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Mini-Review

Impact of Animal and Plant Protein Intake on Cancer Development Risk

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Abstract

The impact of dietary high-quality protein on optimal health continues to be explored. Recent studies have shown that high-quality protein intake is linked to longevity by avoiding premature deaths. Animal proteins provide the nine essential amino acids, easily absorbable iron, and vitamin B_{12}, while plant-based protein sources offer additional nutrients such as dietary fiber, polyphenols, and unsaturated fats. Although protein quality can be defined by the well-known amino acid score (AAS), the protein digestibility corrected AAS (PDCASS) and digestible indispensable AAS (DIAAS) have some limitations for practical use. The mechanistic/mammalian target of rapamycin complex 1 (mTORC1) signaling pathway, which plays a crucial role in cell growth and proliferation, is activated by amino acids and has an impact on cancer development and progression. Compared to animal-based proteins, plant-based proteins are likely to be favorable for reducing cancer development risk from the perspective of the mTORC1 pathway. Plant protein sources optimal for cancer development risk, including methionine restriction, need to be explored, considering age, dietary preference, and cultural differences.

Keywords: Animal Protein; Plant Protein; Amino Acid Score; mTORC1; Cancer Risk

Introduction

The impact of dietary high-quality protein on optimal health and healthy aging continues to be explored, with an acceptable macronutrient distribution range for protein of 10-35% of energy for adults established by the Institute of Medicine [1]. Initially, the emphasis was placed on the effects of high-protein diets, including weight loss, fat mass reduction, and muscle mass preservation, leading to favorable metabolic outcomes due to sustained satiety and increased energy expenditure [2-5]. Recent studies have shown that high-quality protein intake is linked to longevity by reducing premature deaths from cardiovascular diseases, stroke, and cancer [6,7].

As the choice of protein sources influences other components of foods, including macronutrients, micronutrients, and phytochemicals, the amount and type of protein can have specific effects on health outcomes [7,8]. In this minireview, we will focus on associations between protein intake and cancer development risk, describing traits of animal and plant proteins, the mechanistic/mammalian target of rapamycin (mTOR) signaling pathway sensing amino acids, and clinical studies on their associations.

Differences between animal and plant proteins

In general, animal proteins (such as meat, eggs, milk, and fish) are considered more nutritious and easily absorbed by the human body compared to plant proteins (such as legumes, cereals, and nuts). This is because animal proteins provide the nine essential amino acids, easily absorbable iron, and vitamin B_{12}, which is not naturally sourced from plants [9]. On the other hand, plant-based protein sources offer additional nutrients such as dietary fiber, polyphenols, and unsaturated fats [10].

Protein quality can be defined by the well-known amino acid score (AAS). The AAS is determined by the first limiting indispensable amino acid content in the tested protein, and the protein digestibility corrected AAS (PDCAAS) has been adopted as the preferred measurement of protein value in human nutrition [11]. Currently, the Food and Agriculture Organization of the United Nations (FAO) has recommended the digestible indispensable AAS (DIAAS) to replace the PDCAAS for the protein quality assessment [12]. PDCAAS and DIAAS are calculated as follows [13]

- ASS = (mg of limiting amino acid in 1g the dietary protein)/(mg of the same amino acid in 1g the reference protein)
- PDCAAS = AAS × true fecal protein digestibility

- DIAAS = (mg of digestible dietary indispensable amino acid in 1g of the dietary protein)/(mg of the same indispensable amino acid of 1g of the reference protein)

Table 1 shows AAS, PDCAAS, and DIAAS in some animal- and plant-based foods reported elsewhere [11,13,14]. As expected from Table 1, plant-based proteins are generally low in lysine and/or methionine content [15] and are accompanied by antinutritional factors, such as dietary fiber and polyphenolic tannins, leading to lower absorbability compared to animal-based proteins [16]. Consequently, plant-based foods like legumes that have high indispensable amino acid content need to be consumed in greater amounts to meet the recommended requirements [14,15]. Among Japanese people, the quality of proteins generally consumed from the diet has been considered good, since average values, which were calculated from the National Health and Nutrition Examination Survey, of AAS, recommended by the FAO/World Health Organization (WHO) in 1973, PDCAAS, recommended by the FAO/WHO/United Nations University (UNU) in 1985, and PDCAAS, recommended by the FAO/WHO/UNU in 2007, were all above 100% [17]. However, PDCAAS and DIAAS are indicated to have some limitations for practical use [12,15,18].

