Integrative & Functional Medicine | Nutritional Lithium

Lithium And Cancer

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While lithium is typically considered just a treatment for mental health conditions, evidence has slowly been building suggesting protective effects against cancer. An early study explored the rates of cancer in patients with mental health conditions with and without a history of lithium use. They found psychiatric patients on lithium had a 10% lower risk of cancer than psychiatric patients without. They also saw trends towards reduced cancer with increasing lithium intake (Cohen 1998).

A more recent Swedish study found that bipolar patients had much greater risks for cancers of the respiratory, digestive and endocrine systems. Risks for these cancers were 1.47, 1.72 and 2.6 times higher, respectively. However, patients with bipolar disorder that were on lithium had these cancer risks reduced back to the level of the standard population (Martinsson 2016). A similar study out of Taiwan compared bipolar patients on lithium to those on anticonvulsants. They found a 27% reduction in risk of cancer with lithium, noting that the higher the dose, the greater the reduction in cancer risk (Huang 2016).

Lithium and Cancer: Potential Mechanisms

Targets of Lithium

For all its complexity, there are only a few confirmed targets of lithium that show enzyme inhibition and biological consequences at achievable lithium concentrations: inositol monophosphatase and the related magnesium-dependent phosphomonoesterases and glycogen synthase kinase-3 (GSK-3) (Hallcher 1980, Phiel 2001). These enzymes all have a magnesium binding site, and lithium, with an ionic radius similar to magnesium, appears to block magnesium binding, inhibiting the enzymes.

GSK-3

Probably the best studied of these enzymes is GSK-3. GSK-3 is a protein kinase that phosphorylates other proteins. It was initially discovered to phosphorylate the enzyme glycogen synthase, which inhibits the production of glycogen. Lithium, by decreasing GSK-3 activity, promotes glycogen production. This has been shown repeatedly in cellular studies that found increased glycogen in liver, muscle and white blood cells in response to lithium (Rodriguez-Gil 1993, Furnsinn 1997, Choi 2000).

And while GSK-3 phosphorylates glycogen synthase, it also has multiple other targets as well. GSK-3 can phosphorylate Wnt signaling β-catenin, genetic transcription factors, RNA splicing factors, translation regulators, protein kinases, and cytoskeletal proteins. Due to the diversity of its targets, GSK-3 has been described as potentially regulating every aspect of cellular function (Sutherland 2011).

GSK-3 and Cancer

Of relevance to cancer are the effects of lithium on GSK-3, cellular signalling pathways, and resulting changes in oncogenes. The Wnt signalling pathway and the hedgehog signalling pathway are both relevant to cancer and regulated by GSK-3. As such, lithium can influence both pathways by decreasing GSK-3 activity.

The Wnt Signaling Pathway

GSK-3 phosphorylates Wnt signalling pathway β-catenin. Phosphorylation targets β-catenin for destruction and elimination. β-catenin activates target genes, including the oncogene MYC. When GSK-3 is inhibited by lithium, β-catenin levels increase and MYC is more strongly activated.

While MYC is considered an oncogene, it has both pro and anticarcinogenic activity. In lower levels, MYC can promote cancer. At higher levels it has anticancer activity, helping promote apoptosis of cancer cells (Harrington 2019). GSK-3 inhibitors, like lithium, increase levels of MYC, helping increase its anticarcinogenic effects to inhibit cancer cells (Kotliarova 2008).

The Hedgehog Signaling Pathway

Interestingly, research shows that lithium has opposite, suppressive effects on other oncogenes that are associated with the hedgehog signalling pathway. The hedgehog signalling pathway is involved in fetal development, cellular growth and cellular reproduction. It has been implicated in a number of cancers as well. In response to lithium, the pathway has a biphasic response. The key signalling protein glioma-associated oncogene homolog 1 (GLI1) initially increases, then decreases over time. With decreased GLI1, the hedgehog signalling pathway is inhibited overall. Decreased activation of the hedgehog pathway interrupts cell cycle progression, replication and induces apoptosis in cancer cells. These effects are tied to decreased activity of a number of different oncogenes influenced by the pathway (Ma 2019, Peng 2013).

Lithium and Cancer In-Vitro

Preclinical work exploring the effects of lithium on cancer cells shows distinct promise. Lithium has been shown to increase apoptosis in numerous cancer cell lines, including choroidal melanoma, pancreas, liver, non-small cell lung, leukemia, head and neck squamous cell and stomach cancers (Zhang 2021, Li 2015, Lan 2013, Zubcic 2020, Wu 2018). For treatment, most of the research focuses on lithium as an adjunctive therapy in combination with other cancer therapies to increase cancer cell death and improve overall survival.

Lithium and Cancer In-Vivo

Early work with glioblastoma has shown potential benefits. Glioblastomas are aggressive brain tumors with an average life expectancy of less than two years. Increased GSK-3 activity also correlates with worse outcomes. A drug cocktail, including lithium, was trialled in seven glioblastoma patients and demonstrated increased survival (Furuta 2017).

However, a separate clinical trial, exploring the effects of lithium on low-grade neuroendocrine tumors did not find benefits and enrollment was discontinued early with only 13 patients receiving treatment (Lubner 2011). Other clinical trials with lithium and cancer are ongoing. Hopefully, with more research, we can expand our understanding of lithium and its potential use in cancer treatment.

Conclusion

Lithium has potential benefits for modulating signaling pathways related to several oncogenes that are relevant to cancer. While research is ongoing, the use of lithium as an adjunctive therapy to improve cancer outcomes is still in the very early stages with a need for a better understanding of the dynamics and complexities of lithium’s actions. With more research, lithium may take its place alongside other therapies as an adjunctive treatment for cancer.

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