Proposed DCB concept in response to the NIH 10 year Health Nutrition Plan:
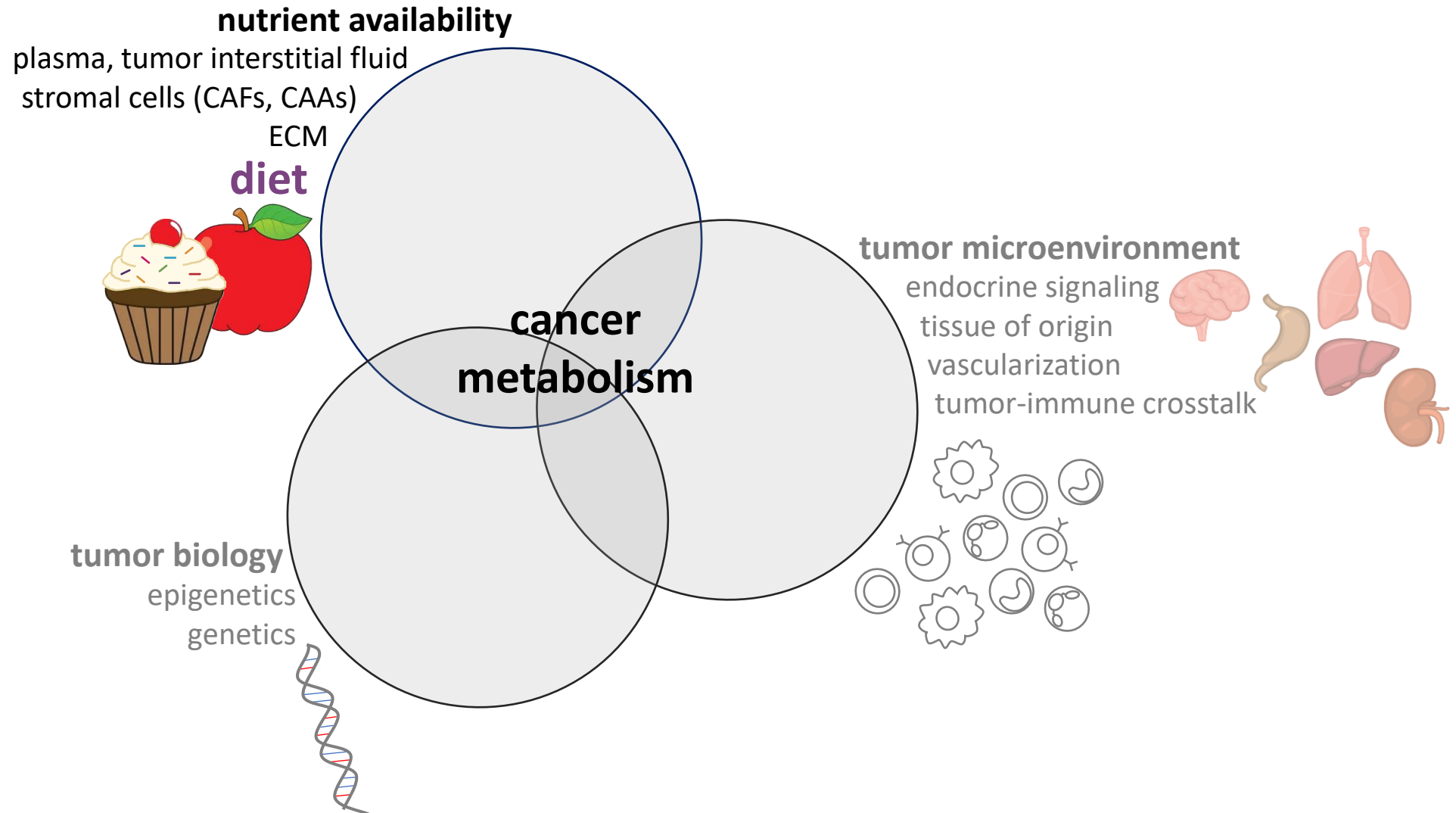