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De novo diacylglycerol synthesis from glucose: a forgotten link between the warburg effect, endogenous tumor promotion, and RAS-driven carcinogenesis. Implications for radiation therapy of cancer

Abstract

The Warburg effect – aerobic glycolysis with massive glucose consumption and lactate production – is a hallmark of cancer. In 1989 we demonstrated in EJ-H-RAS-transformed BALB/3T3 fibroblasts that glucose is not merely a fuel but the substrate for *de novo* synthesis of 1,2-diacylglycerol (DAG) via the glycolytic intermediates dihydroxyacetone phosphate and glycerol-3-phosphate. This glucose-derived DAG, rich in saturated fatty acids (palmitate), accumulates constitutively, activates protein kinase C (PKC), and subverts agonist-stimulated inositol lipid metabolism. Because PKC is the intracellular receptor for phorbol esters (classic tumor promoters), RAS-transformed cells autonomously generate both the initiating oncogene (RAS) *and* the promoting signal (endogenous DAG/PKC). This creates a complete, self-sustaining multistage carcinogenesis loop inside a single cell. The observation, cited only few times in 37 years, suggests that, in this specific experimental context, glucose can serve not only as an energy source but also as a substrate for the generation of an endogenous, phorbol-ester-like promoter. Modern knowledge on lipid reprogramming, PKC isoforms in RAS-driven cancers, and ketogenic-diet trials validates this 1989 mechanism and calls for its resurrection as a therapeutic target. These findings carry direct implications for oncological radiotherapy, as constitutive glucose-derived DAG/PKC signaling may contribute to radioresistance in RAS-driven tumors (supported by evidence linking DAG/PKC to ionizing radiation responses, ROS and survival signaling) and therefore represents a rational target for radiosensitizing strategies.

Keywords: warburg effect, protein kinase c, endogenous tumor promotion, RAS oncogene, glucose metabolism, ketogenic diet, radiation therapy

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Introduction

In 1989 we reported in *FEBS Letters*[1] that EJ-H-RAS-transformed fibroblasts exhibit elevated steady-state levels of 1,2-DAG when prelabelled with [^{14}C]glucose, [^{3}H]glycerol or [^{14}C]palmitic acid, but not with [^{14}C]arachidonic acid. Insulin, which stimulates *de novo* DAG synthesis in normal cells, had no further effect in RAS transformants – the pathway was already maximally activated. Neurotransmitter-induced inositol phosphate responses were amplified, while PDGF- and thrombin-stimulated responses were blunted. We concluded that RAS induces *de novo* DAG synthesis along the glycolytic route and subverts receptor–phospholipase C coupling.

A companion paper[2] showed that this glucose-derived DAG causes permanent PKC activation and down-regulation, exactly as phorbol esters do. These findings were largely overlooked. The dominant narrative remained that the Warburg effect provides only rapid ATP and biosynthetic intermediates. We now know it does far more. The same glucose-dependent DAG/PKC axis that drives autonomous tumor promotion may also contribute to radioresistance in RAS-driven cancers, thereby opening a mechanistic rationale for metabolic radiosensitization strategies in oncological radiotherapy.

In the present article, the original 1989 studies by our group were used as starting points; additional papers were considered if they addressed *de novo* DAG synthesis from glucose, constitutive PKC activation in transformed cells, lipid reprogramming in cancer, or the intersection of these pathways with ionizing radiation responses. A focused literature search was performed in PubMed, Google Scholar and Web of Science from 1989 to 2026. Primary search terms included combinations of "diacylglycerol" OR "DAG", "de novo", "glucose", "protein kinase C" OR "PKC", "RAS", "Warburg", "oncogene", "transformed cells" and related variants. Preference was given to peer-reviewed primary research and relevant reviews; non-peer-reviewed sources and purely technical methodological papers were excluded unless they provided essential context.

Glucose as substrate for an endogenous phorbol-ester mimic

In normal cells, insulin stimulates *de novo* phosphatidic acid (PA) and DAG synthesis from dihydroxyacetone phosphate (DHAP) → glycerol-3-phosphate → lyso-PA → PA → DAG.[3] RAS oncoproteins hijack this insulin-like pathway constitutively. The resulting DAG is palmitate-rich, structurally suited to activate conventional and novel PKC isoforms via the C1 domain – the same domain that binds tumor-promoting phorbol esters (TPA/PMA).