Animal proteins	AAS (%)	Limiting AA	PDCAAS (%)	DIAAS (%)
Beef, dried	100	Val	99	112
Milk, powder	100	Trp	100	116
Egg, powder	100	His	100	113
Plant proteins	**AAS (%)**	**Limiting AA**	**PDCAAS (%)**	**DIAAS (%)**
Wheat, flour	53	Lys	48	40
Barley, dried	70	Lys	53	47
Rice, ground	58	Lys	53	57
Soybean, isolate	100	Met + Cys	100	100

Table 1: Protein Digestibility Corrected Amino Acid Score (AAS, PDCAAS) and Digestible Indispensable AAS (DIAAS) in certain animal- and plant-based foods.

AAS, with the limiting AA, was calculated from the protein digestibility of the target food and its PDCAAS shown in the article [11]. DIAAS was obtained from distinct articles [13,14].

mTOR signaling pathway sensing amino acids

The mTOR is an evolutionarily conserved and critical node through which cells coordinate growth signals and nutrient availability to synthesize proteins, lipids and nucleic acids [19]. As such, the mTOR signaling pathway is involved in an increasing number of pathological conditions, including cancer, obesity, type 2 diabetes, and neurodegeneration [20]. Figure 1 illustrates the mTOR signaling pathway stimulated by growth factors and amino acids. Growth factors and hormones, such as insulin, insulin-like growth factor 1 (IGF-1) and epidermal growth factor (EGF), stimulate mTORC1 (mTOR complex 1) activity through two signaling cascades: the phosphoinositide 3-kinase (PI3K)/Akt and Ras/mitogen-activated protein kinase (MAPK) pathways. mTORC1 is also sensitive to nutrient levels, such as amino acids, particularly leucine, arginine and glutamine. When local concentrations of amino acids exceed a certain threshold, Rag GTPases adopt their active configuration and interact with Raptor to promote mTORC1 recruitment at the lysosome. By the spatial regulation at the lysosome membrane, mTORC1 activation is supposed to occur only when amino acids and growth factors are available [21]. In addition to promoting anabolic processes, mTORC1 activation suppresses catabolism through the inhibition of autophagy [22,23].

Because the mTOR signaling pathway plays a crucial role in cell growth and proliferation, deregulation of mTOR signaling occurs in up to 80% of human cancers through gain-of-function or loss-of-function (proto-oncogene or tumor suppressor gene) mutations in the pathway [24]. Besides mutagenesis, it is conceivable that mTORC1 signaling pathway activated by amino acids has an impact on cancer development and progression. Among indispensable amino acids, methionine-induced activation of mTORC1 requires the methyl donor S-adenosylmethionine [23,25], synthesized from methionine and ATP through the methionine cycle of one-carbon metabolism [26]. In this connection, it is intriguing that methionine restriction has been reported to extend lifespan and inhibit cancer cell growth across different species, although the underlying mechanisms are not fully understood [27-29]. mTORC1 is a central regulator of protein synthesis, particularly at the initiation step of mRNA translation, by phosphorylating the translational machinery, including the eukaryotic initiation factor 4E (eIF4E)-binding proteins and the ribosomal S6 kinases 1 and 2 (Figure 1). It should be noted that the initiation codon is for methionine. Thus, methionine is essential for normal growth and development; however, methionine restriction seems to be also involved in extending lifes-

