

# Cancer cell and Nutrition

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### The Molecular Link from Diet to Cancer Cell Metabolism

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#### Abstract

Malignant cells remodel their metabolism to meet the demands of uncontrolled cell proliferation. These demands lead to differential requirements in energy, biosynthetic precursors, and signaling intermediates. Both genetic programs arising from oncogenic events as well transcriptional programs and epigenomic events are important in providing the necessary metabolic network activity. Accumulating evidence has established that environment factors such as diet has a major role in shaping cancer cell metabolism. For metabolism, diet and nutrition are the major aspects of the environment and have emerged as being a key component in determining cancer cell metabolism. In this review, we will discuss these emerging concepts in cancer metabolism and how diet and nutrition influence cancer cell metabolism.

#### eTOC Blurb

Altered nutrient uptake results in changes to metabolic pathway activity and is a common feature

# Nutrition and diet

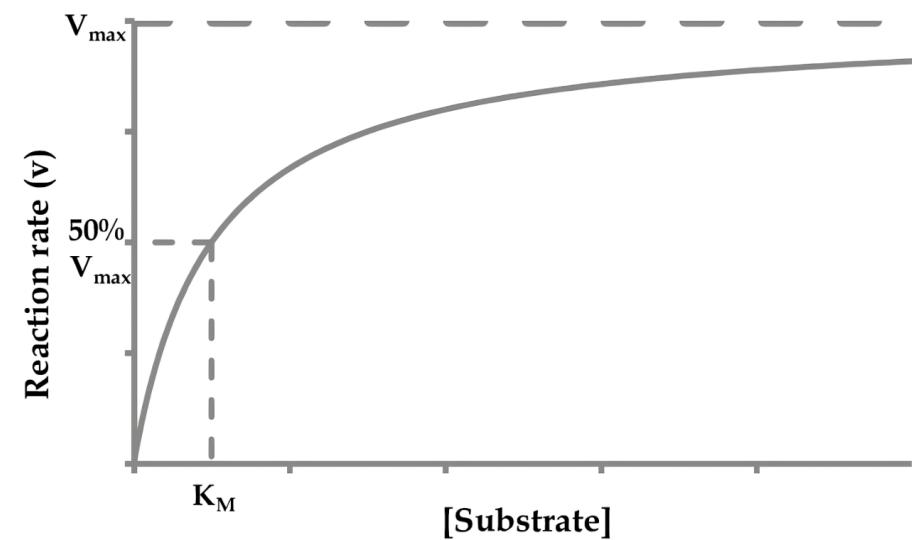
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Nutrient availability in the plasma begins with dietary intake, and concentrations of metabolites vary dramatically based on their intake from the diet (Mentch, 2015). Certain diets are known to be associated with some aspects of health. For example, Mediterranean diets has been associated with longer lifespans. Conversely, Western diets are associated with obesity, cancer, and coronary heart disease. Interestingly, diets such as formations of plant-based diets have long been investigated as cancer therapy (Gerson, 1978).

## Cancer and Michaelis Constant.

Nutrient availability exerts control over cellular metabolism through multiple mechanisms. The cellular uptake of nutrients from the surrounding microenvironment is one such process, which is regulated tightly by the kinetic properties of active transporters, including their Michaelis constants. (Cox, 2000). Physiologically, cancer cells encounter concentrations of nutrients which are at or above those found in corresponding normal tissues.

These increases in nutrient availability influence the rate of nutrient uptake which then propagate to changes in metabolic flux through the metabolic network and downstream functions (Palm, 2017).



## What to do ?

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- Caloric Restriction.
- Fasting.
- Dietary Amino Acid Balance in Cancer- Serine and Glycine Metabolism.
- Gut Microbiome.