Thus, RAS-transformed cells manufacture their own tumor promoter from glucose. This explains the classic two-stage model of carcinogenesis[4] occurring *endogenously*:

- **Initiation**: RAS point mutation (irreversible).
- **Promotion**: chronic, glucose-driven DAG → PKC signalling (reversible until fixation).

No external promoter is required. The cell has both the initiator and the promoter.

Glucose as substrate for an endogenous tumor promoter

The Warburg effect is routinely described as inefficient ATP production compensated by high flux. Our 1989 data reveal a darker reality: excess glucose is diverted into *de novo* DAG, a potent second messenger that:

- activates PKC → proliferation, survival, invasion;
- alters receptor coupling (amplifies GPCR, desensitizes RTK pathways);
- acidifies the microenvironment via lactate, favouring metastasis;
- feeds lipid signalling loops (mTORC2, SREBP1, HIF-1α) now recognised in modern lipid-reprogramming literature.[5]

Reducing glucose availability (ketogenic diets, 2-deoxyglucose, GLUT1 inhibitors) therefore does not merely "starve" ATP; it removes the substrate for an endogenous TPA-like molecule. This is why ketogenic interventions show striking efficacy precisely in *KRAS*-mutant pancreatic, colorectal and lung cancers – models that mirror our 1989 EJ-H-RAS system.

Modern validation and therapeutic implications

Since 1989:

- Hyperglycaemia-driven *de novo* DAG/PKC signalling is textbook in diabetic vascular complications.[4]
- Cancer cells rewire fatty-acid metabolism downstream of oncogenes (PI3K/AKT/mTOR, MYC, RAS) to sustain *de novo* lipogenesis and DAG pools.[6,7]
- PKCε directly promotes *de novo* lipogenesis and tumour growth via PKM2 nuclear translocation.[8]
- PKC inhibitors and DAG-kinase modulators are in clinical trials.[9]

Our 1989 mechanism integrates these threads: the Warburg effect is not a passive adaptation but an active generator of oncogenic lipid signals. Targeting glucose → DAG → PKC (dietary carbohydrate restriction + PKC modulators + GLUT/PKM2 inhibitors) offers a rational, multi-hit strategy against RAS-driven malignancies (Figure 1).