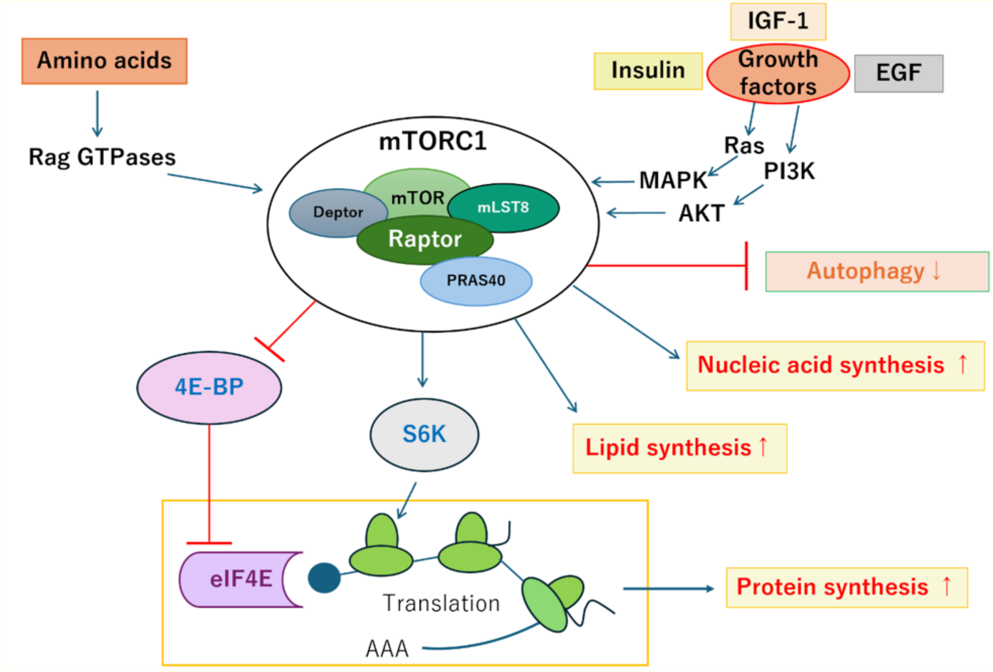

Figure 1: Schematic representation of mTORC1 signaling pathway. Amino acids and growth factors activate mTORC1 through Rag GTPases and the PI3K/Akt and Ras/MAPK pathways. mTORC1 phosphorylates 4E-BP to inhibit its function of suppressing eIF4E and phosphorylates S6K to promote ribosome biosynthesis, resulting in increased protein synthesis. Similarly, mTORC1 also increases the synthesis of lipids and nucleic acids. Additionally, mTORC1 suppresses autophagy, an important process for the digestion and recycling of cellular organelles.

pan induced by caloric restriction [30,31]. Since leucine is a potent activator of mTORC1, the restriction of dietary leucine intake is also expected to inhibit cancer cell growth [32,33]. However, such effects seem to be attenuated by leucine in degraded proteins through autophagy, as leucine is the most heavily used amino acid in the human proteome [32].

Associations between protein intake and cancer incidence or mortality

Table 2 shows recent relevant reports on associations between dietary protein or methionine intake and cancer risk. A valuable meta-analysis of prospective cohort studies reported by Naghshi, *et al.* [6] revealed that intake of plant protein was associated with a lower risk of all-cause mortality and cardiovascular disease mortality, but not with cancer mortality. However, interesting data on the association between dietary protein and cancer mortality were included in two studies in this meta-analysis. One study in the United States reported by Song, *et al.* [8] showed that, as a minor finding, the substitution of 3% energy from plant protein for egg protein was associated with 21% lower cancer mortality. In another study from Japan reported by Budhathoki, *et al.* [34], it was predicted that an isocaloric substitution of 3% energy from fish protein or plant protein for animal or processed meat protein reduced cancer-related mortality (hazard risk, 0.61 or 0.50). Thus, from a mortality perspective, plant protein intake is considered to have a small but favorable effect on cancer progression or mortality compared to animal protein intake.

