

LE Magazine December 1998

REPORT

Methylation, Epigenetics and Longevity

A new study, partly funded by the Life Extension Foundation, hopes to demonstrate how increasing the body's methylation through proper nutritional supplementation may extend life span.

By Craig Cooney

The other night I was watching the movie *Gattaca*, a film about a future time when we are all identified by our dna sequence. Of course, with this dna sequence-based identity comes lots of distinctions of class, with some people given opportunities in life and others shunted to menial tasks. One of the distinctions in the movie that can be made from dna sequence is anticipated life span, to the year.

Even today we know that dna sequence alone only determines, at best, a broad life-span range. Most laboratory mice and rats are grown as genetically identical strains through inbreeding, yet these groups of genetically identical mice and rats die over quite a range of time. For example, most mice of the C57BL6 strain living in similar conditions will die between 18 and 33 months of age (e.g. Finch 1990, Blackwell et al. 1995). That's similar to most humans dying between 50 and 90 years of age, and humans are not even genetically identical, nor do we all eat the same food, drink the same water or live in the same environment.

The point is, if genetics called the whole tune, the C57BL6 mice should all drop dead on a Tuesday afternoon, precisely two years, three days and six minutes after their birth. So why don't they?

It has long been known that normal mammalian cells grown in laboratory culture will become senescent, stop growing and eventually die. These normal cells grown in laboratory culture dishes lose something called "dna methylation" the more they grow and divide (Wilson and Jones 1983). In contrast, tumor cells, although low in dna methylation to begin with, don't necessarily lose more dna methylation as they grow and divide. The fact is, tumor cells are immortal.

Methylation is the passing of a chemical fragment called a methyl group (a carbon atom linked to three hydrogen atoms) from one molecule to another. This chemical "tag" acts as an all-important signal and structural modification throughout our bodies (Mitchell 1998). Although there are many uses of methylation, dna methylation is one of the essential, and one of the most important, uses of methyl groups. In fact, if methylation of dna is limited or prevented, mouse embryos won't develop and life just stops (Li, et al., 1992).

In whole animals, dna methylation also is lost with age. In 1967, Dr. Boris Vanyushin and co-workers in Moscow described this process in salmon, and later showed that dna methylation was lost with age in most tissues studied in cattle and rats (Vanyushin et al. 1973, Romanov and Vanyushin 1981). Likewise, scientists in the U.S. and Japan showed loss of dna methylation with aging in many tissues of mice (Singhal et al. 1987, reviewed in Cooney 1993).

Dr. Vincent Wilson and co-workers showed that the longer an animal species' life span, or the greater the doubling potential of a cell type, the better it is able to maintain its dna methylation. Their studies indicate that humans maintain their dna methylation much better than do mice, and, as we know, humans live much longer than any type of mouse.

These studies raised the possibility that manipulating dna methylation in the laboratory might alter the life span of cells or whole animals. We now know that short treatments with dna-methylation inhibitors significantly decrease the doubling potential or "life span" of normal human fibroblast cells (Holliday 1986, reviewed in Cooney 1993).

Can methylation enhancement, in turn, increase life span?



A few years ago, the Life Extension Foundation began to recognize the broad involvement of a substance called S-adenosylmethionine (SAME) - an "active" source of methyl groups, a high-energy source made from atp, our cells' "energy currency," and the amino acid methionine-and methylation in health and longevity. Dr. Paul Frankel introduced Foundation President Saul Kent to my research on methyl supplementation and epigenetics. The Foundation agreed to support this research and together we organized a project, called Methylation, Epigenetics and Longevity.

There are several objectives of this project, including determining whether long-term dietary methyl supplementation or SAME supplementation in rats will effect changes in longevity, in age-related pathology, and in such molecular parameters as dna methylation, SAME, a reaction product of SAME called S-adenosylhomocysteine (sah), and homocysteine, the most important biochemical risk factor for vascular disease (Frankel & Mitchell 1997). Another objective is to determine if measures of dna methylation, SAME, and homocysteine in the blood are indicators of longevity and can act as biomarkers of aging.

I proposed that deficiencies in methyl metabolism exist from the time animals are young. A short-lived species, such as a mouse, would have evolved a more severe inherent deficiency in methyl metabolism than a long-lived species such as a human. Importantly, these methyl deficiencies would have evolved in animals eating a balance of nutrients found in food from nature, and would therefore be at least partially dependent on the diet.

Thus, I proposed that by manipulating the diet so that the nutrients for methylation are increased, it may be possible to control these deficiencies. This is why we don't, and never did, get all the vitamins we need from our food (Cooney 1993). We need healthful longevity, yet the vitamins in our food only "warranty" most of us for youthful reproduction!

