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ORIGINAL PAPERS

A Preliminary Mini-Review on the Relations Between Lipofuscin, Aging and the Oxidative Stress Status - the Possible Implications of Gut Functionality

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Abstract
Recently gut microbiome, genetics, and epigenetics have been incresingly cited for being involved in aging and longevity. In addition, the oxidative stress status also has a significant role in the context of aging and longevity, where also lipofuscin take place and become a hallmark of aging. Thus, in this mini-review we highlighted the role of the gut microbiome in aging and longevity, and its relationship with antioxidants in the prevention of age-related diseases. We also discussed the possible mechanistical aspect for the interactions between lipofuscin, oxidative stress, and aging, and we reveal additionally a new theory of aging based on the complex interactions among genetics, microbiome, environment, aging and longevity.

Keywords*:* Lipofuscin, Oxidative stress, Aging, Longevity, Microbiome

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Introduction

Lipofuscin a lipid peroxidation final product [1], called also the "aging pigment" is a yellow-brown pigment under the conventional microscopy, it is practically increasing in aged individuals than in young ones [2] it was demonstrated that lipofuscin is a hallmark of aging, and it is inversely correlated with longevity usually it accumulates in postmitotic cells [3] like neurons, cardiac myocytes and skeletal muscle fibers as reviewed in [4]. Lipofuscin accumulations are well- known as a strong marker of aging [4] and it is a time-dependent phenomenon, it results from various genetic and environmental conditions [5], Lipofuscin is highly oxidized cross-linked protein (30-58%) and lipid (19-51%) clusters. researches described the formation of lipofuscin in the cytosol, that was caused by oxidative stress .also mitochondria play an important role in lipofuscin formation where the mitochondria the place for intracellular

energy source also susceptible to oxidation stress [6] it was hypothesized that, lipofuscin is formed within secondary lysosomes, as result of interaction between two process, the production of partially reactive oxygen species by mitochondria and the autophagocytotic degradation within secondary lysosomes, which described as follows, the ferrous reactive ion and H_2O_2 interact together and form hydroxyl free radicals (OH), inducing lipid peroxidation which lead to intermolecular cross-linking and formation of lipofuscin [7]. Chemically the composition of lipofuscin has been studied, the obtained results indicate that lipofuscin are composed of 30-70% proteins " (glycine, valine, alanine and proline, several hydrolytic enzymes), 20-50% lipids (Cholesterol, phospholipids, triglycerides, free fatty acids, bis (monoacylglycero) phosphate, ubiquinone, dolichol and phos-phorylated dolichol, 4-7% carbohydrates (mannose, N-acetylglucosamine, glycine, glucose and galactose) and metals in trace amounts (Iron, copper aluminum, zinc)" [8], [9] lipofuscin characterized by autofluorescence under fluorescence microscope "Ex: ~440; Em: ~600 nm" [10] lipofuscin is usually found in nerve skin and cardiac cells due to nature of lipofuscin as it accumulated in the lysosomes and cell cytoplasm of long-lived post-mitotic and senescent animal cells on the other hand, other cells which can be proliferate show a low abundant in this pigment as it may dilute it like in glia cells there are also lipofuscin but it should be in less amount than neurons as glia cells are subjected to division, but high concentration of lipofuscin is suggested to be due to from the transfer of neuronal lipofuscin to glia cells, Labile cells like bone marrow have the ability to dilute accumulated lipofuscin, but postmitotic cells such as neurons are not able to do so. mainly lipofuscin found in neurons, skeletal muscle cells and retina but retina has special interest concerning lipofuscin distribution because lipofuscin found in the retina is different from that of other body tissues [11], [12] also lipofuscin can alter cellular proteostasis which also called (protein homeostasis) is a mechanism which control synthesis, folding, trafficking, translation and degradation of proteins also it considers to be a major factor in neuronal activity, in the aging of this mechanism become less effective, which surely can be lead to diseases such as Parkinson's disease [13], Huntington disease (due to lipofuscin accumulation as it observed in the brain of patients) [14], [15] and other aging diseases like Alzheimer's disease [16] There are some of the studies suggesting that cytotoxicity occurs as the end product of process starting with an accumulation of lipofuscin that causes inhibition of proteasome which functions to degrade unneeded or damaged proteins like oxidized proteins which finally leading in increasing free radicals as reviewed in [12], [17]