Regarding methionine in Table 2, a meta-analysis of published observational studies, reported by Wu, *et al.* [35], indicated an inverse association between dietary methionine intake and breast cancer risk among postmenopausal women (relative risk, 0.94), but not among premenopausal women. On the other hand, Khairan, *et al.* [36] reported that higher dietary methionine intake was associated with an increased risk (hazard ratio, 3.45) of esophageal cancer among non-drinkers in Japan, where most of the non-drinkers were presumably women [37]. In that study, the mean methionine intakes were 1.2g/day for the lowest quintile (non-drinkers, 47%) and 2.2g/day for the highest quintile (non-drinkers, 54%). A prospective case study reported by Sun, *et al.* [38] showed that decreased methionine intake after breast cancer diagnosis was associated with a lower risk of all-cause and breast cancer mortality. It is suspected that the association between dietary methionine intake and cancer risk possibly exhibits a U-shaped patten [26]. In relation to plant protein, it is interesting that peripheral methionine appearance was much lower following plant protein than animal protein in young males [39] and in older adults [40], probably due to factors other than the amount of methionine or protein digestibility.

A large body of evidence endorses that protein has an important role in exercising and sedentary people, and the ideal protein intake is contingent upon the physiological state [41]. In the United States population, high protein intake was associated with an in-

Authors	Country	Study	Results	Ref.
Naghshi S., *et al*. 2020	USA, Canada, Asia, Europe	Meta-analysis	Intake of total, animal or plant protein was not significantly associated with cancer mortality.	6
Song M., *et al*. 2016	USA	Prospective cohort	Substitution of 3% energy from plant protein for egg protein was associated with 21% lower cancer mortality.	8
Budhathoki S., *et al*. 2017	Japan	Prospective cohort	Substitution of 3% energy from plant protein for red meat protein or processed meat protein reduced cancer-related mortality (hazard risk, 0.61 or 0.50).	34
Wu W., *et al*. 2013	USA, China, elsewhere	Meta-analysis	High methionine intake was associated with decreased breast cancer risk among postmenopausal women (relative risk, 0.94).	35
Khairan P., *et al*. 2021	Japan	Prospective cohort	Higher methionine intake was associated with an increased risk (hazard ratio, 3.45) of esophageal cancer among non-drinkers.	36
Sun Y., *et al*. 2022	USA	Prospective case	Decreased methionine intake after breast cancer diagnosis was associated with low risk of breast cancer mortality among American postmenopausal women.	38

Table 2: Epidemiological studies on associations between dietary protein or methionine intake and cancer risk.

crease in serum IGF-1 level and cancer mortality among subjects aged 50-65, with animal-derived proteins accounting for a significant proportion of the association [42]. On the contrary, among older people, high protein intake was associated with low cancer and all-cause mortality in the United States [42] and in China [43]. Although the mechanisms explaining the associations between protein intake and healthy aging are not easily explained, dietary protein and exercise can activate the mTORC1 signaling pathway, which decreases with age, leading to improved muscle protein synthesis [44]. High protein intake, regardless of its source, was associated with a low prevalence of frailty among old Japanese women [45]. In the United States, higher plant protein intake was associated with a lower Frailty Index, mediated by a lower abundance of lipid metabolites and a higher abundance of tryptophan-related metabolites [46].

Overall, plant-based proteins are regarded as favorable for healthy aging, including the reduction of cancer development risk and the prevention of physical and cognitive impairment. For now, cancer-bearing patients are occasionally recommended to adhere to plant-based diets like the Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH), vegetarian diet, and whole-food, plant-based (WFPB) diet [47]. As described in this study, plant protein sources and the plant-to-animal protein ratio optimal for reducing cancer development risk or adjunctive treatment, including methionine restriction, need to be selected, considering age, dietary preference, and cultural differences.

Conclusion

The impact of dietary high-quality protein on optimal health continues to be explored, recent studies have shown that high-quality protein intake is linked to longevity by avoiding premature deaths. Compared to animal-based proteins, plant-based proteins are likely to be favorable for reducing cancer development risk from the perspective of the mTORC1 pathway. Plant protein sources optimal for cancer development risk, including methionine restriction, need to be explored, considering age, dietary preference, and cultural differences.

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Author Contributions

YA designed the study and wrote the manuscript. RK contributed to the section "Differences between Animal and Plant Proteins"; and HS and TI contributed to the section "mTOR Signaling Pathway Sensing Amino Acids". All authors approved the final version of the manuscript.

Conflicts of Interest

The authors have declared that they have no potential conflicts of interest.

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