTH[44]. Undertaking such studies would likely require the development of a genetic model in which glucose acquisition is eliminated at multiple points along the osteoblast linage.

In summary, the study by Esen et al.[27] provides new insights into PTH's mode of action by expanding its functional role to cellular biogenetics. Conceptually, the study is a prime example of the state of the field of bone science, which is increasingly recognizing the importance of understanding the integrative biological role of the skeleton and the importance of metabolic programming in cellular function. Continuation of this line of experimentation will certainly expand our understanding of skeletal physiology and may ultimately aid in the management of metabolic disease on multiple levels.

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