The Methylation, Epigenetics and Longevity project will test new important markers for our health, in particular blood SAME and white blood cell dna methylation. We know that homocysteine levels increase with age in humans (Brattstrom et al. 1994). In contrast, T-cell dna methylation declines as we age and is likely a cause of autoimmune disease (Yung et al. 1995). How blood SAME changes with age isn't known for sure, but when blood SAME is low, it causes depression and is a risk factor for heart attack.

Despite all of this, tests for these conditions are not routinely done. The planned metabolic measures in our study will help relate this work to other important areas of health in addition to longevity, and something called epigenetics, which can be defined as the heritable control of the expression and use of dna sequence (see the sidebar story on the following page).

Methylation has a huge number of effects in addition to affecting dna methylation in normal cells, as well as cancer cells and aging cells. Low dna methylation of blood T-cells appears to cause some lupus and rheumatoid arthritis in humans and causes autoimmune disease in mice (Yung et al. 1995). Methylation also is used to make melatonin (the "sleep" hormone), adrenaline (the fight-or-flight hormone), acetylcholine (a neurotransmitter), creatine (for muscle energy metabolism), carnitine (involved in fat burning in mitochondria), and choline (fat mobilization and cell membrane fluidity).

Understanding methyl metabolism and the effects of methyl supplements is important for understanding the biochemical processes that affect our health. For example, methyl metabolism is essential for the metabolism and transport of fats and cholesterol, for the metabolism of several neurotransmitters and in the action of antidepressant drugs. Blood SAME is low in depressed humans (Alpert and Fava 1997) or after drug abuse in mice (Cooney et al. 1998). Folic-acid deficiency appears to prevent the effectiveness of certain anti-depressant drugs, including fluoxetine (the active ingredient in Prozac), and SAME itself is an effective antidepressant in humans (Kagan et al. 1990, Fava et al. 1995, Alpert and Fava 1997).

Methylation is also important for repair of age-related protein damage in our nervous systems and throughout our bodies. In fact, this type of repair is essential for longevity in mice. If a certain SAME-dependent protein-repair gene is disabled or "knocked out" in mice, the animals live only for about seven weeks (in a range of three to nine weeks), instead of their normal 20 to 30 months (Kim et al. 1997). In humans, this type of repair appears to be important in a number of areas, including repairs that may help prevent Alzheimer's disease and cataracts.

Maintenance of dna methylation is not only essential to our health in the long term (in avoiding cancer and aging), but it also appears to have a daily role in maintaining our chromosomes, immune systems and in suppressing viral infections.

Like nearly all chemical reactions in our bodies, dna methylation is accomplished using a protein catalyst, an enzyme. For dna methylation, the enzyme is called dna methyltransferase, which facilitates the methylation reaction by positioning SAME and the cytosine base of dna very close to each other. dna methyltransferase is like a three-dimensional reusable molecular scaffold for positioning these molecules conveniently where the work needs to be done. dna methyltransferase also uses zinc to help bind dna, although the full role of zinc is not yet known (Bestor 1992).

Let's take a look at nutrition and methyl supplements, and how they might have an impact on the heritable control of the expression and use of dna sequence (epigenetics).

SAMe is needed for dna methylation and for most enzymatic methylation in cells. SAMe is found mainly inside our cells and tissues, and can readily be measured in the red cells of our blood (Wise et al. 1997). We probably get only a tiny fraction of our SAMe directly from food, but we need methyl metabolism to produce SAMe, and methyl metabolism is dependent on a dietary source of the absolutely essential nutrients vitamin B12, folates, methionine and zinc, and of conditionally essential nutrients such as choline and betaine.

These co-factors are like essential tools needed on the protein scaffold to get the job done. Methyltransferase enzymes using SAMe are inhibited by the reaction product sah. Consequently, the dna methyltransferase enzyme requires SAMe, is inhibited by sah, and also uses zinc as a co-factor. sah is broken down to homocysteine and adenosine. Homocysteine can then be recycled by methyl metabolism to produce methionine and, subsequently, SAMe.

We know that methyl-deficient diets will cause liver cancer, vascular disease and shorter life span in animals. This was published in 1946 by Salmon and Copeland, who showed that a choline-deficient, low-methionine diet caused liver cancer in rats, and in 1954 by Wilgram et al., who showed that choline deficiency caused atherosclerosis and death in young rats. The importance of methyl groups in avoiding liver cancer was later more clearly shown and extended by Dr. Lionel Poirier and co-workers (see Poirier 1994), and the role of homocysteine in arteriosclerosis has been shown for humans as first proposed by Dr. Kilmer McCully in 1969 (see McCully 1997). (For a full explanation of McCully's contribution to the study of homocysteine, see *Life Extension* magazine, November 1997.)

Continuation of Article

[Back to the Magazine Forum](#)

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

LifeExtension[®]

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.