# Caloric Restriction.

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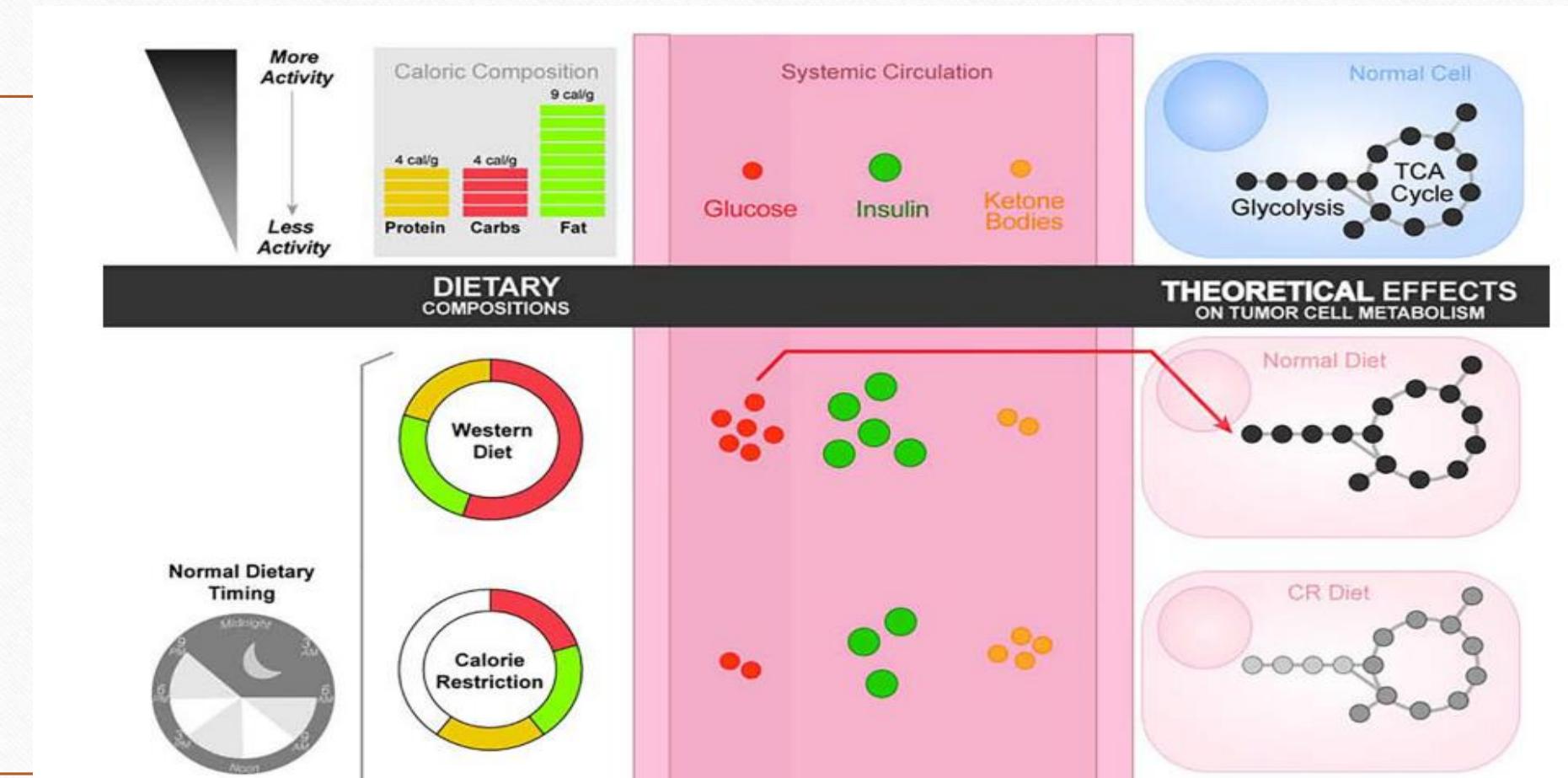
). Numerous animal studies show that CR can prevent many cancers, as well as restrict progression and metastasis (Lv et al., 2014). These positive effects have been shown in cancers from diverse tissues including mammary, lung, prostate, brain, bladder, pancreatic, hepatic, skin, colorectal, and ovarian (Castejon et al., 2020; Lv et al., 2014). The molecular mechanisms believed to underlie these effects have been largely attributed to reduced circulating levels of several hormones such as growth factors and cytokines. Particularly, CR has been associated with lower levels of circulating IGF-1, which is known to engage signaling networks involving RAS/MAPK and PI3K/AKT/mTOR which are common dysregulated pathways in cancers (Goncalves, 2018).

# Caloric Restriction

In addition, CR has been linked to decreased glycolysis and alterations in FA membrane composition, with decreased levels of polyunsaturated FAs (PUFAs) and increased monounsaturated FAs (MUFAs) (Jove et al., 2014). Both increased fatty acid oxidation and decreased membrane polyunsaturation are thought to help protect cells from oxidative damage (Weinberg, 2015). CR has also been shown to alter other metabolic pathways including the carnitine shuttle pathway, sphingosine metabolism, and methionine metabolism (Green et al., 2017). In the future, targeting metabolic pathways to assess the extent that altered metabolism caused by CR can exert anti-cancer effects will be interesting.