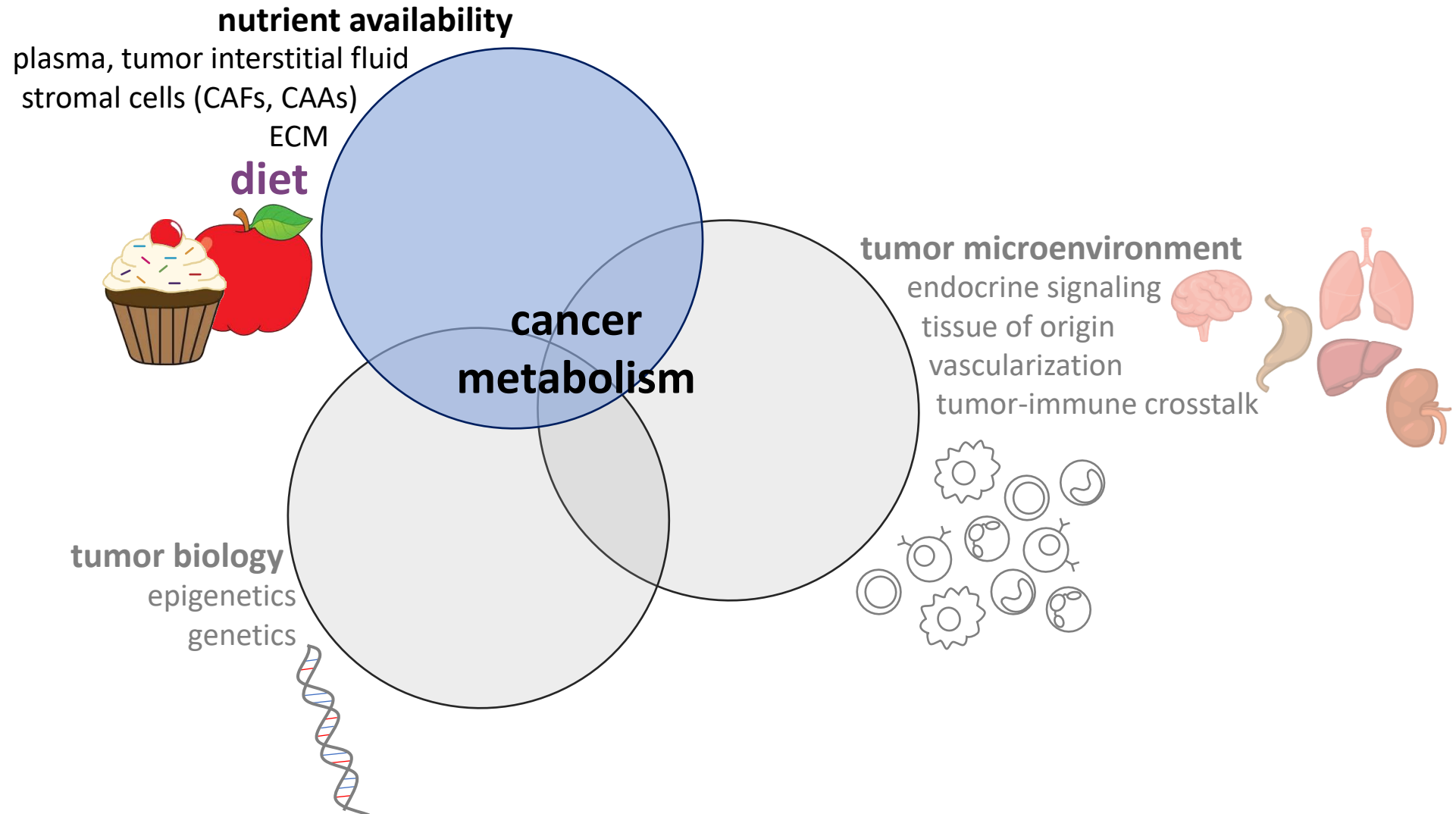
Fundamental studies of dietary influences on lipid-mediated mechanisms of tumor growth and progression
