Cancer Treatment Results Altered by Soy and Gut Microbes

Researchers demonstrated that phytochemicals and their microbiome-derived compounds regulate the anticancer activity of phosphatidylinositol 3-kinase (PI3K) inhibitors (PI3Ki).

The findings challenge previous assumptions by demonstrating that the effectiveness of these drugs is not primarily governed by dietary carbohydrate content, but by the presence or absence of certain plant-derived compounds and their microbial metabolites.

Dietary interventions influence drug response and disease progression. Preclinical studies suggest that diets can slow tumor growth and improve anticancer drug activity.

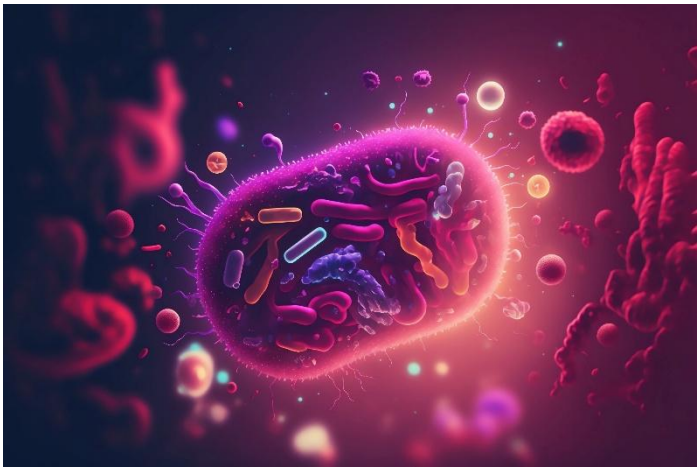
The ketogenic diet (KD) has drawn attention for its ability to enhance therapeutic responses, even in pancreatic cancer. While KD does not affect pancreatic tumor growth, it synergizes with chemotherapy and PI3Ki, slowing tumor growth and prolonging survival.

However, this study reveals that the mechanism of synergy is independent of carbohydrate restriction and instead relates to dietary phytochemical content and the gut microbiome.

Diets differ in several aspects beyond their macronutrient composition. For instance, standard rodent chow contains unrefined foods (e.g., soybean, fish), but a rodent KD contains purified components (e.g., milk-derived casein, oils).

These purified diets differ from chow in various dimensions. Importantly, both ketogenic and control purified diets lack many phytochemicals present in standard chow, which are abundant in plant-based ingredients like soy.

Identifying which aspects of diets drive outcomes is essential when comparing diets differing in multiple dimensions.



Study and Results

Researchers created a carbohydrate-rich control purified diet (CPD) that matched chow in macronutrients but used purified ingredients. This allowed for direct comparison with chow to isolate the effects of phytochemicals.

The anticancer activity of a PI3K alpha-specific inhibitor, alpelisib, was tested on pancreatic KPC allografts in mice using both CPD and KD diets.

While the diets did not directly reduce tumor size, both CPD and KD sensitized tumors to alpelisib. KD combined with alpelisib resulted in weight loss, whereas CPD allowed mice to maintain their body weight.

This suggested that alpelisib was better tolerated with CPD. Similar trends were observed with other PI3K inhibitors and in breast cancer models. CPD's improved tolerability emerged as a therapeutic advantage.

Researchers hypothesized that microbiome changes might underlie the diet-PI3Ki synergy. They tested this using mice fed chow or CPD, treated with or without alpelisib and/or an antibiotic cocktail (ANVM).

Antibiotics alone did not affect tumor growth, but in chow-fed mice, they enhanced the efficacy of alpelisib to levels comparable to those seen with CPD. This effect was not further improved when antibiotics were added to CPD.

Among individual antibiotics, ampicillin showed the strongest effects, while vancomycin and metronidazole exhibited weaker effects. Neomycin showed no benefit.

Both KD and CPD increased alpelisib serum levels. The antibiotic cocktail also raised alpelisib levels in chow-fed mice, with ampicillin having the most impact.

The team found that maintaining higher trough drug levels (not just peak levels) was crucial for effective tumor control.

They ruled out microbial metabolism as a major factor after finding no breakdown of alpelisib by fecal bacteria in vitro. Instead, intravenous studies showed that CPD and antibiotics slowed alpelisib clearance, pointing to altered host metabolism.

Liver gene expression analysis showed that CPD, KD, and antibiotics all suppressed several drug-processing genes, including Cyp3a11, the mouse equivalent of human CYP3A4.

Ritonavir, a CYP3A inhibitor, further increased drug exposure in chow-fed mice, confirming the liver's role in metabolizing alpelisib. Similar effects were observed in cynomolgus monkeys.

Researchers speculated that soy in chow induced Cyp3a11. They replaced casein with soy protein in CPD, which decreased drug exposure. This might stem from the protein or phytochemicals in soy isolate.

To separate these variables, a new CPD was designed using a soy phytochemical extract, while maintaining casein as the protein source. This also decreased drug exposure, indicating the role of soy-derived compounds.

Further experiments revealed that interactions among phytochemicals, microbiota, and liver enzymes shape PI3Ki effectiveness. Surprisingly, isoflavones were not the key compound.

Using a bioassay-guided approach, researchers identified soyasapogenol B (SSBag), a soy-derived microbiome metabolite, as the active constituent. Soyasaponins from soy are converted into soyasapogenols by the microbiome.

Soy contains two soyasaponins—SSA and SSB—converted into SSAag and SSBag, respectively. These aglycones are not present in chow but accumulate in mice fed soy-rich diets with intact microbiota.

Both SSAag and SSBag activate mouse PXR, which controls drug-processing genes. SSAag showed stronger activation. Mice fed CPD with just 0.1% SSA had increased Cyp3a11 expression and alpelisib metabolism.

This diet reduced the anticancer efficacy of alpelisib. Antibiotics reversed these effects, confirming the microbiome's role in producing active soyasaponin metabolites.

Conclusion

This study confirms that the synergy between ketogenic diets and PI3K inhibitors depends not on low carbohydrate intake, but on the absence of specific phytochemicals that alter drug metabolism.

Microbiome-derived soyasapogenols activate liver enzymes that metabolize PI3K inhibitors, reducing their effectiveness. Diets free of these phytochemicals maintain higher drug levels and improve tumor control.

Future research should identify the bacteria responsible for soyasapogenin production and explore whether their presence correlates with drug exposure and treatment response in humans.

Species-specific differences in metabolism necessitate further investigation for human translation.

Source:

https://www.news-medical.net/news/20250602/How-soy-and-gut-microbes-alter-cancer-treatment-results.aspx