Oxidative stress is the condition that happens due to imbalance between reactive oxygen species (ROS) and antioxidants [18] there are a variety of

studies suggest that lipofuscin accumulation is due to oxidative stress as reviewed in [19], [20] but it is not only oxidative stress it also because of the inability of removing oxidatively damaged structure take into account that the mitochondria are the main source of oxidative stress [21] Oxygen itself has an important role in the cell, as cell respiration which is an essential process for the cell [22] however the excess oxygen can cause unbalance in cell function[23], given the fact that oxidative stress enters in many impairments in the cells especially the brain ones [24], lipofuscin increases this risk of oxidative stress [3]. Moreover, lipofuscin can produce oxidants in senescent cells however the amount is moderate [25] oxidative stress has been linked with a variety of disease including age-related disease even the age-related development of cancer [26], [27]

Denham Harman was first one who proposed association between aging and the degenerative diseases under the free radical theory of aging [28], [29] It is known that lipofuscin is inversely correlated with longevity, and as we mentioned above lipofuscin and oxidative stress have been correlated with some age-related diseases, going to insights into these finding, and ask what should be the relation between lipofuscin, oxidative stress, and aging?, as we have shown in (**Fig.1**) the process should be starting first with oxidative stress which will promote and enhance lipofuscin formation, the oxidative stress may is triggered by a deficiency in antioxidants and an increasing in ROS production but there is another pathway which starts first with impaired in cellular proteostasis and eventually leads to lipofuscin formation and accumulation which will enhance the production of ROS [6], [8], [12], [19], [30]–[32]

