Caloric restriction for anti-aging

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Credit: Herschel Walker MMA

(Medical Xpress)—The idea that reducing the amount of food you eat can slow metabolism and extend lifespan has been around for a while. Only recently has it become more mainstream. On sites like the popular Fight Aging forum, caloric restriction is a regular topic of scientific discussion. In Silicon Valley, intermittent fasting isn't called dieting,

instead it's now "biohacking."

A recent paper published in *GeroScience* by researchers at the University of Oklahoma provides some much-needed food for thought in the field of caloric restriction. The title, "Role of DNA methylation in the dietary restriction mediated cellular memory," suggests some underlying mechanisms have been uncovered that can explain the presumed healthful benefits of dietary restriction (DR). If so, then what is the nature of these apparent relationships, and what are their benefits?

Somewhere between correlation and causality lies the frequently employed phrase "plays a role in." The way I read things here, there are at least three or four variables at play upon which we might impose a natural sequence or order via the scheme (1 >2 > 3 >4):

Dietary Restriction > Decreased Methylation Of Certain Promoters > Increased Expression Of The Genes Under Control Of Those Promoters > Cell Memory In The Form Persistent Changes To Parts 2 And 3.

While several genes (Pomc, Hsph1, and Nts1) and their inclusive islands of methylation were clearly operated on by dietary restriction, the most important findings were found within the Nts1 gene. Nts1 encodes the Neurotensin Receptor 1. This G-protein transduces whatever message is locally supplied by the 13-amino-acid-long neuropeptide neurotensin signal. This message intimately depends on cell type and where the cells are found.

Centrally, neurotensin functions in the hypothalamus, a place where each nucleus contains unique neuronal subtypes specializing in the production of a few eclectic signal molecules. Perception of hunger and satiety are believed to be integrated there, as is the nutrient-dependent control of subsequent food- sensing and food-seeking behaviors. It is therefore a logical place to further explore the established links between nutrients

and epigenetic changes like methylation.

Neurotensin acts to lower blood pressure, raise blood sugar, lower body temperature and confer antinociception. Another pathway leads to the release of prolactin and luteinizing hormones, ultimately through activity in the arcuate nucleus (where the Pomc neurons are also found) via its own set of constructed peptides. The hypothalamus in turn is supplied with signals, nutrients, and even mitochondrial products from the rest of the brain via the thick fiber bundle from the hippocampus known as the fornix.

It has been argued that these diverse hypothalamic and pituitary mediators represent so-called reliable or "honest" signals conforming to the "handicap principle"—otherwise popularly known as the "peacock effect." One example of this would be the steroid and vitamin D synthesis chains whose rate-limiting steps are frequently resident in the mitochondria. These expensive and rare (i.e., difficult to replicate and active at very low concentration) signals of metabolic state get funneled to the body at large through individual kingpin neurons residing at apex positions in the brain.

In peripheral regions, neurotensin's major local effects are in the small intestine, where it leads to secretion and smooth muscle contraction via enteroendocrine cells. It also acts to preserve intestinal stem pool, which is why the authors make special mention that memory effects in methylation of the Nts gene may be critical there.

The primary experimental manipulation performed here was to place mice on a DR diet for a few months and then return them to a normal diet for another few months and see what happens. Perhaps unsurprisingly, significant changes in gene expression were noted within one month of the initial DR. After normal feeding, the authors found both reduced methylation at three key CG sites in the Nts gene promoter

using standard bisulfite amplicon sequencing, and also an overall increase in expression of Nts1 transcripts using RNA-Seq techniques. This confirms their initial hypothesis flowing from DR to a cell memory effect.

While these expression and methylation findings are all well and good, I think at this point we need to ask a question that might be on the minds of any red-blooded American:

How on Earth does Herschel Walker, top mixed-martial arts competitor today at age 55 and still widely regarded as the greatest college running back of all time, manage to crank out over 1500 push-ups, 1500 sit-ups, 1500 pull-ups, followed up by a grueling sprint and long-distance workout, each day, every day, while eating nothing but a small dinner of salad, soup and bread?

I am not presenting Hershel's claims above as facts to be swallowed whole by the reader, but rather offering them up as something we must potentially account for. Putting up those kinds of numbers, ie. physical work produced from calories burned, is simply not possible by any known man-made machine, and is just barely imaginable for one of flesh and blood. So how does he maintain a stout 225 lb frame while mere mortals attempting to subsist on lumpy green shakes would rapidly shrivel and etiolate? In other words, what, exactly, is his nuclear DNA, mitochondrial DNA and epigenetic state?

To answer that, we would probably need to do more than a quick cheek swab and sequencing from somebody like 23andMe. In fact, we'd have to do a lot more to understand something as fickle as epigenetics, which can purportedly respond to any given sandwich with a cascading butterfly effect of changes. In many instances, these changes are not limited to simple cell memory, but rather can be experimentally extended into heritability and beyond.

So we must dive deep into our evolutionary roots to uncover the origins, and thereby implications of what methylation really is. It is widely held that methylation in its most ancient incarnation first arose in bacteria for purposes of transposon control. Regarding transmission of acquired characteristics like diet, it is notable that bacteria are essentially full-blown Lamarckian creatures—their immediate daughter fission products directly express the full metabolic life history of the parent.

The transposon idea may have some substance, because methylation is a powerful transcriptional repressor in animals, plants and protists that, at least in CpG environments, can ensure permanent silencing of rogue transposable elements. Furthermore, methylation tends to repress genes of multicellular organisms that need to be silenced in most but not all differentiated tissues. Yet bacteria do not take methylation to the extent that higher mammals like ourselves do. In fact, one of the ways in which our immune system recognizes and deploys our own bacterial endosymbionts, the mitochondria, is by the very absence of any methylated mtDNA should their nucleoids get released into blood.

Another major clue is that between generations in mammals, DNA methylation patterns, including many imprinting and X-inactivation marks, are largely erased and then recreated to various levels of fidelity at several key stages. The first is a "genetic reboot" consisting of deliberate demethylation and remethylation during gametogenesis. The next two happen first in preimplantation period of the zygote and then in the blastula stage, where the CpG islands are shielding from a bulk methylation wave so that a global repression phase allows housekeeping genes to be deployed through the entire blastula. After that, methylation patterns become tissue and cell type specific to permit stable differentiation.

At the most basic level, many aspects of genome-wide methylation are quite predictable. For example, it has been suggested that the use of

thymine in DNA as opposed to uracil in RNA evolved for error-control purposes because any deleterious uracils generated by spontaneous deamination of cytosine could be more easily recognized and removed. 5-methylcytosine has its methyl group at the same spot thymine does, which is the only thing that distinguished thymine from uracil. CpG methylation is evolutionarily costly, because over time, methylated cytosine spontaneously deaminates to thymine.

The maxim that hypermethylated CpG in promoters leads to repression of gene expression is not always the case. In a paper recently published in *Science* the authors looked at 542 human transcription factors and found that for many, particularly homeodomain proteins active during development, methylated promoters enhanced transcription. Another study revealed that a reliable biomarker of chronological aging can be extracted by looking at methylation at 353 sites in the human genome. This, perhaps, is the kind of data we need to answer the question posed above. Namely, how Herschel Walker can look like he does while basically running on fumes, while many top powerlifters and bodybuilders with comparable physiques claim to require anywhere from 5000 to 10,000 calories a day.

More information: Archana Unnikrishnan et al. Role of DNA methylation in the dietary restriction mediated cellular memory, *GeroScience* (2017). DOI: 10.1007/s11357-017-9976-8