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Salutogenesis and beyond

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Abstract

In the present hypothesis paper on paradoxes in preventive medicine, which also deals with the indocility of biological functions, the following issues will be addressed. First, a definition of salutogenesis will be given, providing the origin of this notion of health preservation and disease prevention. Then, four paradoxes of the biology of health will be discussed. The first deals with the biomarkers of aging. The second addresses the good and bad of the much praised antioxidants. The third details how the mammalian transporter of rapamycin pathway plays a discreet but fundamental role. The fourth explores the yin and yang effects of the secretory profile of senescent cells. In conclusion, the need for a new paradigm in preventive medicine will be proposed.

KEYWORDS

aging, health, longevity, prevention, salutogenesis

1 | PREAMBLE

Hygeia the goddess of health, one of the daughters of Asclepios, is said to have been the one to overtake the secret of immortality from her father's legacy. Yet, how did that occur? Asclepios himself was fathered by Apollo from the Trakkaian princess Koronis. She herself was to be killed by Apollo because of her infidelity while she was still pregnant. Asclepios was removed from his dead mother's body by caesarean (Asclepios means "to cut open"). His life gave rise to the mythological link between medicine/aging/longevity/immortality because the young Asclepios was *in fine* raised by the centaur Kheiron who instructed him in the art of medicine and longevity (Figure 1). Asclepios was killed by Zeus because he had definitely transgressed his limits, transmitting the clue of immortality to mortals.

Each of Hygeia and her sisters had inherited a facet of the art of Apollo, the god of Sciences: Hygeia was the personification of health, Panacea was the goddess of universal remedy, Iaso that of recovery from illness, Aceso that of the healing process, and Aegle was the goddess of beauty, splendor, glory, magnificence, and adornment. "Hygeia the Health" also played an important part in the worshipping of their father Asclepios.

Although Asclepios was more directly associated with healing, Hygeia would have liked to avoid her father's pain and the efforts he displayed to cure disease. She therefore began to suggest remedies and *food* to prevent diseases. Hygeia was thus associated with the prevention of sickness and the continuation of good health. The Romans also considered Hygeia as the goddess of personal health, *Valetudo*, and social welfare, *Salus*. In the orbit of Hygeia lay the concepts of medicine, food, remedy, and prevention of disease.

2 | DEFINITION OF SALUTOGENESIS

Salutogenesis (Bischof, 2010) is by definition the care about conditions and mechanisms that contribute to the maintenance of a healthy condition (*Salus*). It is opposed to pathogenesis, the mostly academic science aiming at unraveling the implications of strategic changes leading to disease. Thus, great attention is brought to the etiopathogenesis of disease, by dissecting the semiology, symptoms, syndromes and concepts of systemic, and iatrogenic or endogenous causes of disease. As Antonovsky puts it in 1993, currently the paradigm of pathogenesis is still operating in research and clinical practice and even the attempts of a preventive medicine or a biopsychosocial model would not alter the limits of the concept. As an alternative, he introduced the concept of "salutogenesis," considering that each society develops its own hypothesis on which to build clinical and experimental practices, in health and disease. Obviously, health institutions will depend on the milestones achieved within the paradigm a society recognizes as its own. In the industrial societies of Europe and the United States, this paradigm lies in the biomedical model, and its philosophy is the "pathogenic paradigm." Its basic hypothesis states that certain pathogens, or inducers of disease, threaten the integrity of a living organism, considered as causative with respect to the abundance or deficiency of environmental conditions (Antonovsky, 1993).

In order to better understand this change of perspective, we have to consider that Aaron Antonovsky (1923–1994) initially focused on research about stress. As a medical sociologist, he tried to emphasize the "sense of coherence"[1] of the individual as protecting him/her from

FIGURE 1 The centaur transferring the secret of immortality to Asclepios

disease and possessing healing properties. In 1979 and 1987, he published "Health, Stress and Coping" and "Unraveling the Mystery of Health." Health is what is mysterious, not disease. This new perspective consists in enforcing lifestyle choices and encouraging behaviors that are health-conservative, instead of putting efforts in unraveling the causes that compromise health.

"Salutogenesis" thus encompasses an art of living, subtracting the health issue from the pure medical and scientific expertise, and transforming it into a matter of values, ethics, and social sciences.

