Abolition of mitochondrial substrate-level phosphorylation by itaconic acid

Macrophages are cells of the immune defence system. When they sense the presence of bacteria, one of their genes -called 'Irg1'- switches on. As a consequence of this, macrophages start to produce and secrete a substance called 'itaconic acid'. Itaconic acid kills bacteria.

Except macrophages, other cells of the human body do not express Irg1 and therefore cannot produce itaconic acid. However, production of itaconic acid in macrophages comes at the expense of 'rewiring' endogenous metabolic pathways in a way that disrupts the normal harnessing of energy from nutrients. For macrophages, this is inconsequential because they will literally sacrifice themselves in the battle against bacteria anyway. But the realization that the switching on of Irg1 interferes with normal metabolism could be useful for two very different applications:

1) Itaconic acid is one the most promising building blocks in the industrial manufacture of chemicals. Currently, itaconic acid is produced commercially by fungi possessing the Irg1 gene; however, to this date, its production is too expensive to compete with alternative building blocks. Understanding the effects that itaconic acid may have in normal metabolism could lead to devising appropriate modifications to the fungal metabolism so that it can produce it more efficiently, i.e. cheaper.

2) In cells, the vast majority of energy present in nutrients is harnessed through pathways requiring oxygen (coming from the air that we breathe) which operate in the interior of organelles, termed mitochondria; in addition to that, within mitochondria there are also other pathways that can unleash energy from nutrients that do not require the presence of oxygen.

Production of itaconic acid demands the specific disruption of metabolism that yields energy from nutrients in the absence of oxygen.

Tumor cells are likely to rely in the metabolic pathways that harness energy in the absence of oxygen. This is not too surprising: some tumors grow so rapidly that they 'outgrow' their own blood supply and thus become hypoxic. Therefore, the introduction of Irg1 in tumor cells could prove to be an efficient strategy for depleting the tumor from energy, thus thwarting its ability to grow.

Publication

Abolition of mitochondrial substrate-level phosphorylation by itaconic acid produced by LPS-induced Irg1 expression in cells of murine macrophage lineage.
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