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Editorial

Longevity Therapeutics: The Involvement of *EDA2R*, the "Self-Destruction Gene"

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1. Introduction

Plasma Ectodysplasin A2 Receptor (EDA2R) has emerged as one of the most robust tissue-agnostic biomarkers of biological aging, and importantly, appears to be causally involved in "inflammaging"—the chronic low-grade inflammation that drives age-related decline—rather than merely reflecting it. This makes it a particularly attractive target for future therapeutic development.

The mystery of existence and the enigma of time have always captivated and concerned humanity. Time is the only non-renewable resource; it cannot be reclaimed. We aspire to long lives, yet we seldom take meaningful action toward this aim. Nevertheless, the pursuit of longevity remains a perennial and central challenge in modern medicine, and its relevance has never been greater [1]. Among the numerous hypotheses and theories of aging, one phenomenon stands out: "inflamm-aging," or "inflammaging," a phenomenon of chronic low-intensity inflammation that accompanies the aging of the human body and a number of age-related diseases. This immunometabolic concept in aging and age-related diseases has been studied extensively by Claudio Franceschi and colleagues at the University of Bologna, Italy [2,3].

Stephen R. Spindler at the University of California, Riverside, proposed that "regulatory pathways similar to those invoked by caloric restriction may be involved in determining human longevity" [4]. The hypothesis that certain medications can have the same physiologic effects as calorie restriction was evaluated using glucoregulatory and other drugs. For example, metformin treatment for 8 weeks showed better results than the same period of calorie restriction in inducing specific changes in gene transcript levels. Spindler referred to observations of mean and maximum lifespan increases in metformin-treated HER-2/neu mice and introduced the term "longevity therapeutics" for the use of such microarray biomarkers for identifying potential pharmaceuticals that may be used to extend lifespans.

Recently, Ildus I. Ahmetov (Central Research Laboratory, Kazan State Medical University, Russian Federation), who is currently affiliated with Liverpool John Moores University, UK, and Marco Bolis (Istituto di Ricerche Farmacologiche 'Mario Negri' Milano, Italy and Università Della Svizzera Italiana, Bellinzona, Switzerland), along with their research group, identified the Ectodysplasin A2 Receptor gene (*EDA2R*) as being associated with accelerated human aging—the "aging gene" [5]. We propose that the *EDA2R* gene controls the process of inflammaging (as defined by C. Franceschi) and, therefore, represents the

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genetic counterpart of this phenomenon, serving as the "self-destruction gene." Barbera et al. [5] discovered that increased expression of the *EDA2R* gene is a universal hallmark of aging and mediates inflammatory responses, regardless of the organ, tissue, or even species.

EDA2R (also termed XEDAR or TNFRSF27) is a member of the tumor necrosis factor (TNF) receptor superfamily [6–8]. It is known for its role in ectodermal development—skin, hair follicles, glands—but has emerged as a major player in aging biology. As humans age, EDA2R protein levels increase in plasma-derived samples, indicating that the observed effects are not solely transcriptional [5]. This elevation is tissue-independent and is particularly pronounced in models of accelerated aging [5]. The *EDA2R* gene is located on the X chromosome (Xq12) and is located close to the androgen receptor gene in the human genome, suggesting potential co-regulation [9].

2. A Key Component of Proteomic Aging Clocks

In a study of plasma proteomics, sixty proteins were found to be associated with aging-related conditions. Among these proteins, EDA2R was in the top twenty for various metabolic aging phenotypes [10]. EDA2R is implicated in baldness and the metabolism of estradiol, testosterone, and high-density lipoprotein [5]. It ranks consistently among the top predictors of biological age across both sexes and is a key component of the proteomic aging clock [11].

