American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
January 10th, 2018
Second Wednesday of Every Month
5:30 PM Pacific / 6:30 PM Mountain / 7:30 PM Central / 8:30 PM Eastern

Clinical Pearl: Modified Citrus Pectin, Galectin-3 and Cancer: Regulating Tumorigenesis, Metastasis, Inflammation, Fibrosis, and Immune Response

Galectin-3
Galectins are a group of lectins characterized by a galactose-specific carbohydrate recognition domain (CRD) with affinity for beta-galactosides. Galectin-3 is a chimeric protein with an N-terminal domain necessary for homodimerization, a C-terminal domain with a single CRD, and a collagen-like sequence.

- COOH—terminal carbohydrate recognition domain
- Strong binding affinity for galacto-oligosaccharides
- Regulatory roles in cancer tumorigenesis and metastasis, inflammation, fibrosis, and immune response
- Expressed in the nucleus, cytoplasm, cell surface, and extracellular microenvironment (stroma)

Galectin-3 as a Biomarker

- Elevated levels of galectin-3 in the serum have been linked to the development of several different cancers as well as cancer metastasis
- Preclinical cancer models have shown galectin-3 to be associated with tumor cell transformation, invasive behavior, and metastasis.
- Galectin-3 has the potential to reflect changes in cancer status, as well as uncover other indicators of disease progression including inflammation, angiogenesis, and immunosuppression.
- Galectin 3 has potential clinical value as a prognostic oncology biomarker. Based on the preliminary data, the galectin-3 assay could become a contributing tool to help clinicians monitor treatment response and tumor progression, but further clinical studies evaluating galectin-3 levels and cancer progression are warranted. [Eliaz & McKee, 2014]

Galectin-3 and Inflammation

- Biologically active marker for high risk
- Elevations of Galectin-3 levels correlate with multiple elevated risk factors and predict outcome
- Galectin-3 is a is an active agent with multiple effects
- Promotes:
    - Metastasis
    - Inflammation
    - Fibrosis
- Elevation associated with:
    - Cancer
    - Cardiovascular Disease (CHF, endothelial dx)
    - Diabetes
    - Chronic Hepatitis
    - Kidney Disease
    - Inflammation and Fibrosis

Galectin-3 and Cancer

- Tumor Growth Factors binds to EGFR & VEGF
- Activates Oncogene Bcl2 in cytoplasm (anti-apoptotic)
- Promotes Metastasis and Angiogenesis (endothelial signaling)
- Aggregation of Cancer Cells (cell adhesion)

Galectin-3 and Immune Evasion:
Promotes Tumor Cell Immune Escape:

- Promotes Apoptosis of T Cells
- Tumor cells secrete galectin-3 and induce apoptosis of T Cells,
- Promotes Immune Escape mechanism during tumor progression through induction of apoptosis of cancer-infiltrating T-cells [De Oliveira et al, 2010] [Funasaka, Raz & Nangia-Makker, 2014]
- Reduce Cell Adhesion in the extracellular matrix (ECM)-Stromal Remodeling
- Modifies Collagen
- Promotes Metastasis [De Oliveira et al, 2010]

Galectin-3 as a Biomarker: Testing Galectin-3 Levels

- Non-fasting blood test for Galectin-3 (recommend LabCorp)
- Monitor every 3-6 months in patients with active disease (20% population will have changes within this time interval); helpful to get baseline from the start of working with patient
- Elevations reflect increased inflammation, fibrosis and hyperviscosity
- Approved as a CVD risk factor assessment
- Both prognostic and diagnostic

Levels
> 17.8 ng/ml: High risk of mortality
Goals
Hx of CA or CVD: < 12.0 ng/ml
No Evidence of Disease: < 14.0 ng/ml

Elevations may reflect other disease inflammatory disease processes:

- Diabetes
- Heart Failure & Endothelial Disease
- Hepatitis
- Renal Failure

Modified Citrus Pectin - Lowers Galectin-3

What is Modified Citrus Pectin? From inner peel of citrus fruits enzymatically modified pectin cleaves the molecule exposes binding sites for galectin-3 very small size enhances absorption

Modified Citrus Pectin (MCP) – Pectins are a family of soluble fibers naturally occurring in various plant cell walls, along with cellulose, and are especially abundant in the skins of apples and citrus fruits. They are viscous, gel-forming (by absorbing water), and contain chains of various polysaccharides.

Naturally occurring pectins are not digested by human digestive enzymes, but are used as food by GI bacteria, which ferments them into short chain fatty acids, which in turn benefits the colonic cells. They have been shown to help prevent adherence of pathogenic bacteria, stimulate peristalsis, and soften the stool (due to water absorbing capacity).

Modified citrus pectin (MCP) is the result of processing naturally occurring pectins in order to decrease the size of their polysaccharide chains.

Modified Citrus Pectin & Cancer Cells

- A complex water soluble indigestible polysaccharide obtained from the peel and pulp of citrus fruits
- Modified by means of high pH and temperature treatment, to affect numerous rate-limiting steps in cancer metastasis

Galectin-3 & Modified Citrus Pectin:

- Inhibits Tumor Cell Adhesion, Tumor Growth, Metastasis and Angiogenesis
- Increases apoptotic responses of tumor cells to chemotherapy
- Inhibits galectin-3 anti-apoptotic function
- Chelating agent for heavy metals promoting detoxification

MCP Binds to Galectin-3 molecules

- Blocks tumor cell aggregation
- Blocks docking of cancer cells
- Blocks interactions with endothelium necessary for angiogenesis (surgery)

MCP induces activation of human blood lymphocyte subsets T, B and NK-cells [Ramachandran et all, 2011]

MCP Dosing [Dr. Isaac Eliaz M.D.]
NO ACTIVE DISEASE
- < 12-14.0 ng/ml 5 g (1 level tsp) daily (maintenance dose)
- 12-14.0 -17.8 ng/ml 10g-15g daily (2-3 tsp)
- >17.8 ng/ml 15g-25g daily
- < 17.8 ng/ml 15 grams MCP daily remission
- > 17.8 ng/ml 20-25 grams MCP daily active disease
    - continue for 3 years at this dose
    - after 3 years follow maintenance dose schedule

Tips:
- Best taken as a powder mixed with water or juice; dissolves more quickly in warm water
- Soluble Fiber: causes bloating and diarrhea in some patients
- Chelating agent: best taken away from other nutrients (food and supplements) by 30 minutes; helpful in detoxification with binding metals
- High in sodium (be mindful with hypertensive patients)

Ocimum spp. BASIL (Labiatiae)
Ocimum gratissimum (African Basil, Brazilian Basil)
Ocimum sanctum (Tulsi Indian Holy Basil)

- Inhibits Galectin-3 cleavage
- Prevents Angiogenesis.
- Inhibits Matrix Metalloproteinases MMP (enzymes that eat into the extracellular matrix that allow tumor cells to invade)

SUMMARY
Galectin-3 has been shown to influence many significant biological processes linked to cancer development and progression, including:
- cell adhesion
- proliferation
- differentiation
- mRNA splicing
- cell-cycle progression
- immune system evasion
- inflammation
- angiogenesis
- apoptosis

Modified Citrus Pectin
- Binds to Galectin-3 C-Terminal Carbohydrate Binding Domain
- Changes the Conformation of G-3
- Inhibits its multiple actions by preventing G-3 binding with its ligands

Recent Article Highlight

Cancer-related cognitive impairment in adult cancer survivors: A review of the literature Victoria J Bray,1,2 Haryana M Dhillon,3 Janette L Vardy4 Cancer Forum Volume 41 Number 1 March 2017

- Several main categories of causes:
  - Neurotoxicity of chemotherapy treatments,
  - Toxicity of environmental impacts,
  - Direct toxicity of tumor cells;
  - Immune dysregulation combined with high levels of inflammatory cytokines that can cross the blood-brain barrier, disrupting and damaging neurons
  - Genetics - patients who are more susceptible
- Cancer itself produces elevated cytokines and matrix metalloproteinases that damage the blood brain barrier leading to neurotoxicity, neuroinflammation and cognitive impairment.
- Cognitive impairment affects 70% of patients even before treatment is initiated
- Cognitive impairment primarily damages the hippocampus (memory), both structural and functional changes occur as well as the pre-frontal cortex (cognitive and executive functions)

RESOURCE: Letter to a stage IV patient who wants to decrease the dose of her supplements

Attached please find a copy of a letter written to patient to help them to understand the rationale for complying with therapeutic dosing and to manage taking a large number of supplements daily for the long term to achieve outlier outcomes.

