microRNA are the real regulators of gene transcription.

Plant polyphenols affect many microRNA in beneficial ways, promoting a reduction in inflammation.


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MicroRNA are non-coding short lengths of nucleotides (19-23 nucleotides) that have regulatory control over whether an mRNA will be transcribed into a protein or degraded by the cell. MicroRNAs affect specific mRNA and their proteins but may be able to affect 100s of them so it is not a simple thing to study or to say miRNA type A does this one specific thing consistently every time. Chronic illnesses have been found to show patterns in which miRNA are present in different amounts than in normal health, whether up or down regulated - not typical.

Good news - plant polyphenols seem to provide very beneficial and multiple effects on microRNA and the downstream mRNA, protein transcription, and chemical pathway activation or inhibition. (Milenkovic, et al., 2012) Some nutrients in foods have also been found to modulate miRNA expression, including retinoic acid and folate, amino acids, fatty acids. (32-35, cited by Milenkovic, Jude, Morand, 2013) paywall, copyright protected.

Nine polyphenols were tested and found to effect similar miRNA and similar pathways - reducing oxidative stress and inflammation and improving blood lipid chemistry in the apo e -/- knockout mouse used in the study in comparison to normal/wildtype mice. The plant polyphenols helped correct the differences in up or down regulated miRNA expression that were seen at baseline between the apo e -/- mice and the control group. Of the nine polyphenols - pomegranate peel and citrus peel would be good sources, including quercetin, and curcumin was also used. (Milenkovic, et al., 2012) More about the apo e -/- mouse study after this link:

A literature review and background information about microRNA (miRNA) was posted by Doorless Carp this morning: *MicroRNA miR-21, Cancer and Circadian Rhythm Related Cardiovascular Accidents* (substack.com)

DoorlessCarp's Scientific Literature Reviews

MicroRNA miR-21, Cancer and Circadian Rhythm Related Cardiovascular Accidents

Last updated: 3rd December '22. Background Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation (2018) miRNAs are small non-coding RNAs, with an average 22 nucleotides in length. Most miRNAs are transcribed from DNA sequences into primary miRNAs (pri-miRNAs) and processed into precursor miRNAs (pre-miRNAs) and mature miRNAs. In most cas...

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Pomegranate phytonutrients and others promote health by promoting miRNA that up and down regulate genes in beneficial ways due to the control of mRNA by microRNA (miRNA). Milenkovic, et al., analyzed the effects of nine dietary polyphenols on apolipoprotein E (Apo E) deficient mice which had altered lipid metabolism and control group mice. The polyphenols were tested separately and changes in miRNA were measured. Interestingly the baseline differences in microRNA between the Apo E deficient mice and control group were found to be somewhat normalized by the polyphenol treatment. Many genes that were down or up regulated differently in the Apo E -/- mice, than the control mice, were improved more toward normal function with polyphenol treatments. All of the tested polyphenols were found to affect five of the same microRNA. The biological pathways modulated by the five miRNAs were then identified and thirty were also being affected by the modulation of mRNA. (Milenkovic, et al., 2012)

What were the tested polyphenols? Drumroll... the phenolic acids: caffeic and ferulic acid; and the flavonoids: quercetin, anthocyanin, catechin, proanthocyanin, hesperidin, and naringenin; and curcumin. The animals were supplemented with one of the polyphenols for

a two week time period. (Milenkovic, et al., 2012)

Pomegranate peel or fruit is a source of caffeic acid, catechins, anthocyanins and proanthocyanins, and some quercetin. Citrus peel is a good source of hesperidin and tangerine specifically is a good source of naringenin. Both are considered citrus bioflavonoids. Hesperidin and citrus bioflavonoids are very effective for the respiratory symptoms of COVID19. Curcumin is found in turmeric root or powder.

And the five microRNA? Note, that while five were affected by each of the nine polyphenols, each polyphenol up or down regulated many miRNA. Five were found to overlap for all of them. Caffeic acid modulated the fewest at 29 miRNA changes, and hesperidin the most with 97 miRNAs differentially expressed. See: (Table 1, Milenkovic, et al., 2012) The apo e -/- mice had 119 miRNAs with a difference in up or down regulation than the control mice (27 down- and 92 up-regulated).