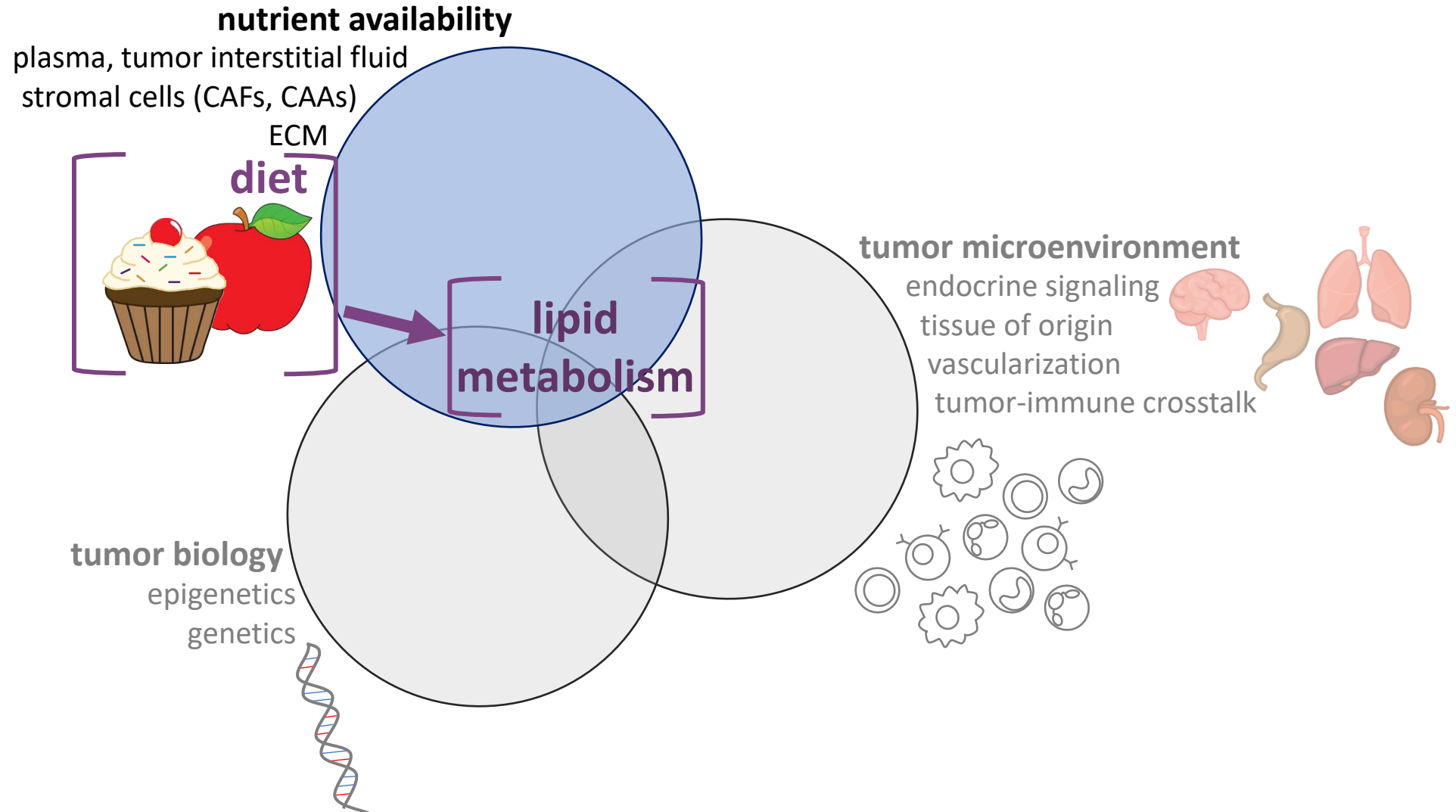
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Joint NCI BSA/NCAB
June 13-15, 2022