3 | THE PARADOXES OF HEALTH BIOLOGY

Bearing this in mind, let us move to our second point, the crucial aspect of health and its preservation, especially in the elderly. As pointed out in a recent contribution, indeed "individuals are not equal when dealing with aging and the chronological age is often different from the biological age" (d'Alessio, 2018). The concept of biological aging is quite recent and introduces again a change of perspective in what has long seemed a linear evolution from embryogenesis to the senescence status of an organism.

3.1 | Biomarkers

Today, we have access to an increasing number of markers, able to draw a portrait of our organic "self" and allowing us to appreciate how well our organism is maintaining (and for how long) a sort of indefinite functionality. As reported by Lewis and Grandi (2018), specific cell types receive outside signals and act as sensors reacting to sound or light waves. These cell types die as an individual is aging, which translates in a decrease of the ability to detect related signals. Similarly, mechanical stimuli that would go unnoticed give rise to an itching sensation because of the loss of specific sensory cells. As reported by Feng et al. (2018) "during aging, the loss of specialized skin cells called Merkel cells results in allokinesis."

To be able to constantly escape one own's physical definition of aging is thus not only a matter of tracking silent chronic disease markers (pro-inflammatory cytokines, fibrinogen), or the progressive failure of the immune system efficiency, or fighting on the front of the cardiometabolic syndrome by tracking insulin, glycemic index and HOMA-IR (Homeostasic Model Assessment of Insulin Resistance), LDL (Low Density Lipoproteins), cholesterol, or fibrinogen. Epigenetic modifications do occur, because stress and lifestyle are setting the conditions for them. Identifying these subtler parameters could thus ideally allow us to slow deleterious phenomena. If not resulting in optimal aging, this at least might allow to uproot the incredible anguish linked to the perspective of humans' increased longevity, which remains an unsolved problem (Box) nobody is ever addressing.[2] Close to this come nevertheless the opinions expressed by Kaufman (2010) with the remark that "developments in clinical intervention are having a profound impact on health and health behaviors in late life and on ideas about longevity and the appropriate time for death. The fact that the *timing* of death is even considered to be a controllable event is a relatively new cultural phenomenon." Proactivity is questioned here, more than early intervention.

Box:

When I get older losing my hair - Many years from now **-**Will you still be sending me a Valentine - Birthday greetings bottles of wine **-** If I'd been out till quarter to three - Would you lock the door - Will you still need me, will you still feed me -**When I'm sixty-four** - **You'll be older too** -And if you say the word - I could stay with you - I could be handy, mending a fuse - When your lights have gone - You can knit a sweater by the fireside - Sunday mornings go for a ride - Doing the garden, digging the weeds - Who could ask for more - Will you still need me, will you still feed me -When I'm sixty-four. The Beatles.

In fact, longevity seems a matter of timing, but what timing are we talking about? The timing of preventive clinical interventions (Landau et al., 2017)? As Kaufman (2010) points out, "the choices of the self-promotion of longevity, through technological proficiencies henceforth constitute an opportunity for the emergence of new forms of subjectivity." In other words, I define myself though the strategies I choose to adopt to face my longevity, this starting from a very young age. We are more and more familiar with the idea of early intervention in prevention (Landau et al., 2017). Inevitably, a calculation about "how much *time left* is wanted in relation to age" glides into our thinking. In an environment of constant escalation of biomedical opportunities, we appreciate the question about "what kind of subject emerges when longevity, imbued with the technological, becomes a reflexive practice and an object of intervention and apparent choice" (Kaufman, 2010).

3.2 | The fascinating story of antioxidants

One example of how fast we have gone in losing sight of the right way is the fabulous success of the consumption of antioxidant nutraceuticals and cosmeceuticals, which has now been lasting for about 30 years. People just believe in antioxidants. They totally ignore that they can become prooxidants in the body, especially when associated to vitamins or metal ions such as iron, leading to a Fenton reaction instead of restoring, soothing, and preventing. Moreover, the regular consumption of antioxidants makes the benefits of exercise vanish, capturing the increase of Reactive Oxygen Species (ROS) by mitochondria (Trewin, Berry, & Wojtovich, 2018). According to Barry Halliwell, the antioxidant strategy is deleterious, as it inhibits the endogenous production of antioxidants (Halliwell, 2011; Halliwell, 2012). He precisely mentions: "Far more is known today about endogenous anti-oxidant defenses and how they are