# Western Diet and Caloric Restriction.



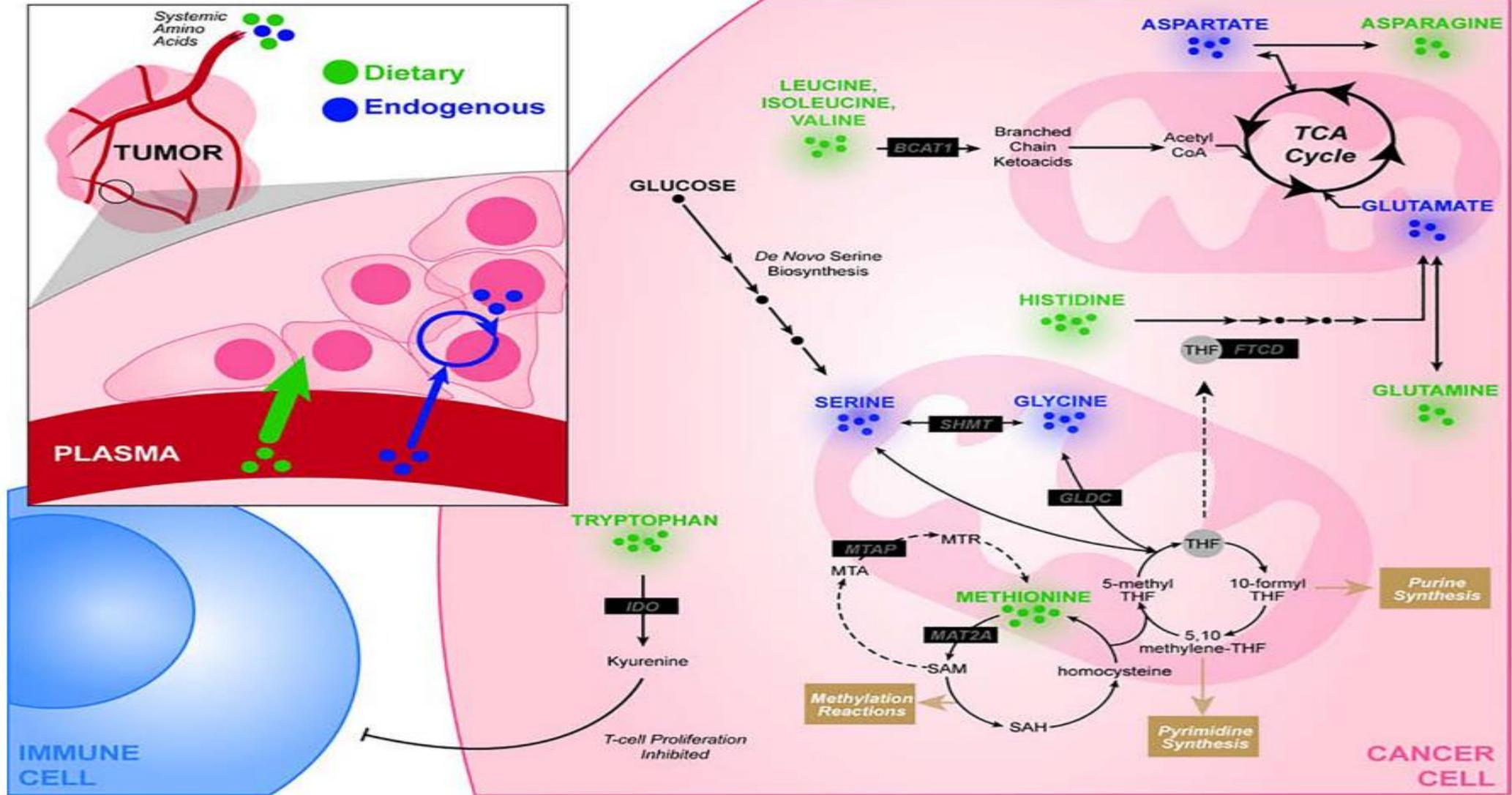
# Fasting

Mechanistically, fasting is thought to be protective towards non-neoplastic cells because hormonal and metabolic changes during fasting direct normal cells towards a stress-resistance state characterized by a switch from growth processes to maintenance and repair (Di Biase, 2017; Lee et al., 2012; Nencioni et al., 2018). Cancer cells are unable to adopt this stress-resistance state and therefore not protected or sensitized to stress. Fasting and “fasting-mimicking diets” may also improve cancer outcomes by enhancing anti-cancer immune function through the promotion of T cell-mediated tumor cytotoxicity (Di Biase et al., 2016).