3. EDA2R as a Biomarker and a Driver of Aging

Elevated EDA2R levels are correlated with many diseases, including accelerated biological aging, dementia, and higher all-cause mortality [12]. EDA2R actively drives aging, with its overexpression inducing inflammation and tissue damage, whereas its inhibition mitigates these effects. Binding of EDA-A2 to EDA2R induces the trimerization of the receptor, which leads to the recruitment of TNF receptor-associated factors, TRAF3 and TRAF6, leading to the activation of three pathways. This results in the activation or regulation of genes involved in immune responses, inflammation, apoptosis, and cellular stress [12], which may also be triggered by age-related increases in blood lipopolysaccharide (endotoxin) levels [6]. Thus, the EDA2R/EDA-A2 axis may play a pivotal role in mediating age-related inflammatory and degenerative processes in tissues [12].

Elevated plasma EDA2R protein levels are associated with accelerated biological aging, as measured by biological clocks such as PhenoAge, and are negatively correlated with healthspan, longevity, and telomere length [13]. Elevated expression of the *EDA2R* gene in blood was found to be consistently associated with higher levels of C-reactive protein, a key marker of systemic inflammation [5]. Elevated levels of EDA2R in blood plasma are associated with a wide range of diseases, including various cancers, heart failure, coronary heart disease, atrial fibrillation, diabetes, obesity, neurodegenerative disorders, and osteoarthritis [14,15].

4. Muscle Atrophy and Sarcopenia

EDA2R signaling promotes muscle loss and glucose intolerance. Upregulated *EDA2R* expression in muscle tissue is associated with aging, denervation, cancer cachexia, and muscle atrophy, and aging-related sarcopenia [5,16,17].

5. Disease Risk and Accelerated Aging Comorbidities

Various aging-related comorbidities—such as type-2 diabetes, fatty liver disease, insulin resistance, and obesity—can further amplify the activation of the EDA2R/EDA-A2 pathway by influencing ligand levels [5]. EDA2R has also been identified as a protein biomarker associated with cognitive impairment in older adults. Harris et al. [18] reported

that elevated levels of EDA2R are associated with smaller total brain volume, smaller gray matter volume, and less normal-appearing white matter volume. EDA2R is among the most prognostic proteins for dementia, with increased levels detectable 10–15 years before clinical diagnosis [19,20]. Given the important role of endotoxin in the pathogenesis of age-related diseases and the classification of endotoxin aggression as a pre-disease state or universal factor in disease pathogenesis [21], it is probably involved in increasing *EDA2R* gene expression.

Barbera et al. emphasize that the *EDA2R* gene functions not only as a biomarker of chronic inflammation but also as a contributing factor to aging [5]. Furthermore, the expression of this gene is positively correlated with increasing age in all human organs studied; moreover, it has been found to be particularly elevated in over 100 diseases [5]. This gene can be considered, in our opinion, to be the human body's "self-destruction gene." Now, human aging could be formulated as the self-destruction process of the organism through its immune system with the participation of the *EDA2R* gene, endotoxins, and stress phenomena. Targeting the *EDA2R* gene may unlock new therapeutic avenues not only for treating age-related diseases but also for slowing the aging process and extending the human lifespan. If, according to Barbera et al. and Farrington et al. [3,5,7,12], calorie restriction, physical activity, *Ginkgo biloba*, and metformin can reduce *EDA2R* gene expression, it is plausible to hypothesize that other natural bio-antioxidant complexes, such as garlic, ginger, turmeric, and several other plants, may have similar effects.

6. What Can Lower EDA2R?

Although specific *EDA2R* antagonists are not yet available, interventions such as calorie restriction, physical activity, and specific supplements show promise in lowering EDA2R levels [12]. Natural compounds such as Ginkgolide B (from *Ginkgo biloba)* and the exercise-induced metabolite betaine have been shown to downregulate *Eda2r* expression in aged mice, suggesting potential geroprotective strategies [22,23]. It may also be possible to specifically inhibit the expression of *EDA2R* via RNA interference technology [24,25].

The findings of C. Franceschi, I.I. Ahmetov, M. Bolis, and colleagues [2,3,5] can be applied in anti-aging therapy, inspiring optimism regarding the achievement of longevity and representing one of the greatest scientific achievements in medicine in this century.

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