Questions & Answers

Kamron Keep: **60 yo patient with stage 1 breast cancer who is taking 2 tablets of an adaptogen and 2 tablets of an anti-inflammatory in the morning. These tablets cause severe nausea and can induce vomiting. How do you work with people who have a desire to be compliant with supplements but can't take them?**

- Something else is likely going on with this patient (such as anxiety, tightening of diaphragm). May not be the pills themselves that are the problem, rather aggravating a physiologic or emotional trigger. (Pt has a hx of gastralgia since childhood)
- Adaptogens are not toxic and are not typically allergenic. Anti-inflammatory herbs do not typically cause these symptoms, although every pt is unique and may have a reaction to any substance
- Recommend: Stop the supplements and look for the root cause
- Thorough upper gastrointestinal history and exam (i.e pt has a. history of esophagitis, GERD or other regurgitation issues in response to foods); consider achlorhydria
- Open up the pills and mix them into something more food-like (nut butter, yogurt, shake) to make them more dilute when they enter her stomach
- Ensure the pills are taken with food
- Try different forms of nutrients that may be easier to digest (powders, tinctures, etc.)
- Consider support for rebuilding the stomach lining
- For more sensitive gastrointestinal tracts, consider slowing down how quickly and how many supplements taken at one time; have patient put daily supplements in bowl to take at different intervals throughout the day

Kamron Keep: **60 yo patient with stage 1 breast cancer on Arimidex. Good diet, exercise, acupuncture but is still experiencing joint pain and mood changes. Aromatase inhibitor has been switched to Exemestane. Is there anything that can be done to support side effects of aromatase inhibitors?**

- Aromatase inhibitors - inhibit the enzyme aromatase which converts androgens to estrogens in the tissue. By lowering tissue estrogen, the number of estrogen receptors and the growth signal from estrogen is decreased in estrogen receptor positive cancers;
- Estrogen receptors are present in tendons and ligaments contributing to joint pain and decreased ROM
- Recommendations:

    - Optimize vitamin D_3 (50-80 ng/nl, goal for 75 ng/ml)
    - Incorporate more stretching to increase and maintain full ROM and flexibility
    - Consume an inflammatory diet
    - Stay well hydrated to keep connective tissue and cartilage more plump
    - Anti-inflammatory nutrients at therapeutic doses (omega 3 fatty acids, curcumin)
    - Acupuncture
- To reduce post-menopausal weight gain engage in low impact, high intensity interval training (20 minutes total daily) over endurance cardiovascular training to burn more fat and build more muscle tissue

Judy Pruzinsky: **You talked about having RBC levels checked for magnesium. Is Genova and Doctor's Data the only labs to order such? Could a patient order that through any of the conventional labs? Also would you please give us a list of other such minerals (ind, D, iron) etc that we should not be testing through conventional labs?**

- RBC magnesium can be ordered from all medical clinical labs. They are not a specialty functional medicine test. Magnesium is primarily found in intracellular and mitochondrial space.
- Serum levels don't reflect intracellular levels
- Magnesium becomes depleted by surgery, chemotherapy, and stress
- Platinum chemotherapy agents cause nephron to leak magnesium

Judy Pruzinsky: **Do you use Scutellaria Baicalensis and Baicalin differently?**

- Scutellaria baicalensis is one of the most widely used botanicals in Traditional and Modern Chinese Medicine in the cancer setting
- Multi-tasker: has anti-inflammatory properties; inhibits proliferation
- Baicalin is a polyphenol that is a phytochemical in the Scutellaria baicalensis plant; it is not available as an isolate to use pharmacologically
- Need to use the whole plant as an extract
- Panaxea International (Daniel Weber) - plant isolate provider for some isolates, but not for baicalin

Judy Pruzinsky: **What is your opinion of 5-fu cream for basal cell carcinoma?**

- 5-Fluorouracil - chemotherapy agent, an antimetabolite, anti-mitotic; inhibits enzyme thymidylate synthetase; prevents tumor cells from completing mitosis and inhibits DNA replication
- Topical local dose of 5-fu in cream is used to treat top layer of basal or squamous cell carcinoma; topical 5-fu cream is preferable over systemic dose
- Standard of care is to use at intervals (2 weeks on and 2 weeks off)
- Acupuncture points distal and proximal to treated area may improve outcome, decrease inflammation, promote immunity and repair consider skin points LI4 SP10, LI11
- Consider new immunotherapy topical drugs for basal and squamous cell carcinoma are less toxic

Judy Pruzinsky: **I remember you talking about DNA damage and how it could be 10-20 years before you get a diagnosis though the damage has been occurring for that long. How long does it take to repair? I'm thinking of a potential new cancer diagnosis of a long term patient. Pt has maintained a good diet, lots of veggies, some good protein, healthy fats, done bi-annual liver detoxes for over ten years and have cleared up a lot of metabolic syndrome originally from a high carbohydrate diet. Pt isn't terribly stressed and gets enough sleep. Is there anyway to get a sense of when you might think DNA damage has actually been reversed?**

- When the DNA in a cell becomes damaged the normal process of apoptosis or autophagy is initiated and the aberrant cell is destroyed if the DNA is not repaired. This is the normal process.
- When DNA repair does not occur some of these cells become malignant. This cannot be repaired.
- In the presence of malignant cells the first therapeutic goal is to contain the aberrant cells or eradicate them and reduce tumor burden
- To support normal protection of the genome - support p53 function.
- Astragalus is one of many herbs that support healthy p53 function (astragalus is also an immune modulator)

Resources

Bray, V. J., Dhillon, H. M., & Vardy, J. L. (2017, March). Cancer-related cognitive impairment in adult cancer survivors: A review of the literature. In Cancer Forum (Vol. 41, No. 1, p. 46). The Cancer Council Australia.

De Boer, R. A., Van Veldhuisen, D. J., Gansevoort, R. T., Muller Kobold, A. C., Van Gilst, W. H., Hillege, H. L., ... & van Der Harst, P. (2012). The fibrosis marker galectin-3 and outcome in the general population. Journal of internal medicine, 272(1), 55-64.

De Oliveira, J. T., De Matos, A. J., Gomes, J., Vilanova, M., Hespanhol, V., Manninen, A., ... & Bernardes, E. S. (2010). Coordinated expression of galectin-3 and galectin-3-binding sites in malignant mammary tumors: implications for tumor metastasis. Glycobiology, 20(11), 1341-1352.

Eliaz, I., McKee, D. L. (2014, September). Galectin-3 as an Oncological Biomarker: A review of its possible role in cancer treatment response and disease progression. Natural Medicine Journal (Vol. 6 Issue 9)

Funasaka, T., Raz, A., & Nangia-Makker, P. (2014). Galectin-3 in angiogenesis and metastasis. Glycobiology, 24(10), 886-891.