Three miRNAS were observed to be down-regulated by all nine tested polyphenols (mmu-miR-30c-1*, mmu-miR-374* and mmu-miR-497b*) and two miRNAs were found to be up-regulated (mmu-miR-291b-5p and mmu-miR-296-5p). See: (Table 2, Milenkovic, et al., 2012)

There were other overlaps, five additional miRNA were affected by eight of the polyphenols and nine more by seven of the polyphenols. The direction of change was the same, either up or down regulated similarly be the various polyphenols, except for two (miR-1 and miR-466c-5p) which varied with the type of polyphenol.

What this suggests to me along with the finding that the changes seen between apo e -/- mice and control were largely corrected by the polyphenols – is that the phytonutrients are helpful in similar ways. They need to protect themselves from oxidative stress from sun and weather.

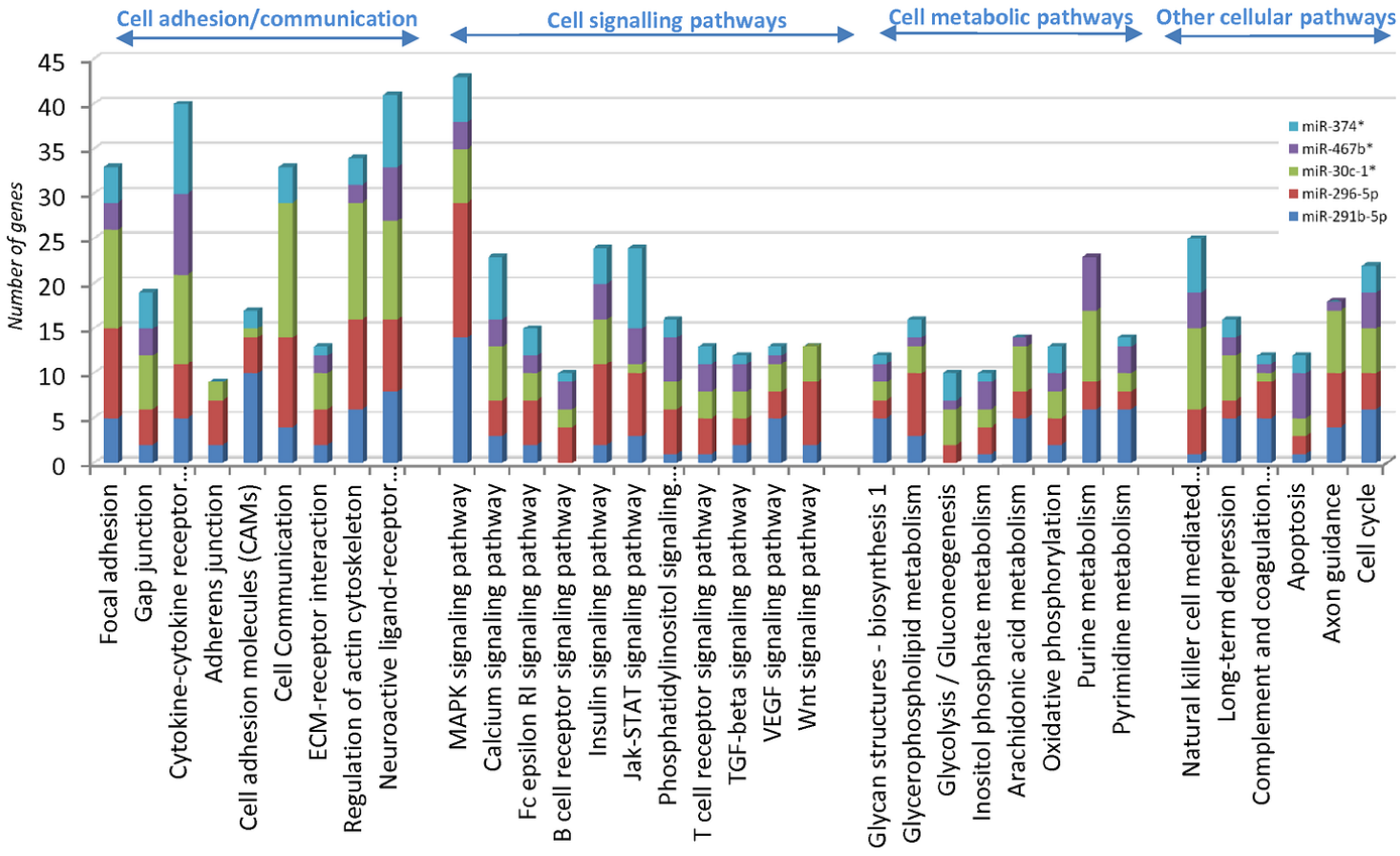
More exciting questions – what pathways/what functions of health were affected in common by the five miRNA's that were all modulated by the polyphenols?

