

Leveraging the self-healing abilities of our body to promote healthy longevity

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In the course of aging, all living organisms experience a decline in physiological function and homeostasis leading to death. This natural phenomenon aroused scientific interest in the last decades with investors pouring billions of dollars in research programs for lifespan extension. Although a few eccentric billionaires may be chasing immortality, it should be clear that extending lifespan might have little or no benefits for our societies if individuals are living with one or several chronic diseases like ischemic heart disease, diabetes, obesity, cancer, or neurodegenerative diseases¹. Those affected can suffer from a reduced quality of life and side effects of taking medication. The high costs of treatment are a burden for the individual and the taxpayers. This is why the concept of 'healthspan' extension is more relevant to our aging modern societies.

Most studies targeting lifespan extension have been done with laboratory animals in the search of a 'magic bullet'. Numerous studies have been manipulating metabolic pathways like the insulin/IGF-1 signaling and the target of rapamycin (TOR) pathway by pharmacological substances like rapamycin and spermidine². A large number of research projects in the field of aging aim at finding new drugs because these areas can be highly profitable for companies. However, the dependence on drugs for treating diseases can have sinister consequences when they become unavailable for socioeconomic or political reasons, or when these drugs have side effects³.

Some new projects are using moon-shot technologies like cell reprogramming intervention to reverse the course of cellular development, hoping that aging can be

treated like a disease⁴. These are beautiful and elegant scientific demonstrations, but nobody knows whether these technologies would be effective in promoting healthy longevity in humans. What we know is that complex strategies requiring advanced technological knowledge are costly to develop, often individualized, and thus only benefit a limited number of wealthy patients. This is a barrier to gene therapy which has been known for decades⁵.

The enthusiasm for highly technological approaches sponsored by billion-dollar investments should thus not distract the scientific community from the study of more simple natural and non-pharmacological approaches.

'Low-hanging fruits' like prevention is a first line of defence and a question of healthy lifestyle. Poor diets lead to one in five deaths⁶. Healthy nutrition, regular physical exercise, limited consumption of alcohol, or no smoking, may increase life expectancy by 14 years in women and 12 years in men⁷. Adding fasting periods would further increase life expectancy by 20 years⁸. Being active and normal weight was associated with a gain of 7.2 years of life compared to being inactive and obese⁹. One could thus wonder what would happen to animals eating a 'cafeteria' diet if they were undergoing cell reprogramming therapies to try to rejuvenate.

The self-healing abilities of our body can be stimulated. Cells have evolved a variety of mechanisms to detect and repair damages, on macromolecules like DNA but also on dysfunctional cells which can be eliminated by programmed cell death or apoptosis¹⁰. Detoxification mechanisms which can be stimulated are present in many tissues in order to

inactivate and eliminate harmful substances¹¹. Most of our tissues also have a pool of stem cells which can be stimulated to replace damaged cells. Whole tissues like the liver and the skin have self-healing properties¹².

While sleep and fasting have been considered as 'non functions' by opposition to the known useful physiological functions of physical exercise and eating, recent studies have shown that they allow cell regeneration, waste clearance and modulating energy metabolism^{13,14}. Chronic sleep deprivation has been linked to a number of health problems, negatively impacting physical and mental performance. Besides the consolidation of neuronal networks and memories, during sleep the brain is thought to clear out waste products and protect against neurodegenerative disorders¹⁵. Concerning fasting, our research program at the Buchinger Wilhelmi Clinics has revealed multiple mechanisms by which regular long-term fasting, lasting for several days up to weeks, can normalize risk factors for chronic diseases, including high blood pressure¹⁶, high cholesterol¹⁷, elevated blood glucose levels¹⁸ or fatty liver¹⁹. It improved total antioxidant capacity and reduced damages of free radicals^{20,21}. Fasting is even known to lead to a rejuvenation of tissues through the activation of autophagy²² and the stimulation of stem cell divisions²³. Furthermore, fasting improves well-being¹⁸, can help to adapt to a healthier lifestyle and increases self-esteem and empowerment²⁴.

Exposure to environmental pollutants can also have a variety of deleterious effects on human health which can be avoided by preventive measures²⁵. Pesticides can disrupt cell function through different mechanisms including generation of oxidative stress²⁶, disruption of hormone signaling²⁷, alteration of the gut microbiome²⁸ or of fetal development²⁹. Some chemical toxicants can also interfere directly with metabolic pathways leading to an acceleration of aging. For instance, exposure to persistent organic pollutants such as dioxins or polychlorinated biphenyls can shorten telomere length, which is considered as a marker of aging³⁰. The term 'gerontogen' was coined to describe these agents³¹. Altogether, exposure to toxic chemicals has high societal costs. Endocrine disrupting chemical exposures could cost in the hundreds of billions of euros per year only in the EU³².

There is a need for pragmatism to find solutions which suit a world in which societies are destabilized by the diminution of the access to fossil fuels and minerals, which are more and more expensive to extract, exacerbating global warming, creating inequalities. With annual costs of €27.7 billion in three European countries combined (Germany, France, Italy), a disease like nonalcoholic fatty liver disease has a large economic and societal burden³³. Although the contribution of hepatic steatosis is increasingly recognized³⁴, it is striking to see the many clinical trials which persist in finding a miracle drug, with no guarantee of success, when some lifestyle interventions like fasting are largely dismissed. While the development of drugs and genomic strategies come with many limitations in their applications, the self-healing

abilities of our bodies can be leveraged at virtually no cost. This is accessible for all, and can ultimately save money for national healthcare systems by reducing the need for costly medical treatments and hospitalizations.

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The views and opinions expressed in this article are those of the authors.