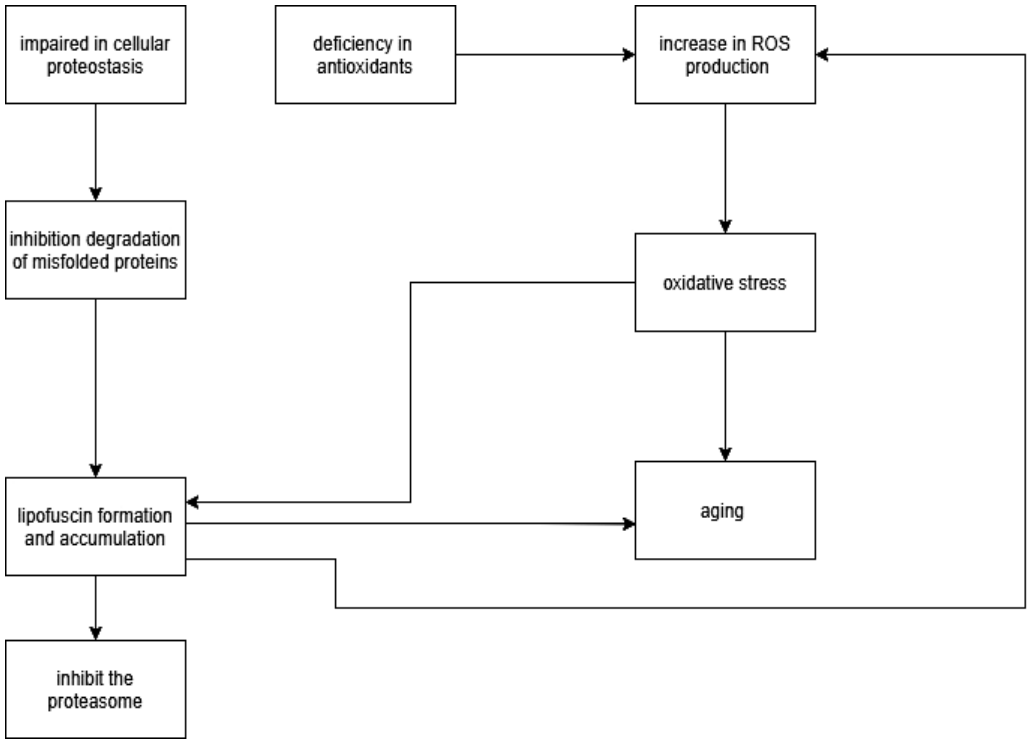

Fig.1. A possible mechanistical aspect of the combination of lipofuscin, oxidative stress and aging– modified after [6], [8], [12], [19], [30]–[32].

Also lipofuscin formation may enhanced by free iron which induced or participated in oxidative stress and it has been reported that free iron is associated with several neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease which consider to be also as aging disease [33], [34] it have been reported experimentally in rats, where is lipofuscin formation induced via free iron as injected into intralumbar [35] going into details of every process we may conclude that impairments in antioxidants play a significant role in lipofuscin formation as it resulting in oxidative stress or oxidative damage finally this oxidative stress lead to lipofuscin formation, but moved back and ask from where these impairments in antioxidants occur and why it occur first it must be a balance in antioxidants and free radicals, without this balance, the oxidative stress will exactly happen, because antioxidant known as a defense mechanism against oxidative stress, Antioxidants is divided into two more categories Enzymatic and Non- Enzymatic, Enzymatic one is like Superoxide dismutase, Catalase, Glutathione systems, which are essentials in protecting cells from oxidative stress on the other hand there are some and Non- Enzymatic like Ascorbic acid, Glutathione, Melatonin, Vitamin E, Uric acid [36], taking into account the

dietary antioxidants like Polyphenols which found in fruits and vegetables and tea can delay aging process and involved in the protection from chronic pathological disease which induced via oxidative stress [37]–[39] an example of antioxidant defense and aging is a mild cognitive impairment which considered to be a stage between cognitive decline of normal aging and decline of dementia and it correlated with propagation of Alzheimer's disease, a study demonstrated a positive correlation between the decreased antioxidant defense and increased lipid peroxidation in MCI and AD patients [40].

Factors may lead to impaired antioxidants

1- Genetics

Some SNPs in antioxidant genes have been reported to impaired antioxidants in several diseases like obesity [41], inflammatory bowel disease[42], Hypertension 'silent killer' which is considered to be a risk factor for cardiovascular disease and kidney failure, coronary artery disease[43]–[45], Prostate Cancer [46] which older people are more likely to have it[47], the obstructive pulmonary disease [48]which could be considered a disease of accelerated aging [49], [50].

2- Diet

Eating antioxidant containing food, may protecting from oxidative stress which consider to be risk factor for aging, age-related disease and chronic diseases, the core of diet not only due to it is nutritional value of some vitamins which considered to be antioxidants but also due to it is ability to modulate gut microbiome which is important factor in antioxidant activity, an example of this is Carotenoids, which defined as plant pigments responsible for red, yellow and orange pigments in many fruits and vegetables, it considered as non-enzymatic antioxidants several studies has been some impact of it on health [51] [52] a review article summarizing the impact of Carotenoids from clinical trials against skin, eye, hepatic, cardiovascular diseases and some types of cancer reported that Carotenoids have shown a significant role in the body's defense against reactive oxygen species [53] and may protect from age-related diseases[54], one of carotenoids is Lycopene which observed in Parkinson's disease and vascular dementia patient in low amount [55] there is a growing evidence that lycopene may protect from cardiovascular disease [56]–[60] also b-carotene was observed in low amount in serum of patients with Symptomatic atherosclerosis[61] dysbiosis which defined as a microbial imbalance in the gut which can lead to various disease as Alzheimer's disease, Cardiovascular disease, obesity, inflammatory bowel disease [62] these diseases also have been also linked with oxidative stress [63]–[66] Carotenoids can delaying the development of dysbiosis and protecting gut homeostasis [67] . higher dietary of non-enzymatic

antioxidant capacity was correlated with decreased risk of death from cardiovascular disease, heart disease, and cerebrovascular disease suggesting that may help to achieve longevity as reported in the study on Japanese adults population [68] also microbiota can effect on mitochondria and inducing oxidative stress [69] take into account that psychological stress like depression may induce oxidative stress and accelerate aging [70]–[73]