## Serine and Glycine Metabolism

**Serine and Glycine:** The intersection of folate and methionine cycles forms the core cellular processing for one-carbon units, molecular building blocks required for the biosynthesis of lipids, nucleotides and proteins as well as a major component of redox maintenance (Locasale, 2013; Yang, 2016). This one-carbon metabolism network integrates nutritional status via inputs of various amino acids, including serine and glycine, to generate functional outputs as shown in Figure 2. Accordingly, restriction of serine and derived glycine in the diet has been shown to attenuate tumor growth in a number of xenograft and autochthonous murine models (Labuschagne, 2014; LeBoeuf, 2020; Maddocks, 2017; Sullivan, 2019). While serine and glycine can both be synthesized *de novo* from glycolysis, increased levels of both serine uptake and biosynthesis suggest that one-carbon metabolism is often altered in cancer. The uses are multifaceted including nucleotide synthesis, sphingolipid synthesis, mitochondrial function, methylation metabolism and redox maintenance (Gao, 2018; Reid, 2018).

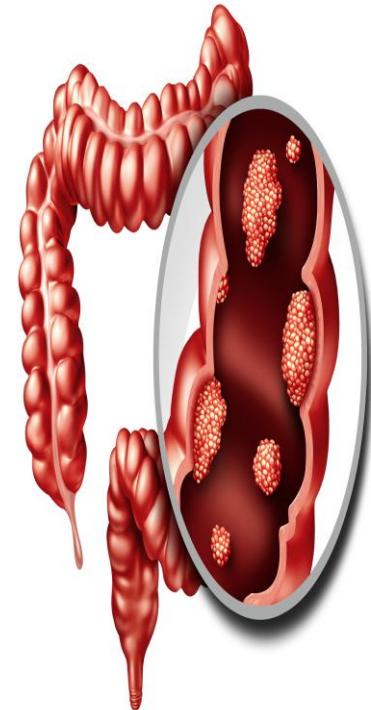


# Gut Microbiome

A discussion of diet remains incomplete without considering the gut microbiome, a consortium of trillions of microbes which contribute in meaningful but poorly understood ways to host metabolism. The microbial composition of the gut microbiome has likely undergone significant adaptations as human diets have evolved over both short and long term time scales, with Western diets high in fats and carbohydrates associated with the evolution of greater populations of polysaccharide-degrading microbiota to extract calories and provide needed food-derived energy and CR associated with increased probiotic microbes and suppressed proinflammatory strains (Turnbaugh, 2009; Zheng et al., 2018). The shifts in the species of microflora which colonize the gut are associated with metabolic phenotypes in the individual host (Perry, 2016; Turnbaugh, 2009).

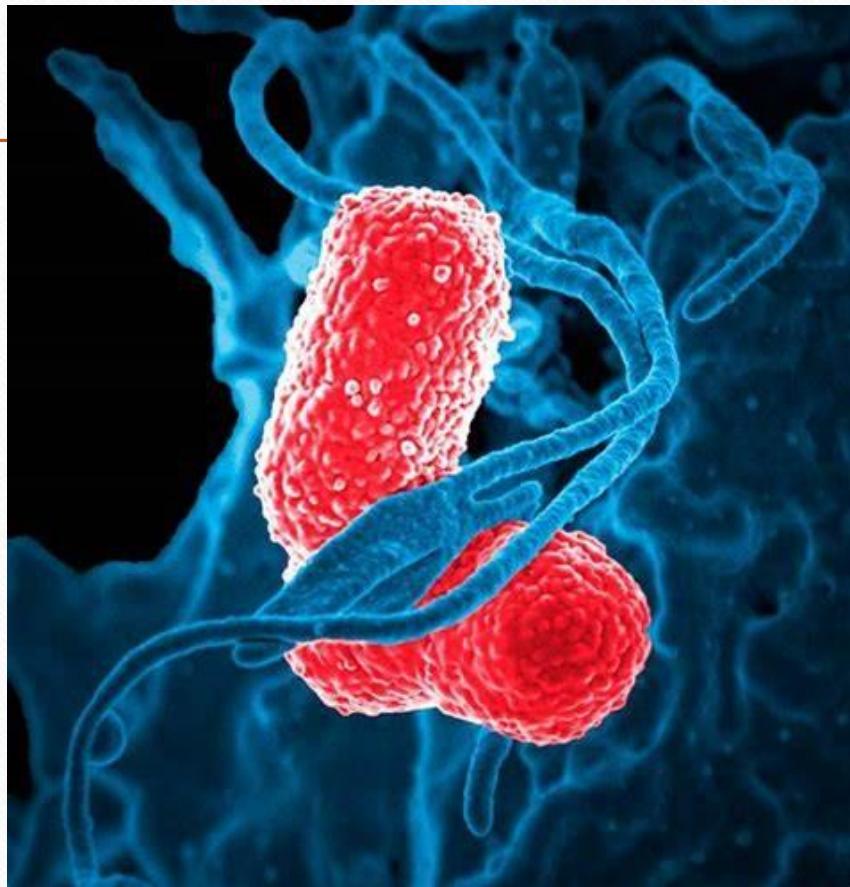
While the precise role of the microbiome in cancer is not well defined, diet-driven changes in gut microbiota are relevant in shaping tumor development, progression, and therapy.