Pricci, F., Leto, G., Amadio, L., Iacobini, C., Romeo, G., Cordone, S., ... & Pugliese, G. (2000). Role of galectin-3 as a receptor for advanced glycosylation end products. Kidney International, 58, S31-S39.

Ramachandran, C., Wilk, B. J., Hotchkiss, A., Chau, H., Eliaz, I., & Melnick, S. J. (2011). Activation of human T-helper/inducer cell, T-cytotoxic cell, B-cell, and natural killer (NK)-cells and induction of natural killer cell activity against K562 chronic myeloid leukemia cells with modified citrus pectin. BMC complementary and alternative medicine, 11(1), 59.

Modified Citrus Pectin
Galectin-3 and Cancer

Regulating Tumorigenesis, Metastasis, Inflammation, Fibrosis, and Immune Response

Dr. Nalini Chilkov, Founder

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Galectin 3 and Cancer

- Elevated levels of galectin-3 in the serum have been linked to the development of several different cancers as well as cancer metastasis
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Galectin 3 as an Oncologic Biomarker

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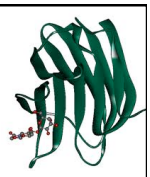
Galectin-3



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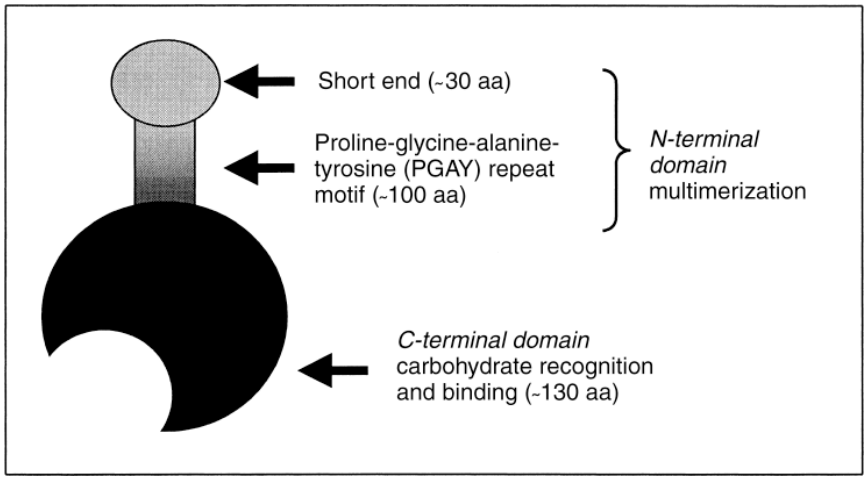
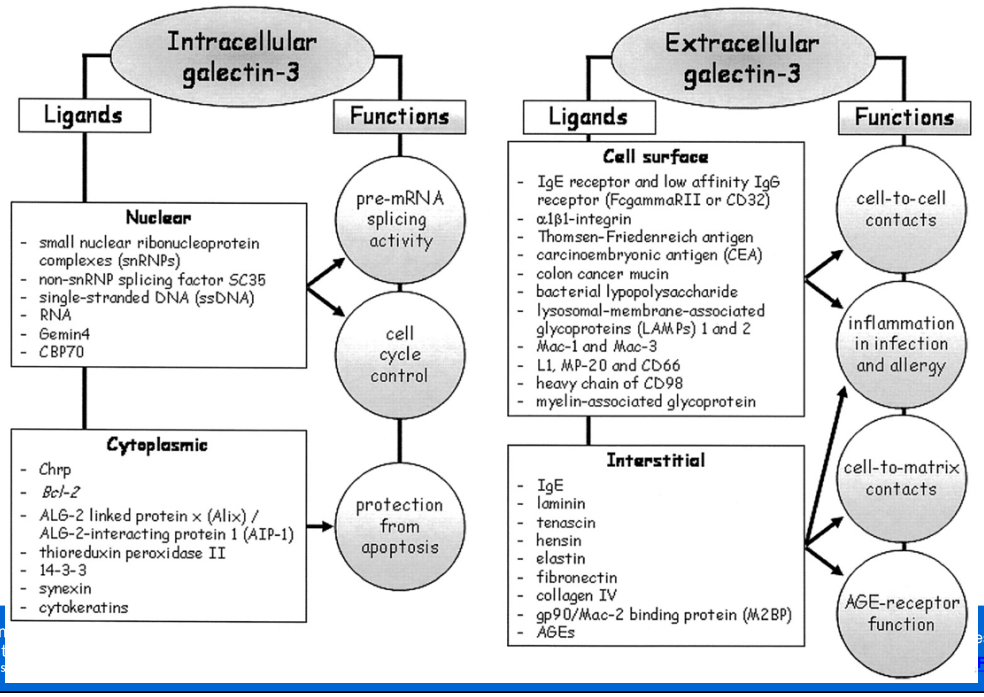
- COOH—terminal carbohydrate recognition domain
- Strong binding affinity for galacto-oligosaccharides
- Regulatory roles in cancer tumorigenisis and metastasis, inflammation, fibrosis, and immune response
- Expressed in the nucleus, cytoplasm, cell surface, and extracellular microenvironment (stroma)

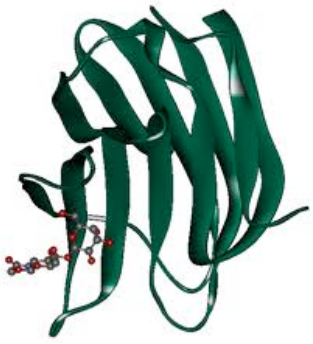
Galectin-3

Role of galectin-3 as a receptor for advanced glycosylation end products
Flavia Pricci, Gaetano Leto, Lorena Amadio, Carla Iacobini, Giulio Romeo, Samantha Cordone, Roberto Gradini, Paola Barsotti, Fu-Tong Liu, Umberto Di Mario andGiuseppe Pugliese





Galectin-3 and Inflammation



Promotes

Metastasis

Inflammation

Fibrosis

Galectin-3 Elevation

Cancer
Cardiovascular Disease (CHF, endothelial dx)
Diabetes
Chronic Hepatitis
Kidney Disease
Inflammation & Fibrosis

Galectin-3 and Cancer

Tumor Growth Factors binds to EGFR & VEGF
Activates Oncogene Bcl2 in cytoplasm (anti-apoptotic)
Promotes Metastasis & Angiogenesis (endothelial signaling)
Aggregation of Cancer Cells (cell adhesion)

Galectin-3 and Immune Evasion

Promote Tumor Cell Immune Escape:

- Promotes Apoptosis of T Cells
- Tumor cells secrete galectin-3 and induce apoptosis of T Cells,
- Promotes Immune Escape mechanism during tumor progression through induction of apoptosis of cancer-infiltrating T-cells

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Galectin-3 and Immune Evasion

Galectin-3

- Induces T-cell apoptosis
- Blocks NK cell functions
- Enables the tumor to escape from the host immune system and to develop

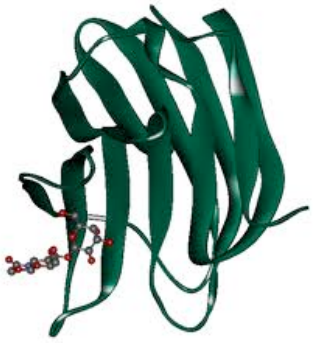
Glycobiology. 2014 Oct; 24(10): 886–891.
Published online 2014 Aug 18. doi: 10.1093/glycob/cwu086