General aspects of the genetics of the longevity-related processes

All process in the cell is controlled genetically, by various pathways of gene expression, however, the environment also has an effect on this expression and it may be various among individuals, which is called Epigenetics or gene-environment interaction, even noncoding sequence like small noncoding RNA plays a role in aging and longevity, longevity is a very complicated process it is controlled genetically and also environmentally additionally there is a role for population genetics in longevity.

Concerning genetics and the evolution theory of aging, the main theory of aging in evolutionary theories of aging is the theory of programmed cell death which first introduced by Dr. A. R. Wallace who proposed that individuals are programmed to die as a result of the force of natural selection, Dr. Williams also proposed a theory of antagonistic pleiotropy, which defines as " one gene control for more one trait one of these traits is beneficial to the organism's fitness", but after reaching to reproductive success an adverse effect of this genes are occurred [74], also the theory of mutation accumulation which introduced by Medawar [75], [76] moreover "Hamilton's forces of natural selection" which first introduced as a theoretically work represented by mathematical equations which display that forces of natural selection were reduced with age, then confirmed experimentally using Drosophila moreover "Hamilton's forces of natural selection" can be used to manipulate experimentally the cessation of aging as reviewed in [77]

Thus, it is generally believed that longevity is a very complex trait, which controlled by various factors genetic and non- genetic factors, the non- genetic factors is an environmental factor, the genetics factors are controlled by many loci, and also noncoding sequence may a has a role in longevity, as there is growing evidence that genetics influence on longevity [78]–[81]

An additional number of studies has been successful in identifying a number of life span genes in short-lived invertebrate models as C. elegans, D. melanogaster, and S. cerevisiae, by knocking out of genes approach but in mammals forward genetics were the used approach used to identify some ageing loci as reviewed in [82] one of first genome wide association study involved in longevity was done by using a 308 individuals belonging to 137 sibships, and they noted that chromosome 4 at D4S1564 region linkage with longevity [83]

study also done by Dr. Reed and his colleagues demonstrated the association between locus near D4S1564 and healthy aging [84] Dr. Puca group continued the research and they identified a SNP in microsomal transfer protein this protein helps produce beta-lipoproteins [85], however this findings later was not proven and the opposite has been proven, there is no association between microsomal transfer protein and longevity [86], [87] . among past years there are some examples of SNPs that have been identified SNPS were identified in many genes like TP73, LMNA, NRXN1, COL6A3, RBMS3, CTDSPL, MB21D2, SDAD1 RCBTB1, RCBTB1 MAPKAP1, PRKCB, APOE and CDH4 as reviewed in [82] one of most important gene influence on longevity is a APOE gene which is responsible for making apolipoprotein E Protein this protein combines with fats to form lipoprotein [88] ε4 allele of this gene is associated with decreasing in odds [89] [90] while also ε4 allele was reported to associate with some ageing related disease as Alzheimer's disease [91]–[94] and Ischemic cardiovascular [95] however some another study reported the opposite [96] and cognitive dysfunction in multiple sclerosis [97] however there is a study reported that there is no association between cognitive dysfunction and impairment in multiple sclerosis and ε4 allele [98] example of another important gene is a FOXO3A gene which functions as a trigger for apoptosis, it has been reported that this gene is associated with longevity in germen and Italian and chinses and Japanese population [99]–[102]In addition to, a functional RNA molecule that is transcribed from DNA but not translated into proteins which are called noncoding RNA, such as microRNAs, small interfering RNAs, long non-coding RNAs, several studies indicated that noncoding RNA plays a role in several age-related diseases like Alzheimer's disease [103], Ischemic Stroke [104], myocardial infarction[105], cancer [106], type 2 diabetes [107], hypertension [108], osteoarthritis [109], Cataract [110], atherosclerosis[111] and another diseases [112]