The availability of macronutrients in the tumor microenvironment is both directly and indirectly impacted by diet

nutrient availability
plasma, tumor interstitial fluid
stromal cells (CAFs, CAAs)
ECM

diet

cancer metabolism

tumor microenvironment
endocrine signaling
tissue of origin
vascularization
tumor-immune crosstalk

tumor biology
epigenetics
genetics

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Recent work suggests that diet-responsive lipid metabolism plays a central role in controlling tumor growth and progression

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Dietary influences on lipid metabolism mediated tumor growth and progression is a timely and significant topic to study

new advances

- recent discoveries* present unique scientific opportunities

- models that *begin* to incorporate the tumor microenvironment

- methodological innovation
  - *metabolomics & lipidomics*
  - *computational & mathematical models*
  - *systems approaches*

remaining challenges

- biological complexity
  - *tumor microenvironment*
  - *lipid biochemistry*

- quantitation of dietary variables

- insufficient bridges between research on nutrition and fundamental cancer biology

*example references:
2021 Lien *et al*. Nature 599:302   2021 Pascual *et al*. Nature 599:485
2020 Muthusamy *et al*. 586:790   2020 Ringel *et al*. Cell 183:1848

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Fundamental investigations of dietary influences on lipid metabolism are poorly represented in the NCI portfolio

- Previous initiatives related to diet and nutrition have focused primarily on:
    - cancer prevention
    - behavioral science
    - the microbiome

- Most NCI awards that study diet focus on:
    - epidemiology
    - risk & prevention
    - the microbiome

- In FY2017-2021, NCI made 15 awards on 113 competing applications that incorporated diet into mechanistic studies of one or more aspects of lipid metabolism

Proposed concept: dietary influences on lipid-mediated mechanisms of tumor growth and progression

- Two PARs are proposed, using the R01 (5 expected awards; potential to **renew** through the parent) and R21 (3 expected awards) mechanisms, to achieve **three purposes**:

  - *support fundamental studies to identify and define molecular mechanisms through which diet modulates tumor growth and progression through lipid metabolism*

  - *bridge the historically divided fields of nutrition and molecular metabolism*

  - *stimulate research and tool development in this emerging area*

- **Aligns** with Goal 4 of the recent NIH Strategic Plan for Nutrition Research
  - *Goal 4: improve the use of food as medicine*

- **Fills a gap** identified by subject matter experts during the July 2021 Workshop on Diet as a Modifier of Tumor Metabolism and confirmed by program staff

- Will establish and develop a **community of practice** by:
  - *bringing together fundamental cancer biologists and nutritionists (**MPI/co-PI**)*
  - *hosting a required annual meeting for awardees*
  - *establishing a working group*

- Better understanding of dietary influences on cancer metabolism advances the long-term goal of improving nutritional **recommendations for patients**, as well as potential **development of metabolic therapies**

Examples of responsive topics

- What are the molecular mechanisms that moderate the differential effects of different biochemical species of dietary lipids, such as palmitate and linoleic acid, on tumor progression?

- How do diet-driven variations in the level and/or composition of fatty acids in serum or tumor interstitial fluid impact in tumor and stromal cells?
    - lipid-mediated signaling
    - *de novo* lipogenesis
    - mitochondrial function
    - production of reactive oxygen species

- How do known driver mutations such as p53, KRAS, and MYC influence lipid metabolism in tumor cells in response to diet?

- How are alterations in diet-responsive lipid metabolism in tumors buffered or enhanced by the tumor microenvironment?

- What are the molecular mechanisms through which diet-responsive circulating factors such as adipokines and steroid hormones influence cancer cell metabolism and tumor progression?

- How does dietary composition affect lipid metabolism in tumors and the tumor microenvironment in the absence of weight gain?

applications that examine how any of the above topics contribute to health disparities are welcome and encouraged

Judging effectiveness and metrics of success

Evaluation of awards made under this program will be based on measurable performance criteria, including but not limited to:

a) Change in the number of collaborations between nutrition scientists and researchers studying fundamental cancer metabolism, as determined by disambiguated network analysis.

b) Timely dissemination of research findings through preprints and journal articles.

c) Development of novel models and resources, as well as sharing of those resources with the wider scientific community.

d) Active participation in the working group and other related activities.

e) Rigorous adherence to NCI policies and best practices, including data sharing.

Summary

- Dietary nutrients can directly influence tumor growth and progression, through both cell autonomous and non-cell autonomous mechanisms

- The proposed concept **fills a gap** in the NCI portfolio and will leverage recent discoveries and methodological innovations to advance **Goal 4** of the ten-year NIH **Strategic Plan for Nutrition Research**

- Applicants will be expected to include nutritionists through an **MPI/co-PI** structure, establishing bridges between the historically siloed communities of nutrition science and molecular metabolism

- Better understanding of dietary influences on fundamental cancer metabolism will advance the long-term goal of improving nutritional **recommendations for patients**, as well as potential **development of metabolic therapies**

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