regulated, which has led to a deeper understanding of how some ROS can act as signaling molecules. Increasing endogenous anti-oxidant levels (e.g., by supplying 'pro-oxidants') may be a better approach to therapeutics and disease prevention than consuming large doses of 'dietary antioxidants'." This statement is of particular value as it comes from the one author who most contributed to the credibility of the field of ROS and totally reverses the perspective. This is alike to what happened when immunologists began to consider that it would be better to be contaminated by some antigenic challenge during infancy in order to be able to amplify one's immune repertoire thus increasing the probability of efficient defenses, instead of spending energy to constitute a hyper-hygienic environment being deprived from such antigenic "healthy" stimulation.

Coming back to the nutritional supplementation of antioxidants, some of these are indeed naturally contained in food. This has allowed for new food intake rules—the care for its organic origin, the transportation time considered toxic, generating the philosophy of "0.5 km"—implicating the presumed benefits of the antioxidants contained in food (mostly vegetables) or such spices as curcuma.

3.3 | From antioxidants to mTOR

The latter in particular, together with resveratrol and genistein, is also a potent inhibitor of mTOR,[3] the nutrient-sensitive mechanistic kinase target that regulates protein and lipid synthesis, cell growth and proliferation, relevant to cell aging, and influencing the health span and possibly longevity. And here comes the third paradox.

There is current evidence that recommendations to inhibit the mTOR pathway seem to enhance longevity. A serious dilemma occurs as for its interference into neuropathophysiology of depression (Réus, Quevedo, & Rodrigues, 2015). The World Health Organization ranks Major Depressive Disorder (MDD) as the fourth leading cause of disability worldwide and estimates that by 2030 it will be the second leading cause of disease with a high suicide risk in affected patients. It seems that one of the main environmental factors associated with MDD is stress. Indeed, stressful events are highly correlated with the onset and progression of MDD. Several studies have suggested that activation of the mTOR pathway may elicit an antidepressant effect. Among mTOR activators are ketamine, glutamatergic agents, ascorbic acid, creatine, zinc and guanosine, as well as exercise! Undeniably, if antioxidant supplementation *per se* is debatable for its detrimental effects on the benefits of exercise, antioxidants contained in food supplements that inhibit the mTOR pathway would be even more arguable, as active competitors to the antidepressant effect of mTOR. In our perfectly bio-programmed lifespan, would we have to operate a choice when it comes to the timing of our death, between living longer or living happier? A very old question, raised possibly in part by the ambivalence of the mTOR pathway.

4 | SECRETORY PROFILE OF SENESCENT CELLS

The same kind of ambivalence is found in the Interleukine-6 (IL-6) cytokine, once mostly known as a pro-inflammatory adipokine and second messenger of TNF-α. It has also been identified as an anti-inflammatory myokine (Fuster & Walsh, 2014), promoting wound healing, depending on classical cell receptor-based signaling versus trans-signaling bound to the soluble form of IL-6Rα. Depending on environmental stimulations, IL-6 can thus promote an alternative activation of macrophages, atheroprotective actions, insulin sensitizing effects, or up-regulate myokines following exercise. On the other hand, it can also promote and sustain pro-inflammatory actions in several cell types, act as pro-atherogenic, promote insulin resistance, and up-regulate adipokines thus facilitating obesity.

But IL-6 has recently entered the field of senescence, as we know well connected, through inflammation, to aging and cancer. The Senescence and Secretory Phenotype (SASP; Coppé, Desprez, Krtolica, & Campisi, 2010) massively comprises IL-6, thus entertaining the pro-inflammatory trend. However, since cancer is able to totally divert inflammation to its own purposes, SASP may represent a sort of reappropriation of inflammation's genuine terms. Indeed, SASP may even contribute to regenerative phenomena. But what interests biologists is to get rid of senescent cells (why?). Targeted apoptosis (by senolytics) versus local clearance of senescent cells (in specific diseases) have been proposed despite a bivalent contribution to cancer development either promoting or restraining it (Baker, Alimirah, van Deursen, Campisi, & Hildesheim, 2017).