Another example of epigenetics is DNA methylation, which is may occur at CpG islands located with promoter regions some of the studies reported some genes showing age-related DNA methylation like VASHI, RAD50, CD4, APC, P16, HIC1, WT1, OGG, DLC1, FGF8, LOX, DRB1, INFG, LEP, LHX5 also there are some environmental factors may leading to DNA methylation as chemicals and pollutants like mercury, cadmium, lead, arsenic, chromium, smoke and also diet as high-fat diet as reviewed in [113]

Longevity, aging, and the microbiome

It is known nowadays that the microbiome has an impact on health and the alteration of its composition may associate with the healthy body or diseased one [114], it was reported from a variety of animal models including nematodes and monkey even humans that reduction in food intake and prevent malnutrition resulting in extends lifespan [115] microbiome of old individuals was different of younger individuals where the microbiome of old one's shifts to *Bacteroidetes* [116] low abundance of *Coprococcus and Faecalibacterium* were reported in Italian and Chinese centenarians population [117]–[121]Several studies have been liked several age-related diseases and the alteration of the composition of the gut microbiome, like Alzheimer's disease in human and animal model, *Firmicutes and Bacteroidetes* phylum were more abundant in Alzheimer's disease, in particular, in human the following genera were more abundant *Blautia, Bacteroides, Alistipes, Phascolarctobacterium, Gemella*. [122], [123] while in Parkinson's disease patients, *Lactobacillus* was more abundant while *Clostridium coccoides* group and *Bacteroides fragilis* group were lower than controls [124], *Bacteroidetes* and *Prevotellaceae* were less abundant, *Enterobacteriaceae* were more abundant in fecal samples from Parkinson's disease patients [125]

Also in a cardiovascular disease like Symptomatic atherosclerosis, *Collinsella* was enriched in patients with Symptomatic atherosclerosis where *Eubacterium, Roseburia* were found in low abundance [61], patients with stroke and transient ischemic attack show a high abundance of *Enterobacteriaceae, Proteobacteria Escherichia/Shigella,* and low abundance in Bacteroidetes, *Bacteroidales, Bacteroidaceae, Bacteroides* [126] *Firmicutes* and *Bacteroidetes* were found in high abundance while *Lactobacillales, Bacteroides* and *Prevotella* found in low abundance in coronary artery disease patients [127], take into account that genetics may influence of gut microbiome [128] and maybe influence more than environment as reported experimentally in a murine model[129]

The aforementioned aspects could be also related o the fact that there can be a relationship between the gut microbiome, and longevity since gut microbiome can be alternated in some conditions including diseases and diet [130]–[134]

Conclusions

Genetics is not the only the factor that influences on longevity and aging however it considers to be as important while other factors take into account including environment as gene-environment interaction and lifestyle as a diet which strongly effects on the gut microbiome and maintaining gut microbiome homeostasis is considered to be an important factor for longevity based on our review we can reveal a new theory of aging called " genetics, microbiome and environment theory of aging and longevity " which demonstrate all possible aspects interact together to lead to longevity and aging see **Fig.2** oxidative stress seems to be so harmful to occur and it may lead to various impairments in the body it is controlled by both genetic and non-genetics factors which is an environmental condition, avoiding oxidative stress is the best way to reach longevity even if there a genetic susceptibility to induce it but working on environmental effect is considered to be important so if no escape from occurring oxidative stress trying to late the process, will affect on longevity and may increase it. Thus, in our future studies, we will better concentrate our efforts in the understanding of how the connections between lipofuscin and aging are affecting the digestive manifestations, with a special focus on the gut complex functionality.