Galectin-3 and Cancer

Reduce Cell Adhesion in the Extra Cell Matrix (ECM)-Stromal Remodeling

Modifies Collagen

Promotes Metastasis



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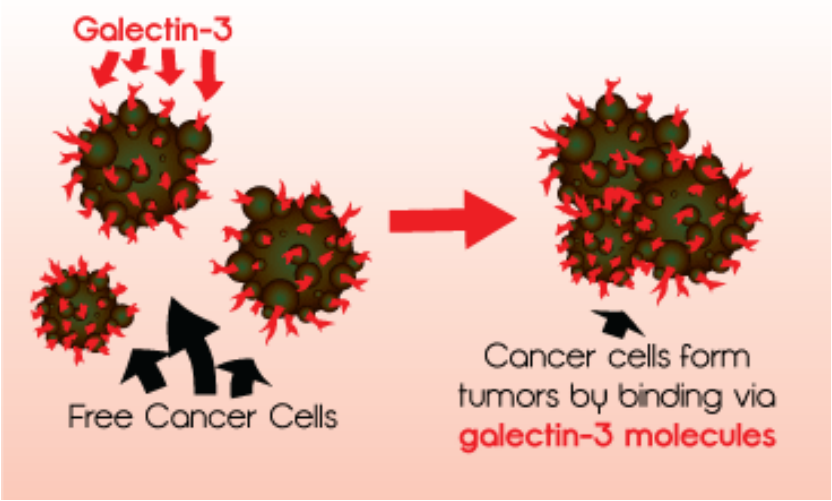
Tumor Cell Aggregation



Galectin-3 in angiogenesis and metastasis

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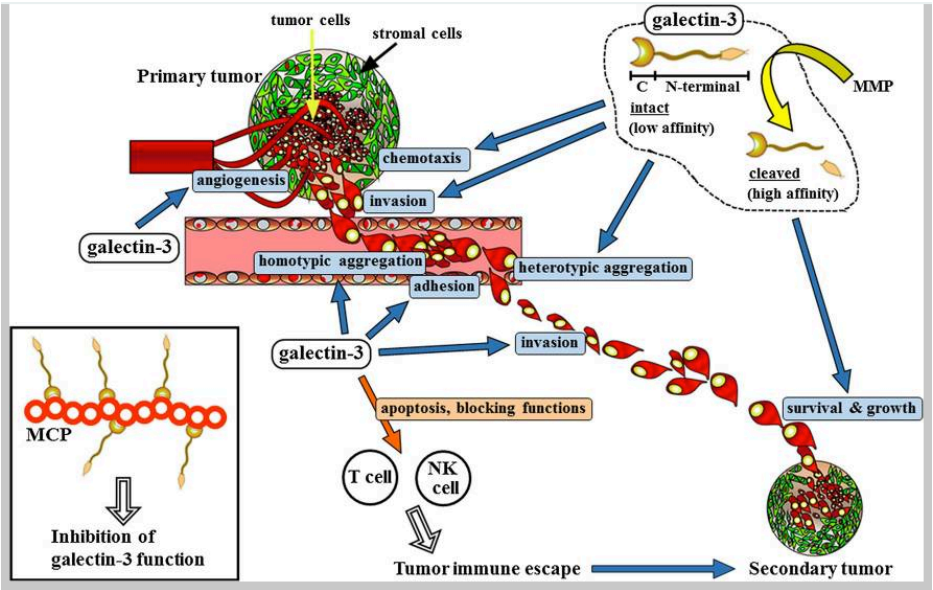


GALECTIN 3 AS A BIOMARKER: TESTING

Testing Galectin-3 Levels

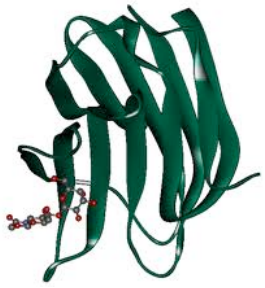
Non-fasting blood test for Galectin-3

Monitor every 3 months in patients with active disease (20% population will have changes within this time interval)

Elevations reflect increased inflammation, fibrosis and hyperviscosity

Approved as a CVD risk factor assessment

Both prognostic and diagnostic



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Galectin-3 Levels

Levels

> 17.8 ng/ml: High risk of mortality

Goals

Hx of CA or CVD:	< 12.0 ng/ml
No Evidence of Disease:	< 14.0 ng/ml

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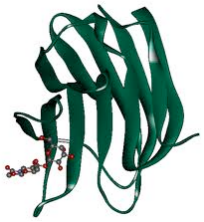
Testing Galectin-3 Levels



Elevations may reflect other disease inflammatory disease processes

- Diabetes
- Heart Failure & Endothelial Disease
- Hepatitis
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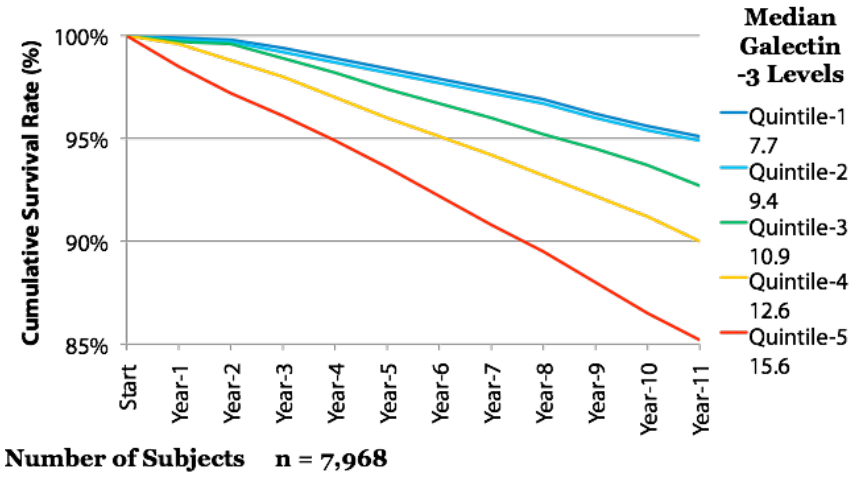
PREVEND TRIAL

Galetctin-3 Levels and All Cause Mortality

The Prevention of Renal and Vascular End-stage Disease (PREVEND) Veldhuisen DJ, *et al*. The fibrosis marker galectin-3 and outcome in the general population. de Boer RA, van J Intern Med. 2012 doi: 10.1111/j. 1365-2796.2011.02476.x.



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MODIFIED CITRUS PECTIN

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Modified Citrus Pectin Lowers Galectin-3

What is Modified Citrus Pectin?

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enzymatically modified pectin

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very small size enhances absorption

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Modified by means of high pH and temperature treatment, to affect numerous rate-limiting steps in cancer metastasis

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MCP induces activation of human blood lymphocyte subsets T, B and NK-cells.

Ramachandran et al. BMC Complementary and Alternative Medicine 2011, 11:59 http://www.biomedcentral.com/1472-6882/11/59

Activation of Human T-Helper/Inducer Cell, T-Cytotoxic Cell, B-Cell, and Natural Killer (NK)- Cells and induction of Natural Killer Cell Activity against K562 Chronic Myeloid Leukemia Cells with Modified Citrus Pectin

Cheppail Ramachandran1*, Barry J Wilk2, Arland Hotchkiss3,4, Hoa Chau3,3, Isaac Eliaz2 and Steven J Melnick1,5

in vitro

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MODIFIED CITRUS PECTIN

Dosing

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MCP Dosing
Dr. Isaac Eliaz M.D.

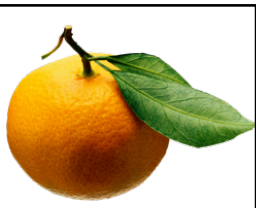
NO ACTIVE DISEASE

< 12-14.0 ng/ml 5 g daily

12-14.0 -17.8 ng/ml 10g-15g daily

>17.8 ng/ml 15g-25g daily

MCP Dosing
Dr. Isaac Eliaz M.D.