Microbial imbalance, or dysbiosis, between colorectal cancer (CRC) tissue and adjacent mucosa has been described in the literature, with neoplastic enrichment of specific microbes like *Fusobacterium nucleatum* (Fn), *Escherichia coli*, and *Bacteroides fragilis* (Collins et al., 2011; Iida, 2013; Nakatsu et al., 2015). In addition, recent evidence has demonstrated co-migration of commensal microbiota within CRC metastases (Bullman, 2017) and microbial influence in modulating antitumor immune activation and therapy response (Jin, 2019;

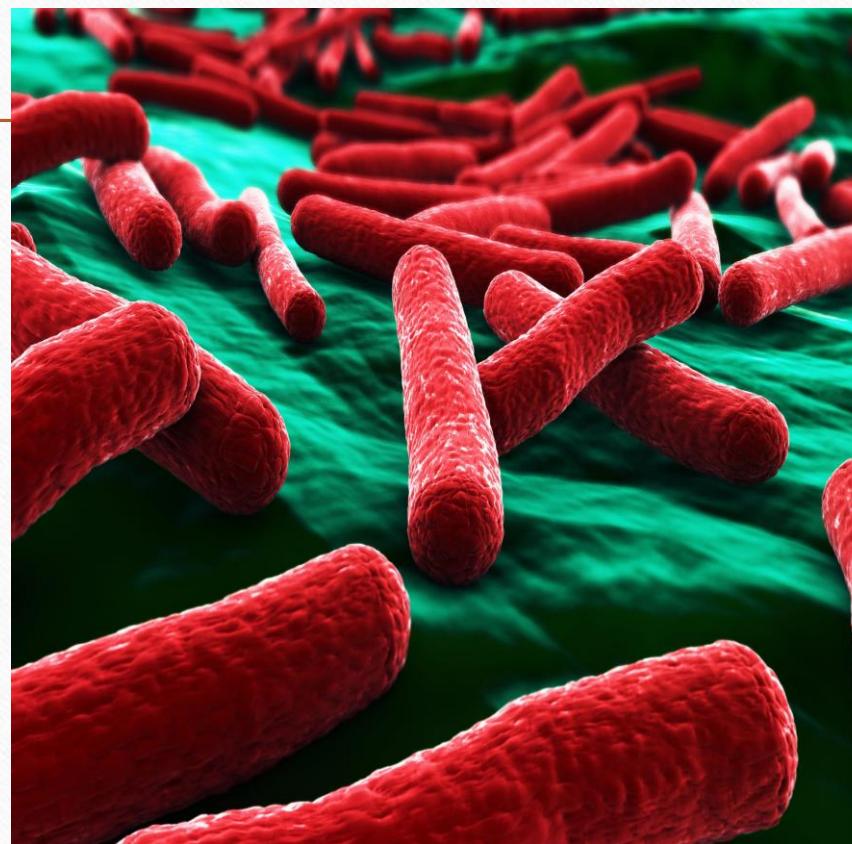


Mechanisms that link cross-talk from microbes to tumor cells are also emerging such as a recent study of NAD<sup>+</sup> metabolism that shows tumor cells can satisfy requirements of NAD synthesis from the provision of nutrients derived from microbial sources (Shats et al., 2020). Given the microbiome is known to exert control over a multitude of cellular and whole-body functions, it is interesting to speculate that additional links between diet and tumor behavior exist(Cani, 2018).

## Fusobacterium nucleatum



## Eschrichia Coli



# Bacteroid Fragilis



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