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> ONE MONTH, ONE PROTEIN <

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In vino vita?

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A prolonged and healthy life is a tempting prospect. Especially in a day and age where there seems so little time to fulfil our ever-growing aspirations. Researchers have been giving a lot of their time to the problem of longevity since the 1930s, when it was first discovered that calorie restriction actually lengthened life expectation in mammals. It took many more years before scientists caught a glimpse of the molecular pathway underlying such a process. And, for the time being, it really is just a glimpse – but an encouraging one. A family of proteins, known as sirtuins (sir-too-ins) or SIRS – an abbreviation of Silent Information Regulators – and which are found all the way from bacteria to humans, seem to have a role in the ageing of cells, and hence the ageing of organisms.

Red Wine and Grapes, Emily Zasada

Courtesy of the artist

Different organisms have different ageing pathways. In yeast, for example, the accumulation of what is known as toxic extrachromosomal rDNA circles (ERCs) is a cause of cell senescence. Whilst in worms, interference in the insulin-signalling pathway has an effect on the organism's longevity. The exciting discovery is that sirtuins have a direct effect in both of these ageing processes. And though they are part of different molecular pathways, their mode of action remains the same.

Sirtuins are NAD-dependent protein deacetylases, which remove acetyl groups from specific target proteins. Their function however depends on the intracellular concentration of nicotinamide adenine dinucleotide (NAD), which in its oxidised form greatly enhances sirtuin activity. In yeast for example, genomic instability, and hence the accumulation of ERCs, stakes its fate. Sirtuins can stall such a fate by acting on certain histones, which they deacetylate. As a consequence, chromatin structure is modified, the lecture of rDNA disrupted and the formation of ERCs hindered.

Cell senescence is delayed by calorie restriction. Calorie restriction probably either shifts the ratio of oxidised/reduced NAD or alters its level, thereby altering sirtuin activity. How? A number of proteins – which are also NAD-dependent – may become less active and release their NAD which is then free to activate the sirtuins. Another hypothesis for an increase in NAD is a metabolic shift to respiration. When glucose is limited, respiration is preferred. An increase in respiration yields a higher rate of electron transport which increases the overall cellular NAD/NADH ratio. Either way, an increase in NAD activates sirtuin activity. And as a result, in the event of environmental stress – such as less food or fungal infection for instance – organisms are given a better chance to survive.

So sirtuins seem to have an overall role as regulators of programmed cell death and cell differentiation, and are more active during environmental stress. In the quest for eternal youth and health, scientists set out to find if they could actually pin down a molecule that triggers off sirtuin activity, instead of just counting on

calorie restriction. A number of chemical compounds were examined amongst which a few polyphenols, which are metabolites found in plants. The most potent activator turned out to be resveratrol, a plant metabolite found in the skins of red and white grapes…and hence in wine. Another plant metabolite, quercetin, is also an activator of sirtuins, although to a lesser degree and is found in olive oil for example. Both compounds are synthesised in response to environmental stress and are already known for their health benefits – namely their antioxidant properties, their capacity to lower cholesterol levels and decrease blood clot formation.

There is a theory that, when there is a lack of nutrients, plants may have the power to 'say' so to other organisms via resveratrol. Animals feeding on plants would assimilate the increased ratio of resveratrol and thereby transfer the warning message to their own organism, i.e. that reproduction has to be halted and survival means undertaken. However, there is reason to believe that organisms other than plants also have their own sirtuin activity enhancers, though they have not yet been identified. Time will tell.

So should we all take to drinking wine? Or adding olive oil to our diet? Statistics have shown that the French – who are keen consumers of red wine – suffer less from the side effects of overweight than do the Americans for example. A Mediterranean diet – which includes not only red wine but also ample amounts of olive oil as well as fresh fruit and vegetables – is also statistically far kinder to humans than a diet of coke, hamburgers and chips. For the gourmet readers: wines produced in cooler regions or areas where grapes are more prone to disease often have more resveratrol. Hence Pinot Noir has high doses of the chemical while a Cabernet-Sauvignon is not so rich in the compound.

High doses of resveratrol stunts its effect on sirtuins, so there is no point in over drinking. Anyhow, nothing has been proved yet. No one can really assert that one glass of wine a day keeps the doctor away. What is more, in human cells, resveratrol ultimately deactivates a tumour suppressor, thus fuelling concerns that increasing resveratrol levels may predispose humans to cancer – though some scientists disagree since calorie restriction *per se* has never proved to do so.

Much more needs to be known about sirtuins. A lot of money could be involved in miracle diets which make you believe that you can eat as much as you like providing you swill it down with a glass of wine enriched with resveratrol. However, scientists insist that the findings are not so much to prolong life than to avoid the bothersome effects of ageing such as neurodegeneration, carcinogenesis and atherosclerosis. So, the message is always the same. Just eat and drink not only healthily but also within reason, and you should be all right.

Cross-references to Swiss-Prot

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