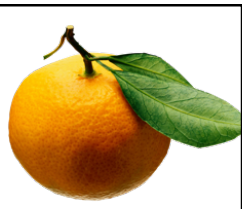
< 17.8 ng/ml 15 grams MCP daily remission

> 17.8 ng/ml 20-25 grams MCP daily active disease

continue for 3 years at this dose

after 3 years follow maintenance dose schedule

Modified Citrus Pectin



Best taken as a powder mixed with water or juice

Soluble Fiber: causes bloating and diarrhea in some patients

Chelating agent: best taken away from other nutrients

Ocimum spp. BASIL (Labiatiae)

Ocimum gratissimum
African Basil, Brazilian Basil
Ocimum sanctum
Tulsi Indian Holy Basil

Inhibits Galectin-3 cleavage
Prevents Angiogenesis.
Inhibits Matrix Metalloproteinases. MMP

SUMMARY

Modified Citrus Pectin (MCP) and Galectin-3

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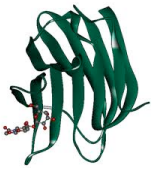
SUMMARY

Galectin-3 has been shown to influence many significant biological processes linked to **cancer development and progress**ion, including

- cell adhesion
- proliferation
- differentiation
- mRNA splicing
- cell-cycle progression
- immune system evasion
- inflammation
- angiogenesis
- apoptosis



Modified Citrus Pectin

- Binds to Galectin-3 C-Terminal Carbohydrate Binding Domain
- Changes the Conformation of G-3
- Inhibits its multiple actions by preventing G-3 binding with its ligands

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Clinician Resource: A Letter to a Stage IV Colorectal Cancer Patient with Liver Metastases
Patient and husband are medical doctors

Dear <Patient>,

It is my honor to be a resource and a support to you.
I understand that as medical doctors the idea of taking handfuls of pills is not within your usual framework. You consulted me as a Stage IV patient with liver metastases.

I see my role as one of supporting you in living with cancer as a chronic illness and to create a tumor microenvironment that is not hospitable to, but rather inhibitive of,
progression and proliferation.

Towards that end, I have provided you with recommendations for nutraceuticals, botanicals, phytochemicals and functional foods as well as diet and lifestyle interventions.

As a Stage IV patient, it is imperative that you continue to take control of the tumor microenvironment…take control over the remaining resistant cells and the tumor stem cells so that you remain with microscopic not macroscopic progressive disease.

Unlike pharmaceuticals, molecules from nature have significant mass and they cannot be shrunk into a few small compact pills. A molecule of magnesium or curcumin takes up a certain amount of space.

We must achieve therapeutic dose ranges in order to exert control over disease progression.

Your husband states:
She is having very difficult time taking 35 to 40 supplements caps per your protocol.
Compliance is becoming an issue.

My question to you is: WHAT IS MORE DIFFICULT…to have active progressive terminal lethal disease, to lose your liver function, to develop obstructive disease, or to take a few handfuls of pills every day?

There is no EASY path as a Stage IV patient…so you will always have something DIFFICULT to face every day. I would rather that the DIFFICULT task is taking your pills and not liver failure, ascites, obstruction, cachexia, etc…

I cannot recommend that you decrease your doses.

It is my experience that the most highly compliant and engaged patients are the ones that remain the outliers and outside the bell curve of expected prognosis. If you are halfway compliant or halfway engaged, you cannot expect those outlier results.

I will tell you personally that I myself take about the same number of supplements I have recommended to you and I have no health issues…rather...I have HEALTH at the age of 65 with no active disease or degenerative issues.

It takes significant work and effort to CAUSE HEALTH, to alter gene expression and function. It does not happen without effort. It takes even more to oppose the virulence of tumor cells, especially metastatic cells. It is work. It not easy. In my opinion, it is very much worth it. But those are my values and my personal choices. It is a very personal choice and decision how you care for yourself and what you choose or do not choose to do to take control of your cancer.

It is a significant shift in paradigm to change from a disease and pathology-focused model to a health focused model. This is especially challenging for medical doctors (generally the least compliant patients!!!!! as I am sure you know!).

You can put the supplements that do not taste bitter into your shake. You can have half a shake in the am and half a shake in the pm and mix in your supplements into the shake to have less pills to swallow. I have children who take all of their supplements at the prescribed dosage…surely you can do this if you are so motivated.

However, you do have to spread out your dosing over the day so that we maintain more stable blood levels over 24 hours each daily cycle and you do not simply excrete all of the good nutrients and phytochemicals into your urine. Do not throw all of your pills into the shake. You will then be nauseous and have expensive urine. If you take a few every hour or so, it is often easier to ingest ALL of the pills by the end of each day.

We are exerting epigenetic effects, signaling gene expression…this is why it matters what you eat and that you continue to ingest all of those signaling molecules in your supplements. Integrative cancer care is about a handful of supplements several times each day. You cannot achieve control at lower doses. There is no way around it.

As you know…this is a marathon. It is my wish that you enjoy a good quality of life and that your disease stabilizes and does not progress.

If you would like to discuss, let me know and we can schedule a chat so that I can give you a pep talk or a kick in the gluts or whatever will inspire and encourage and re-engage you in your own self-care and well being. It is useful to reframe your relationship to pills…these are your friends, your allies, your supporters…not pharmaceuticals with adverse effects.

I hope this has addressed your question…if not, do let me know. Keep going!!!!

Warmest regards,
Dr. NC

CANCER FORUM

Cancer-related cognitive impairment in adult cancer survivors: A review of the literature

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Abstract

Cognitive symptoms are commonly reported by cancer patients. Qualitative research has shown that up to 70% of cancer patients experience symptoms of varying magnitude. Several studies have demonstrated only a weak association between self-reported cognitive symptoms and objective cognitive impairment on formal neuropsychological testing. Conversely, cognitive symptoms have been consistently shown to be associated with other patient reported outcomes, including anxiety/depression, fatigue and quality of life. Cognitive symptoms can have a major impact on individual's personal and professional lives. Initially, the terms 'chemo brain' or 'chemo fog' were used, as it was believed that cognitive changes were a direct result of chemotherapy treatment. It is now clear that the aetiology of cognitive change is more complex, with several studies showing presence of impairment in patients with a new cancer diagnosis, prior to commencement of systemic therapy. The exact aetiology of cognitive impairment is unknown, but it is likely multifactorial. There has been interest in the evaluation of pharmacological and cognitive training strategies for the management of cognitive impairment in cancer patients. Most recently, a large randomised study of a home-based, online cognitive rehabilitation program showed improvements in cognitive symptoms and patient reported outcomes. However, there remains no universally accepted treatment.

In the last two decades, there has been a growing body of research focused on the evaluation of cognitive symptoms in cancer patients. The incident rate varies, but studies in breast cancer patients suggest that up to 70% of patients receiving chemotherapy will self-report some cognitive impairment.[1] The cognitive domains most commonly affected are memory, concentration, information processing speed and executive function.[2,3]

For some patients, their cognitive impairment may be transient, but for a subgroup, these symptoms can be long-standing and have a major impact on quality of life and function.[4,5] Cognition has been recognised as an important component of cancer survivorship, particularly with the improvement in cancer treatments, leading to increased survival times.[6] It is therefore imperative that we better understand these symptoms and how best to treat or prevent them, to ensure that cancer patients are not only living, but are 'living well' after their cancer diagnosis and treatment.