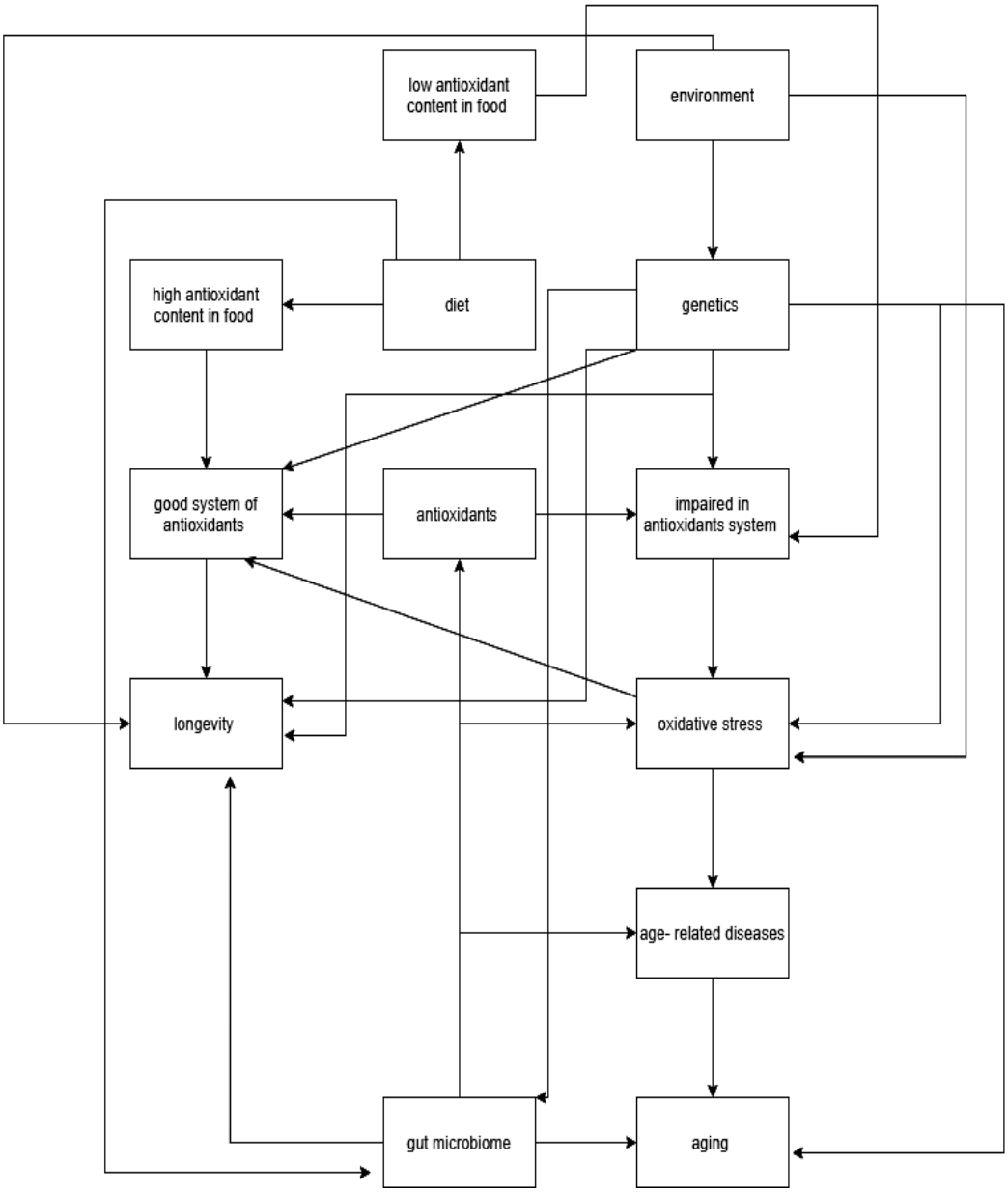

Fig.2. A schematic approach for the " genetics, microbiome and environment theory of aging and longevity " complex interactions – modified after [26], [80], [119], [128], [130], [135]–[150]

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