Nonetheless, despite some confusion, fantastic progress is made in the area of senescence research. In the course of less than 20 years, from being a phenomenon charged with strictly negative imaginary because of its link to aging and chronic disease, senescence has become a new hope for anticancer and noncancer pathologies. Let us have a quick look, to close the brief yet challenging list of controversies discussed, alternating from good to evil beliefs in medicine (Hoenicke & Zender, 2012). In particular SASP has moved from the status of pro-inflammatory agents to pro-regenerative tools.

Cellular senescence is characterized by a state of growth arrest and its secretory phenotype, SASP, has been shown to have tumorigenic as well as anti-tumorigenic properties. SASPs have also been involved in embryogenesis and wound healing. Along these lines, they are also promoting a pro-regenerative response through the expression of stem cell markers and regenerative capacities *in vivo* (Ritschka et al., 2017). Last but not least, senescent cells recruit and activate agents of antitumoral immunity and cancer cells can be rendered senescent by novel compounds. Indeed, senescence enhancement in tumors can be used for cancer therapy. Wang et al. (2017) have reported how they screened for compounds activated during senescence that could be used in cancer, after targeting tumor cells to induce their senescence. Using senescence to deliver "the one-two punch" to cancer cells implies senescence as induction of a vulnerability stressing the cancer cell to death, helped by immune infiltrates delivering senolytic molecules (Figure 2).

5 | A NEW PARADIGM IN PREVENTIVE MEDICINE?

In conclusion, it is difficult to find the proper impact of the results of scientific discoveries into everyday lifestyle behaviors. But, it seems that we have made a force out of a weakness. What applies to mechanisms of senescence and cancer (or other chronic diseases) could apply to several other issues. A hint to a change of paradigm comes out in this moment very clearly from recent results about exercise and nutrition, basically lifestyle.

As pointed out, our preventive mentality threatens to lead us into a timing mindset conditioned by the major issues we try to fight

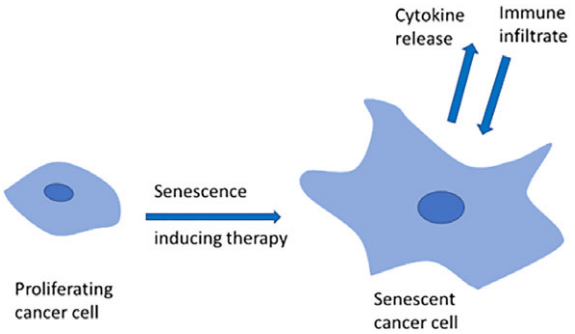

FIGURE 2 Using senescence to deliver a one-two punch to cancer cells Adapted from Bernards R., oral communication at AACR 2018

(aging, chronic disease, disability, depression, and cancer) instead of opening up to the very opposite trend, that is to carefully rethink and modulate what we already know, in order to enhance the possibilities of a health span of quality.

Movement for example is not being discussed any more for its anti-degenerative achievements, but how should we move? To efficiently corroborate anti-inflammatory roots, no sprinter starts are necessary; they are even contraindicated (Bianchi, Tiniakos, Mann, & Wilson, 2017). It seems that the greatest benefit is derived from moderate movement, as said, avoiding to consume antioxidants.

Along the same lines, instead of becoming fetishists of nutritional items because they would fit in the general antiaging timing, while eating, we should respect the gut-brain connection, introducing very simple rules relying on the combination of fibers (or raw vegetables) balanced with probiotics, already indicated more than a century ago (Cavaillon & Legout, 2016) to be essential for longevity and used intuitively since ages. Regular use of such psychobiotics (Sarkar et al., 2016) thus would preserve us from the development of a "leaky gut" that is much the beginning of the end, as it will *in fine* generalize inflammation to the whole body and, via neuroinflammation, lead to "sickness disease," simulating depressive disorders.

CONFLICT OF INTEREST

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ENDNOTES

[1]According to Antonovsky, coherence is composed by three essential components: (a) sense of comprehensibility; (b) sense of manageability; and (c) sense of meaningfulness.

[2]No reference for this issue can be found, the literature is abounding in glorification of the "longevity revolution."

[3]mTOR stands for mammalian or mechanistic (m) Target of Rapamycin

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