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The Warburg Effect: How Does it Benefit Cancer Cells?

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Abstract

Cancer cells rewire their metabolism to promote growth, survival, proliferation, and long-term maintenance. The common feature of this altered metabolism is increased glucose uptake and fermentation of glucose to lactate. This phenomenon is observed even in the presence of completely functioning mitochondria and together is known as the Warburg Effect. The Warburg Effect has been documented for over 90 years and extensively studied over the past 10 years with thousands of papers reporting to have established either its causes or its functions. Despite this intense interest, the function of the Warburg Effect remains unclear. Here, we analyze several proposed biological explanations for the Warburg Effect, emphasize their rationale, and discuss their controversies.

Keywords

Warburg Effect; ATP synthesis; microenvironment acidification; ROS; chromatin remodeling

Glucose Metabolism and the Warburg Effect

The metabolism of glucose, the central macronutrient, allows for energy to be harnessed in the form of ATP through the oxidation of its carbon bonds. This process is essential for sustaining all mammalian life. In mammals, the end product can be lactate or, upon full oxidation of glucose via respiration in the mitochondria, CO₂. In tumors and other proliferating or developing cells, the rate of glucose uptake dramatically increases and lactate is produced, even in the presence of oxygen and fully functioning mitochondria. This process, known as the Warburg Effect, has been studied extensively (Figure 1). However, after careful inspection, it becomes apparent that its benefits for cell growth and survival are not yet resolved. This analysis will focus on several proposals for its function, and in each case we discuss their appeal as well as their drawbacks. Before our discussion of each proposal, we first introduce the Warburg Effect in a historical context with an emphasis on

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Outstanding Questions[NN1]

- Does the Warburg Effect promote the development of cancer or is it a dependency imposed by other cancer-promoting processes?
- How can experimental systems be devised that can conclusively test the proposals for the function of the Warburg Effect?
- Does resolution of any given function of the Warburg Effect have immediate therapeutic consequences?
- Does the function of the Warburg Effect provide insights into its role in tumor evolution?
- Do the requirements of the Warburg Effect provide clues for its function?

Trends

- Both glycolytic and mitochondrial metabolism are essential for cell proliferation in both past and present conceptions of the Warburg Effect.
- Numerous proposals of the Warburg Effect functions have emerged over the years.
- Each of the proposed functions of the Warburg Effect are attractive, but also raise unanswered questions.
- Signal transduction functions for the Warburg Effect appear likely, but are difficult to test experimentally.

