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Reappraisal of the metabolic models in diabetes-A review of the origin of the present bioenergetic models, ignored reports and biases by in vitro models.

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Alcohol production, muscle contraction, diabetes and cancers are some of the ancient curiosities of thinkers from prehistoric times. Present models of intermediary metabolism were developed in the first half of 20th century through in vitro studies based on thermodynamic equilibria of individual enzymes modulating the metabolite fluxes. The putative assumptions of the pathways introduced a bias towards bioenergetic theories dominated in designing the present metabolic pathways. Present models of glycolysis were formulated based on Top-down models, suggesting the breakdown of glucose to hexose diphosphate, which is split to pglyceraldehyde-3phosphate and in a series of reverse fluxes converges on phosphoenolpyruvate (PEP). Pyruvate kinase transfers phosphate to ATP and produces pyruvate. The models depict respiration oxidizes nutrients in mitochondria to produce energy (ATP). Physiologically active cells depend on cytoplasmic pyruvate kinase (PK) for ATP and reduce pyruvate to lactate. In this talk I present a review of three centuries of literature on respiratory physiology, muscle metabolism, propose that oxidative stress induces sestrins, which inhibit mTORC1, activate AMPK, autophagy, unfolded protein response, asparagine synthesis, and lipolysis. Stressed-out cells transform to pluripotent stem cells (PSCs), enter hypoxic microenvironment. TGFB1 deposits collagen but inhibits 4F2HC. PSCs secrete metallo proteases (MMPs), hydrolyze collagen. cAMP induced phosphate uptake hydrolyses intracellular glycogen to ribose phosphate. Fructose metabolites inhibit glucose uptake. HIF1 stabilizes fructose1,6-bisphosphate (HDP1; Harden ester) and promotes fermentation. Glycerolipids, and phosphoglycerate kinase1 (PGK1) promote ATP, phosphoribosyl pyrophosphate (PRPP) synthesis. TP53 induced glycolysis and apoptosis regulator (TIGAR) dephosphorylates HDP1 to fructose-6posphate (Fr6P). Glutamine uptake through neutral amino acid transporters drives Fr6P into glycosylation pathway, which activates the uptake of essential amino acids (EAA) and nucleotide synthesis. TP53 induced GLS2, hydrolyses glutamine and promotes glutathione biosynthesis, while synthesis of cytochrome oxidase (SCO2) promotes O2 uptake. Cyanide resistant respiration oxidizes fats, EAA, Coenzyme-Q, ketone bodies in peroxisomes. Arginine metabolism and pyrimidine synthesis promote citrulline synthesis, which inhibits enolase. Phosphoglycerate mutase (PGAM) inhibits PPP and ribose synthesis. Fumarate acts as the terminal electron acceptor in anaerobic metabolism. Lactate synthesis/entry into cells activates thermogenesis, and pyruvate metabolism. Pyruvate metabolism is controlled by three enzymes, pyruvate kinase, pyruvate carboxylation, and pyruvate aminotransferase. Phosphate activated glutamine metabolism controls mitochondrial respiration and cell differentiation. ATP export into microenvironment activates the cross talk between PSCs and myeloid cells regulates angiogenesis, myelination, and cell death/ survival pathways.

Keywords: EMT, microenvironment, phosphate, fructose, HIF1, TIGAR, lactate shuttles, mitochondria, Oxidative regenerative metabolism.

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