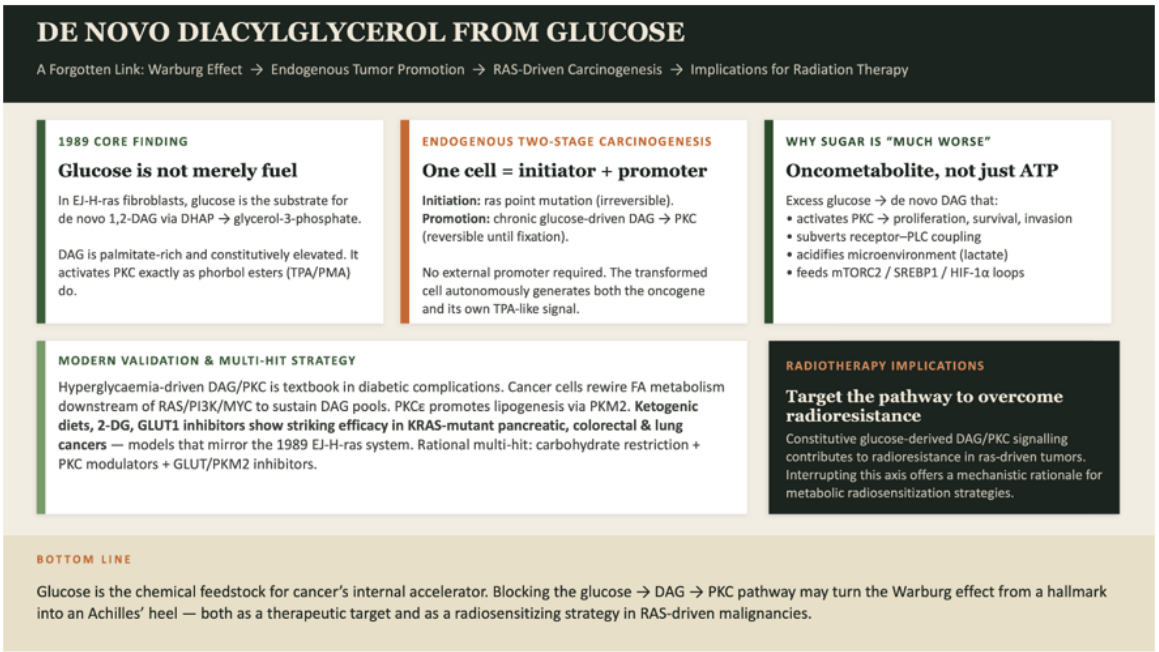

Figure 1 Schematic overview of the 1989 mechanism linking the Warburg effect to endogenous tumor promotion in RAS-driven cells, and its implications for radiation therapy. Glucose serves as substrate for *de novo* synthesis of palmitate-rich 1,2-diacylglycerol (DAG), which constitutively activates protein kinase C (PKC) and thereby generates an intracellular phorbol-ester-like promoting signal. The resulting self-sustaining initiation–promotion loop, modern validation through lipid reprogramming and ketogenic interventions, and the potential contribution of the glucose–DAG–PKC axis to radioresistance are summarized.

It should be noted that the original observations were obtained in a defined experimental system (EJ-H-RAS-transformed BALB/3T3 fibroblasts under conditions of constitutive glucose-driven *de novo* DAG synthesis). The biological impact of this pathway is likely to vary according to several factors, including the specific PKC isoforms expressed, the tumor type and genetic background, local glucose availability, the relative contribution of alternative DAG sources (*e.g.*, phospholipase C-mediated hydrolysis), and the overall metabolic rewiring of the cell. Different PKC isoforms can exert opposing effects on survival, proliferation or apoptosis, and not all cancers display the same degree of dependence on glucose-derived DAG. These contextual differences should be taken into account when considering the broader relevance of the mechanism and its potential therapeutic implications.

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Conclusion

The 1989 observation that RAS-transformed cells use glucose to synthesise their own phorbol-ester-like promoter was ahead of its time. It reframes the Warburg effect as both metabolic reprogramming and endogenous tumour promotion. Thirty-seven years later, with the tools of single-cell metabolomics, PKC-isoform-specific drugs, and precision ketogenic protocols, the time has come to resurrect this work. Glucose is not just fuel for cancer – it is the chemical feedstock for its internal accelerator. Blocking that feedstock may finally turn the Warburg effect from a hallmark into an Achilles' heel.

In the specific context of oncological radiotherapy, emerging evidence indicates that the DAG/PKC axis participates in cellular responses to ionizing radiation. Radiation induces DAG production that contributes to PKC activation,[10] PKC signaling can prevent IR-induced apoptosis and support survival pathways,[11] and elevated DAG levels (via DGKB downregulation) promote radioresistance by limiting mitochondrial ROS/lipotoxicity.[12] While direct experimental links between constitutive *glucose-derived* DAG and radioresistance remain limited, the broader DAG/PKC pathway – including isoform-specific effects on DNA-damage responses, ROS handling and metabolic rewiring – constitutes a plausible contributor to radioresistance in RAS-driven tumors and therefore a rational target for radiosensitizing strategies.

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Authors' contribution

Marco Ruggiero, MD, PhD was responsible for the original experimental work (1989), conceptualization of the present manuscript, methodology, formal analysis, data curation, visualization, and final editing.

Conflicts of interest

The author declares that this article relies exclusively on data present in the scientific literature and in the public domain.

Ethics

This article is original and contains material that has not been submitted or published in any scientific journal. A preprint version of this article was posted in the server of the European Council for Nuclear Research (CERN) https://zenodo.org/records/18865853

Ethical approval

Not applicable.

Consent to participate

Not applicable.

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Advisory

No information in this paper is intended or implied to be a substitute for professional medical advice, diagnosis or treatment.

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