Publications on the Warburg Effect

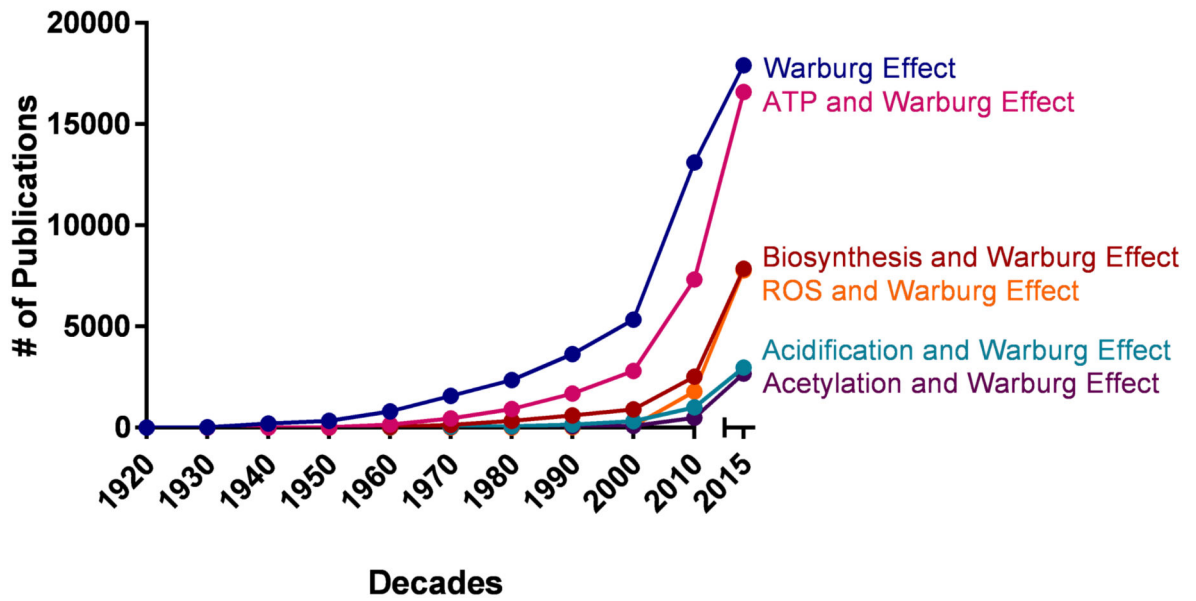


Figure 1. The frequency of publications on the Warburg Effect from the 1920s-2010s

The Warburg Effect has been studied extensively since the 1920s with a surge in the number of publications from the 2000s to today. Many of the proposed functions of the Warburg Effect have also gained vastly renewed interest. Although energy (ATP), biosynthesis, and ROS have been intricately studied in the context of the Warburg Effect, acidification and acetylation have only recently gained attention.

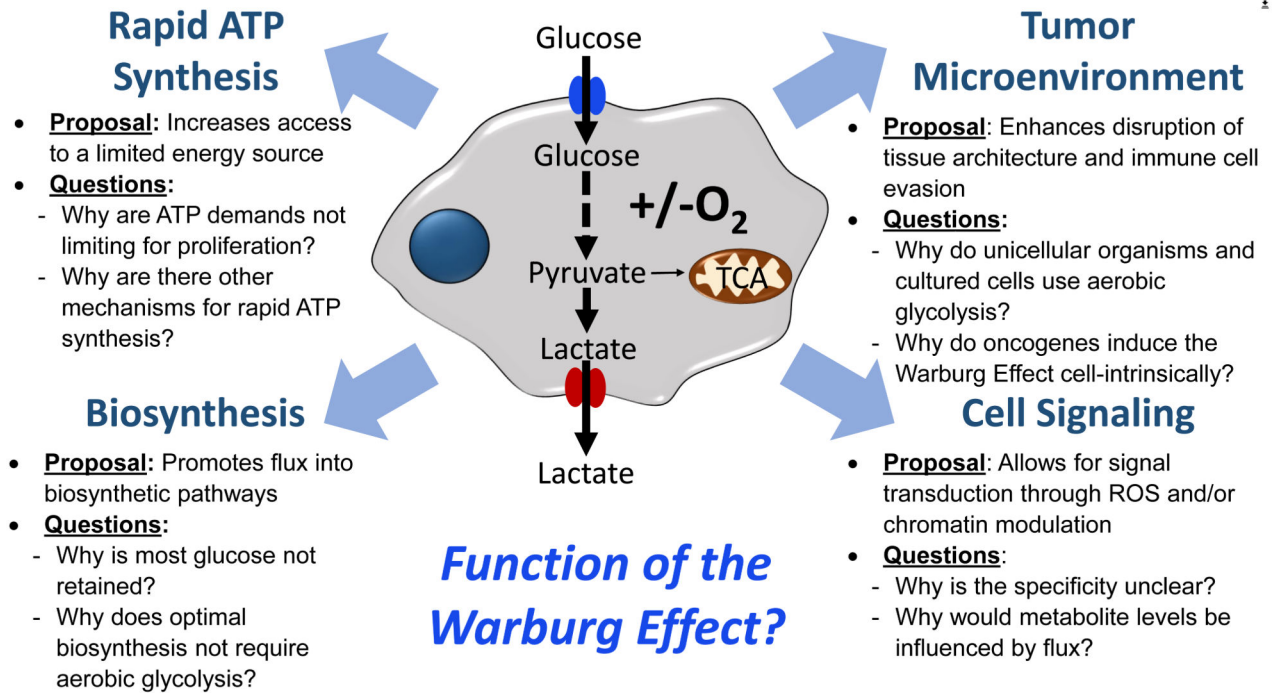


Figure 2. Summary of the proposed functions of the Warburg Effect

The Warburg Effect is defined as an increase in the rate of glucose uptake and preferential production of lactate, even in the presence of oxygen. Each of these functions have been hypothesized to be the function of the Warburg Effect.