History of early research

Initial reports of cognitive changes associated with chemotherapy date back to 1980, in a small study of ten cancer patients.[7] A study by Wieneke et al in 1995 in early stage breast cancer patients, <55 years of age, who had completed adjuvant chemotherapy, found that 75% of patients met the investigators' definition of moderate cognitive impairment on neuropsychological testing. The impairment was not associated with depression, type of chemotherapy, or time since treatment, but there was a positive association with the number of cycles of chemotherapy.[8]

In 1998, Van Dam et al published a cross-sectional study assessing the prevalence of cognitive deficits in high-risk breast cancer patients, <55 years of age, randomised to high (n=34) or standard-dose (n=36) adjuvant chemotherapy, followed by hormonal therapy. They included a

control group comprising patients with stage I breast cancer who had not received systemic therapy (n=34). Cognitive impairment on formal neuropsychological testing was seen in 32% undergoing high-dose treatment and 17% receiving standard-dose treatment compared to 9% of controls (*P*=.043). Patients receiving high-dose chemotherapy reported significantly more symptoms than controls (*P*=.014). However, no association was seen between cognitive symptoms and neuropsychological testing (Spearman correlation 0.03).[9]

A series of cross-sectional studies followed; the majority confirmed findings of early studies, although reassuringly the rates of cognitive impairment post-chemotherapy were lower than that first reported by Wieneke et al.[10-13] However, there remains wide variability in the frequency of cognitive impairment across studies. There are multiple reasons for this including diverse patient populations and cancer treatments, time from treatment, instruments used to assess cognition, lack of a standardised definition of what constitutes cognitive impairment and methodological issues in earlier studies.[14]

The lack of association between self-reported cognitive symptoms and objective cognitive function on neuropsychological testing emerged during these early studies. It was noted that many participants reported cognitive symptoms, but were scoring within normal range on neuropsychological tests. Several factors may contribute including: 1) patients' functioning above the normal range of cognitive performance prior to their cancer diagnosis or systemic treatment, and while their cognition may have declined, it remained within normal range, albeit at a lower level; 2) lack of 'ecological validity' of the neuropsychological testing, i.e. the artificial conditions in which testing is performed is not representative of real life situations in which individuals are most likely to experience cognitive symptoms; 3) the neuropsychological tests are not sensitive enough to detect the subtle cognitive changes typically seen in cancer patients; and 4) self-reported and objective measures of cognitive function are measuring different constructs.

Recommendations for future research

There were a number of methodological limitations with earlier studies. Most used cross-sectional designs, with small sample sizes, and were restricted to young women with breast cancer. Little was known about cognitive function in men or in patients with tumour types other than breast cancer.

The International Cognition and Cancer Task Force made the following recommendations for future studies: 1) longitudinal study design; 2) inclusion of different primary tumour types with no gender restrictions; 3) incorporation of baseline assessment of cognition function prior to initiation of chemotherapy; 4) inclusion of a control group; 5) evaluation of potential underlying mechanisms e.g. imaging, blood parameters; 6) use of neuropsychological tests sensitive to the types of cognitive change reported in cancer studies; and 7) development and validation of self-reported questionnaires specific to cancer patients.[15-17]

Newer generation of studies

Longitudinal studies

A series of longitudinal studies have confirmed the findings of earlier cross-sectional studies demonstrating that a subgroup of patients experience cognitive issues following administration of chemotherapy.[4,18,19] Hermelink et al completed a longitudinal study in 101 breast cancer patients reviewing cognitive function before and immediately prior to completion of neoadjuvant chemotherapy. At baseline, 31% of patients scored within the lower 5% range on neuropsychological testing. On follow-up, deterioration in performance was seen in 27%, with improvement in 28%. There was a significant increase in self-reported cognitive symptoms at the follow-up evaluation.[19]

Kopplemans et al performed a case-cohort study comparing cognitive performance of 196 breast cancers patients who had received chemotherapy (mean of 21 years following diagnosis), with 1509 healthy females. They found that women who had received chemotherapy performed worse on all neuropsychological tests compared to controls. Interestingly, patients experienced less symptoms of depression than controls (*P*=.001), but had more self-reported cognitive symptoms.[4]

Of note, there have been a small number of studies that have not found impairment associated with cancer treatment.[20-23] Jenkins et al performed a prospective longitudinal study evaluating neuropsychological performance in 128 women diagnosed with early stage breast cancer (chemotherapy n=85; endocrine therapy +/- radiotherapy n=43) and healthy controls (n=49). There were no significant differences in cognition between the groups on assessments post-chemotherapy or 12 months later, with no associations between objective neuropsychological testing and self-reported cognitive function, quality of life and distress. However, the latter were significantly associated with one another.[20]

Debess et al examined self-reported and objective cognitive function in 120 women who had received treatment for early breast cancer (chemotherapy n=75, hormone therapy n=26, no adjuvant treatment n=19) in comparison to 208 aged-matched women with no history of malignancy. There were no significant differences in neuropsychological testing between the three patient groups and the healthy controls at baseline or post-chemotherapy. All patients improved on most measures of self-reported cognitive function and psychological distress at six months and patients who did not receive adjuvant treatment, reached a level similar to controls at six months.[21]

Overall, the majority of cognitive studies in women with breast cancer show that approximately 30% have cognitive impairment on objective testing which is frequently sustained up to at least 10 years, with one study suggesting impairment still at 20 years.[4] Most studies found a lack of association between neuropsychological test results and cognitive symptoms.

Studies conducted in non-breast cancer populations

More recent studies have evaluated cognitive function in non-breast cancer populations with a particular focus on colorectal, testicular and gynaecological malignancies.[24-32] These studies confirm that cognitive changes occur in a number of other tumour types, and in both men and women. This is important as it was initially postulated that the cognitive changes in women may be related to abrupt changes in the hormonal milieu induced by chemotherapy, leading to an early menopause.

The largest study reported by Vardy et al was a longitudinal study in 289 patients with localised colorectal cancer: 173 received adjuvant chemotherapy, and 116 did not. There were two additional groups: 72 patients with recurrent/metastatic colorectal cancer, and 73 healthy controls. The rates of cognitive impairment were significantly higher in localised colorectal patients than healthy controls at baseline, six and 12 months (43%, 39% and 46% compared to 15%, 6% and 13%). There was no significant effect from chemotherapy. Self-reported cognitive impairment was more common at six months in participants who received chemotherapy (32%) than those who did not (16%; *P*=.007) or in healthy controls (12.5%), with no significant differences between groups at 12 months.[29]

There is a growing body of work highlighting the presence of cognitive changes in cancer patients before they have commenced systemic treatment.[33-35] Ahles et al compared neuropsychological function of breast cancer patients (n=132) with invasive cancer and non-invasive cancer following surgery, but prior to any adjuvant treatment, with matched healthy controls (n=45). They found 22% of patients with breast cancer had lower than expected cognitive performance, compared to 4% of healthy controls (*P*=.002).[34] As described previously, Vardy et al's study in patients with localised colorectal cancer found more objective cognitive impairment in patients than healthy controls at baseline (45 vs 15%, P<0.001).[33]

Potential explanations for the presence of cognitive changes prior to initiation of systemic treatment include the presence of a common risk factor for both the development of cancer and cognitive changes. Additionally, there may be some intrinsic property of the cancer driving cognitive changes.

Influence of age and comorbidities on cognition

Age is a known risk factor for cognitive decline in the general population. This is particularly relevant in today's oncological practice, with an ageing population and an increase in older patients receiving chemotherapy.

