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Letter to Editor

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How will a GABA deficiency in endocrine pancreas transform stem cells into tumor cells?

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Catabolic hormones: glucagon epinephrine and cortisol act on their receptors to form nutrients: glucose and ketone bodies. Liver glycogenolysis and neoglucogenesis will take place, while muscle proteolysis provides amino acids; lipid stores will deliver fatty acids that are cut into acetyl-CoA, forming ketone bodies. Enzyme phosphorylation controls the pathway directions for synthesizing these two nutrients. Phosphorylation of enzymes is ruled by "switch board" protein kinases controlled by PKA - Src, activated by cAMP. The latter is formed via glucagon or epinephrine acting on Gs coupled receptors stimulating adenylatecyclase. In striated muscle this effect is cancelled, (to escape from predators). Muscle activity increases cytosolic calcium, which re-establishes glycolysis. A calcium dependent phosphatase (calcineurin) neutralizes an inhibitor of PP1 phosphatase, cancelling the neoglucogenic blockade of pyruvatekinase (PK), and pyruvatedehydrogenase (PDH), restoring oxidative glycolysis. Calcium will also stimulate a phosphodiesterase hydrolyzing cAMP, which puts an end to its inhibitory effect on the synthesis of a strong activator glycolysis: fructose 2-6 bisphosphate. In addition, calcium stimulates the membrane incorporation of glucose transporters. Well, tumor cells do open via calcium and phosphodiesterase, the entry of glucose but the PK and PDH stops by phosphorylation are maintained, as if some other inhibitor of PP1 was still present. Evidently, mitotic cells that respond to anabolic hormones insulin, growth hormone– IGF, must synthesize new membranes. The activation of tyrosine kinase receptors elicits via PKB, the stimulation of "switch board" protein phosphatases reversing the effects of PKA. Beside mitosis and cell survival, tyrosine kinase receptors stimulate a phospholipase producing inositol 3 P (IP3) and diacylglycerol (DAG). IP3 induces the release of cytosolic calcium; like for muscles this activates glycolysis; but here DAG stimulates PKC and the synthesis of a new inhibitor of PP1 (CPI-17), when acetyl-CoA must come from fatty acids degradation rather than from glycolysis. Then, PKC stimulates AMP deaminase, which decreases AMP, this cancels the known inhibition of acetyl-CoA carboxylase by AMP dependent kinase; opening the fatty acid synthesis route. A malonyl-CoA intermediate is formed and will close the fatty acid degradation into acetyl-CoA because it blocks their mitochondrial transporter. It is thus crucial to re-establish the glycolytic source of acetyl-CoA. This is done via a decrease of DAG consumed by the lipogenic route, which ends the PKC-mediated synthesis of the CPI-17 inhibitor of PP1. Well, tumor cells cannot do this, because DAG remains elevated; recall that phorbol carcinogens act as DAG. Presumably, the increase of growth hormone that stimulates adipocyte triglyceride lipase, keeps DAG elevated. Thus, mitotic cells cannot open the glycolytic source of acetyl-CoA when the fatty acid source is turned off by malonyl-CoA, they will then have to rewire differently their metabolism. To pass round the bottle neck, phosphoenolpyruvate gets converted to oxaloacetate, while acetyl-CoA will be re-formed from ketone bodies provided by other tissues that are sensitive to catabolic hormones and resistant to insulin. Then, citrate condensation takes place, but citrate quits the mitochondria feeding via: ATP citrate lyase and acetyl-CoA carboxylase the synthesis of fatty acid and lipids of mitotic cells. The metabolic advantage gained by mitotic cells nourished by differentiated tissues, blocks their own differentiation, opening their way for a carcinogenic transformation.

A single failure of GABA controls in endocrine pancreas explains the process. Suppose that insulin is released and that the associated co-release of GABA gets deficient, auto-receptors on beta cells cannot terminate insulin release, a steady insulin leakage will render differentiated tissues resistant to insulin, while responding to glucagon. The GABA decrease, also fails to inhibit glucagon release while insulin is released, which sends a dual message to new mitotic stem cells that have not been desensitized for insulin. The GABA failure also boosts epinephrine release, which selectively inhibits somatostatin release from delta cell, increasing growth hormone actions and DAG production. The result is metabolic rewiring in mitotic stem cells, geometrically increasing their population in an organ they were committed to repair, which starts the carcinogenic process.

Conflict of interest

The author declares that he has no conflict of interest

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