> "Approximately between 500 and 1000 candidate genes were found for each miRNA (complete list and number of target genes can be found in Table S3). We further submitted each list of target genes into the KEGG database to classify the genes into pathways (these pathways are presented in Table S4). Interestingly, among the pathways

> identified, 34 were common with the potential target genes for all five miRNAs. A large number of them are implicated in cellular processes such as cell adhesion, communication and signaling pathways (Figure 3)." (CC-BY the authors Milenkovic, et al., 2012)

In Figure 3 (Figure 3, Milenkovic, et al., combine the number of genes that were affected for a pathway by each of the five miRNA, in a bar graph for each pathway found in common to be up or down regulated by the miRNAs that had been modulated by all of the polyphenols. Visually the bar graph format makes some columns stand out taller, more genes were affected by the total group of polyphenols for that pathway, in the striped pattern made by the number of genes affected by each of the five miRNA. The MAPK signaling pathway is a tall column – meaning it was multiply affected by a larger total number of genes up or down regulated by the tested polyphenols than some of the other pathways.

All nine polyphenols up or down regulated all five of the miRNA and would affect all the pathways below. The tallest columns may be suggesting that the most consistent impact might be in those areas.



Modulation of miRNA Expression by Dietary Polyphenols in apoE Deficient

Mice: A New Mechanism of the Action of Polyphenols, (Figure 3, CC-BY the authors Milenkovic, et al., 2012)

Cell adhesion or communication pathways were also more affected. *Neuroactive ligand-receptor* and *cytokine-cytokine receptor* genes were the next tallest columns, followed by *regulation of actin cytoskeleton*, *ECM-receptor interaction*, and *focal adhesion*.

A middle group of others include *Natural killer cell mediated* and *cell cycle* as stand outs; *Insulin signaling*, *Jak-STAT signaling pathway*, *Calcium signaling pathway*, in the *Cell signaling* cluster along with MAPK; and *Purine metabolism* in the *Cell metabolic pathways* cluster.

This explains why pomegranate is so helpful against cancer and misfolded protein conditions, and pain.

Mitogen-activated protein kinase (MAPK) is inhibited by phytonutrients in pomegranate peel extract (PPE) by the regulation of Fox03, which would decrease unwanted phosphorylation of proteins, observed in an animal-based study in which PPE reduced ototoxicity caused by amikacin (AMK). (Liu, et al, 2017)

Segue to Post Translational Modification of Proteins (PTM) - the addition of an extra chemical group to a protein can modify function and may increase pain or risk of autoimmune antibody formation against the protein type or increase other problems like glycated hemoglobin (HbA1C) in poorly controlled diabetes. Kinases add a phosphoryl (PO3) group to proteins. Pomegranate or other phytonutrient rich foods may inhibit that from happening.

Post Translational Modification of Proteins (PTM)

A study on CNS hyperalgesia by Fujisawa, et al, found post-translational modification (PTM) to be involved in the pain condition rather than increased mRNA expression of the three proteins that were identified. Proteolysis or phosphorylation of proteins was affected by PTM. (Fujisawa, et al, 2008) Post-translational modification of proteins is also seen in autoimmune Rheumatoid arthritis. Auto-antibodies form against the modified proteins which leads to autoimmune damage to healthy proteins. Autoantibodies may be formed in response to PTM of proteolysis or phosphorylation, and also acetylation, carbamylation, glycosylation, glycation, lipidation, and ubiquitination. (Vasudevan, et al, 2021)

Nociceptive pain is considered acute, traumatic injury related, typically, while neuropathic pain may be chronic over-activity of pain signaling nerves. Post-translational modification of sodium voltage gated channels modifies their activity in neuropathic chronic pain syndrome. (Laedermann, Abriel, Decosterd, 2015)

Inflammatory pain is caused by factors released by mast cells, neutrophils, fibroblasts, keratinocytes and inflammatory cells. The chemicals can activate nociceptive neurons and include "*protons (H+), nerve growth factors (NGFs), cytokines (such as IL-1β, IL-6), tumor necrosis factor alpha (TNF-α), prostaglandins (PGE2), several neurotransmitters (serotonin, ATP) and peptides (bradykinin, substance P, CGRP).*" (CC-BY the authors (Laedermann, Abriel, Decosterd, 2015)

Inflammatory pain also increases nociceptive signaling by activating kinases that cause PTM of phosphorylation. (Laedermann, Abriel, Decosterd, 2015)

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6 Comments