Hurria et al studied an older population in a longitudinal study enrolling 45 patients with early stage breast cancer with a mean age of 70 years. Half (51%) reported a decline in memory from baseline to six months post-chemotherapy. Patients who reported a below average memory prior to chemotherapy were more likely to report further memory deterioration after chemotherapy (63%) compared to those reporting their memory to be average or better prior to chemotherapy (27%).[36]

Mandelblatt et al evaluated whether older patients with breast cancer have cognitive impairment prior to systemic therapy.[37] They recruited 164 newly diagnosed early stage breast cancer patients, ≥60 years, together with 182 community controls. The age range was 60-94 years. They found that the breast cancer patients and controls had similar neuropsychological scores. However, those patients with stage II–III cancers had lower executive function compared to those with stage 0–I disease (*P*=.05), with significantly higher impairment among older, non-white, less educated women and those with greater comorbidity.[37]

Ahles et al evaluated age and baseline cognitive reserve in 132 patients diagnosed with early stage breast cancer prior to adjuvant therapy (chemotherapy n=60, no chemotherapy n=72), and 45 healthy controls. A three-way interaction among treatment group, age and baseline cognitive reserve (*P*<.001) revealed older patients with lower baseline cognitive reserve who received chemotherapy had significantly lower cognitive performance compared to the other two groups (P<.003).[38]

These results highlight the need for collection of data relating to comorbidities and pre-morbid function in future cognitive studies. While these data may not be practice changing for the oncology community, it should be carefully considered when reviewing patients with multiple comorbidities and borderline functional status, prior to proceeding with adjuvant therapy that may confer minimal benefits.

There has been a consistent lack of association between self-reported cognitive symptoms and objective cognitive function measured by neuropsychological testing.[9,10,20,39,40] A meta-analysis by Hutchinson et al of 24 studies, found eight reported a significant association between self-reported and objective cognitive function, and often the correlation was weak.[41] This was more likely in studies of breast cancer patients and when the relationship between memory (rather than global cognitive function) and self-reported symptoms was explored. However, both self-reported cognitive symptoms and objective cognitive impairment are important to patients and where possible both measures should be incorporated in to trial designs. Finally, self- reported symptoms are frequently linked to fatigue, worse quality of life and symptoms of anxiety and depression.

Potential mechanisms

The aetiology of cognitive change in cancer patients is not known, but is likely to be multifactorial. Postulated mechanisms include: direct neurotoxic effects of therapy, genetic factors, oxidative stress and immune dysregulation.

Direct neurotoxicity

Traditionally chemotherapy agents, with the exception of methotrexate and 5-fluorouracil, were thought to have minimal penetration through the 'blood brain barrier.' However, a variety of neurotoxicities have been described with many chemotherapy agents.[42-44] Imaging studies using positron emission tomography have shown that detectable levels of certain chemotherapeutic agents can be found in the brain following intravenous administration. While these levels are low, and are not at a level sufficient to cause an anti-cancer therapeutic response, there remains uncertainty whether they are sufficient to alter cognitive function.

Animal studies have suggested that neural progenitor cells and oligodendrocytes are the cell populations most vulnerable to multiple chemotherapeutic agents. Furthermore, repetitive drug exposure resulted in long-term suppression of cell division and prolonged cell death in the subventricular zone, the hippocampus, and major white matter tracts.[45-47]

Genetic factors

One potential candidate marker is the apolipoprotein (APO) EƐ4 gene, a known risk factor for

Alzheimer's disease and other forms of cognitive impairment. Preliminary support for this came from Ahles et al who demonstrated that long term cancer survivors with at least one APOEƐ4 allele scored significantly lower in multiple neuropsychological domains (P<.03-.05).[48] By contrast, the larger colorectal study by Vardy et al found no association with APOEƐ4 and cognitive function.[29]

There has been recent interest in the catechol-O-methyltransferase (COMT) genotype, which is associated with levels of dopamine in the prefrontal cortex of the brain. The COMT valine-158 methionine-158 single-nucleotide polymorphism is associated with increased enzymatic activity resulting in greater degradation of dopamine and less availability of dopamine at the synaptic receptor. Small et al studied breast cancer survivors treated with radiotherapy (n=58), chemotherapy (n=72) and healthy controls (n=204). The COMT valine carriers performed worse on neuropsychological tests (*P*<.009-.033) compared to those without the polymorphism, as did COMT valine carriers treated with chemotherapy compared to healthy control COMT valine carriers (*P*<.001).[49]

Immune dysregulation

Cytokines have an important role in normal brain function, including the modulation of neuronal and glial cell functioning, neural repair and metabolism of a number of important neurotransmitters. Cancer and/or chemotherapy causes activation of the immune system with release of proinflammatory cytokines, many of which have been shown to cross the blood-brain barrier (e.g. interleukin(IL)-1, IL-6, tumour necrosis factor-alpha (TNF-α)) and have been associated with cognitive impairment in other diseases.

Some breast cancer studies have found an association between cognitive impairment and elevation of interleukin IL-6 and TNF.[50,51] By comparison the much larger colorectal study, Vardy et al found no association between global cognitive function and cytokines in blood.[29]

Neuroimaging findings

Recent developments in the field of cognition and cancer include the use of functional magnetic resonance imaging to determine which areas of the brain are activated both at rest and while doing a memory task. Cross-sectional studies in breast cancer survivors who received chemotherapy have found hypoactivation in prefrontal and parietal brain regions.[52-56]

Intervention studies

There are an increasing number of studies focusing on both pharmacological and non-pharmacological interventions for the management of cognitive symptoms in cancer patients. The majority are small and while some have shown promising results, no treatment has as yet been established in main stream practice.

Pharmacological interventions

A number of medications have been of interest in this area and the most commonly evaluated agents include erythropoietin, dexmethylphenidate and modafinil. Results from trials have largely been disappointing. Vardy et al are currently evaluating the Chinese herb, *Ginkgo biloba,* in a randomised controlled trial in breast cancer survivors. Its mechanisms of actions are reported to include anti-oxidant properties, increasing cerebral blood flow, improving glucose utilisation and stimulation of neurotransmitters.

Non-pharmacological intervention studies

Treanor et al recently published a Cochrane systematic review of non-pharmacological interventions for cognitive impairment related to systemic cancer treatment.[57] Their selection criteria included randomised controlled trial of non-pharmacological interventions in survivors of adult-onset cancers who had completed systemic cancer therapy. They identified five randomised controlled trials of six interventions (n=235) in breast cancer patients. Of these, two used computer-assisted cognitive training interventions (n=100); two compensatory strategy training interventions (n=95) and one each meditation (n=47) and physical activity (n=19).[58-62] They found that use of cognitive and compensatory strategy training had beneficial effects on objective cognitive function, self-reported cognitive function, well-being and spiritual quality of life. The evidence for the assessed studies was graded as low quality for physical and mental health outcomes and did not

permit firm recommendations to be made.

Our group recently reported the results of a large longitudinal randomised controlled trial of a web-based cognitive rehabilitation program in cancer patients reporting cognitive symptoms 6-60 months following completion of adjuvant chemotherapy. All participants received a 30-minute telephone consultation outlining cognitive training strategies and were then randomised to the 15-week, home-based intervention or standard care. The study met its primary outcome with improvements in self-reported cognitive function post intervention and these changes were sustained at six months. Importantly, symptoms of anxiety and depression, fatigue and stress were lower in the intervention group upon completion of the program and quality of life was improved at six months. There were no major differences found in objective neuropsychological test results between the groups.[63] Three other small intervention studies have also shown provisional efficacy of cognitive rehabilitation programs.[64-66]

There remain a number of unanswered questions with regards to cognitive interventions in the cancer population, including: the best method of delivering cognitive training; the optimal dose, frequency, and duration of training; how to improve adherence to training; whether benefits translate to real world situations; and, the long-term durability of cognitive training. Similarly, we need to better understand which patients are most at risk of persistent cognitive symptoms with the aim of selecting patients who may benefit from earlier implementation of an intervention.

Conclusion

Cancer-related cognitive symptoms are an issue for many cancer survivors and can have a significant impact on their daily life. As we make advances towards the implementation of effective management strategies for cancer patients reporting cognitive symptoms, it is vital that both health professionals and patients are educated about this important issue. Patients need to be informed about the potential risk of cognitive symptoms, in context of the benefits of treatment, to enable them to make informed choices about their treatment and recovery.

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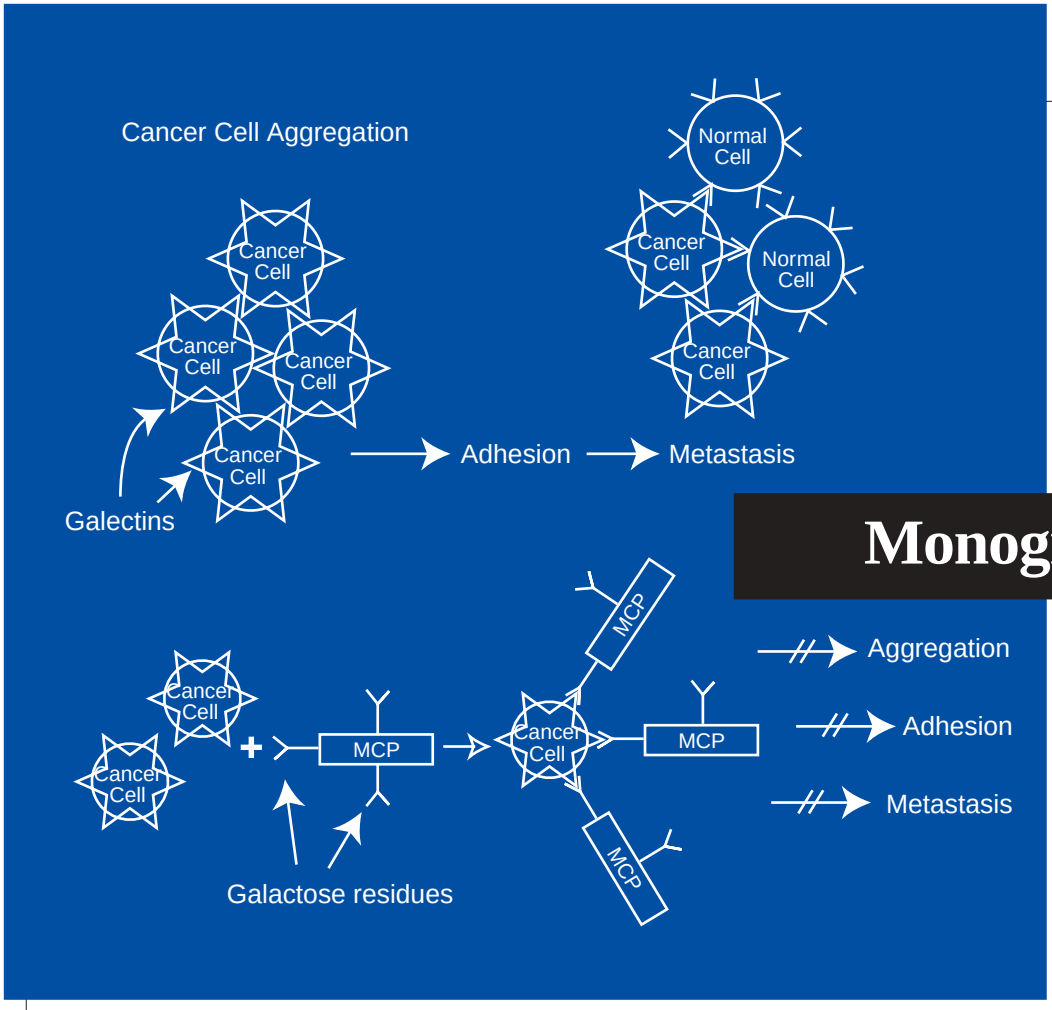

Monograph

Modified Citrus Pectin

Introduction

Modified citrus pectin (MCP), also known as fractionated pectin, is a complex polysaccharide obtained from the peel and pulp of citrus fruits. Modified citrus pectin is rich in galactoside residues, giving it an affinity for certain types of cancer cells. Metastasis is one of the most life-threatening aspects of cancer and the lack of effective anti-metastatic therapies has prompted research on MCP's effectiveness in blocking metastasis of certain types of cancers, including melanomas, prostate, and breast cancers.

Chemistry

Modified citrus pectin powder is produced from citrus pectin via pH and temperature modification that breaks it into shorter, non-branched, galactose-rich, carbohydrate chains. These shorter chains dissolve more readily in water and are better absorbed and utilized by the body than ordinary, long-chain pectins. It is believed the shorter polysaccharide units afford MCP its ability to access and bind tightly to galactose-binding lectins (galectins) on the surface of certain types of cancer cells.[1]

Mechanism of Action

Research indicates that in order for metastasis to occur, cancerous cells must first clump together; galectins on their surface are thought to be responsible for much of this metastatic potential. Galactose-rich, modified citrus pectin has a binding affinity for galectins on the surface of cancer cells, resulting in an inhibition, or blocking, of cancer cell aggregation, adhesion, and metastasis.[1,2] Due to the life-threatening nature of metastatic cancer, most research on anti-metastatic therapies has

either been in *in vitro* cell cultures or in animal studies. Although it is still unclear exactly how these study results translate to humans, MCP studies are promising.[3]

Clinical Indications

Prostate Cancer

Pienta et al examined modified citrus pectin's effectiveness against prostate cancer metastasis in the Dunning rat model. Rats were injected with prostate adenocarcinoma cell lines and given drinking water containing various MCP concentrations. Oral MCP did not affect primary tumor growth, but significantly reduced metastases when compared to control animals.[4] In one human study, Strum et al examined the effect of MCP on prostate specific antigen (PSA) doubling time in seven prostate cancer patients. PSA is an enzymatic tumor marker, and its doubling time reflects the speed at which the cancer is growing. Modified citrus pectin was administered orally at a dosage of 15 grams per day in three divided doses. Four of seven patients exhibited more than 30-percent lengthening of PSA doubling time. Lengthening of the doubling time represents a decrease in the cancer growth rate.[1]

Breast Cancer

As with prostate adenocarcinoma, research demonstrates metastasis of breast cancer cell lines requires aggregation and adhesion of the cancerous cells to tissue endothelium in order for it to invade neighboring tissue.[5] The anti-adhesive properties of modified citrus pectin were studied in an *in vitro* model utilizing breast carcinoma cell lines MCF-7 and T-47D. MCP blocked the adhesion of malignant cells to blood vessel endothelia, thus inhibiting metastasis.[6] A more recent human study examined galectin expression in 27 patients with invasive breast cancer. The study revealed that increasing histologic grades of breast cancer exhibited a decrease in galectin-3 expression, possibly resulting in increased cancer cell motility and metastasis.[7]

Melanoma

One of the better animal models for studying metastasis is the highly metastatic mouse B16-F1 melanoma. Using this system Platt and Raz determined that MCP significantly decreased tumor metastasis to the lung by more than 90 percent. In comparison, regular citrus pectin administration resulted in a significant increase (up to three-fold) in tumor metastases. The researchers concluded MCP's interference in the metastatic process might lead to a reduced ability to form tumor cell aggregates and metastases.[8]

Safety and Side Effects

Because it is a soluble fiber, administration of modified citrus pectin is unlikely to result in gastric intolerance, even at high doses. No pattern of adverse reaction has been recorded in the scientific literature. As with any dietary fiber, MCP at high doses may result in mild cases of loose stool, but this is usually self-limiting and does not warrant discontinuing treatment.

Dosage and Administration

Modified citrus pectin dosages are usually expressed in grams, with a typical adult dosage ranging between 6-30 grams daily in divided doses. This may be modified by the practitioner depending on the patient's clinical status, type of cancer involved, and degree of metastasis. The MCP powder is usually dissolved by blending in a small amount of water, then diluting with a juice of choice.

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