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Original Research Paper

Dermatology

EPIGENETICS AND AGING

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ABSTRACT Aging is an inevitable Biological phenomenon determined by genetic and epigenetic processes. Various studies have indicated aging is associated with progressive changes in epigenetics. Epigenetics is a dynamic process like aging and is affected by DNA methylation, histone acetylation, post translational modifications of histone proteins and varied non-coding RNA expression. These can turn on or off the genetic expression of a particular set of DNA and defects in them lead to aberrant gene expression and genomic instability. Growing number of studies have found out that these epigenomes can be modified by environmental influences, like dietary supplements, exposure to pollutants, caloric intake and biological stress. These epigenetic processes which are transgenerationally inheritable make the cellular organisms prone to aging and senescence. As these epigenetic markers are potentially modifiable, these new studies have opened up innovative therapeutic interventions in aging and other geriatric associated diseases such as Diabetes mellitus type 2, cancer, etc. The aim of this literature review is to give a brief summary of the relation between aging and modifiable factors affecting epigenetics. In the end, we highlight the different measures which are preventive and curative to arrest or modify or reverse the aging.

KEYWORDS : Epigenetics, Aging, Environmental influences, Diabetes mellitus

INTRODUCTION:

Aging is a complex multifactorial biological process shared by all living organisms. It is a time dependent process which affects all physiological functions to gradually decline. Earlier focus of research was on the genes that impact aging, but recently the nongenetic regulation of aging is opening new frontiers to investigate the age related disease processes. Epigenetics include mechanisms regulating gene expression independently of changes to DNA sequence, regulate gene excursion by modulating the structure of chromatin or regulate the binding of transcriptional machinery to DNA. Epigenetic alterations over the course of an individual modify his/her phenotypic appearances.[1] The epigenetic factors which are potentially reversible are leading to the development of newer opportunities to alter the pathways of age-related diseases. The most astonishing outcome of the research about the nongenetic control of aging is the possibility of age "reversal".[2] The epigenetic factors related to aging are involved in pathogenesis of diseases like cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases.[3] Epigenome mediated cellular alterations have emerged as a crucial link between intrinsic genetic makeup and extrinsic environmental influences.[4] These epigenetic factors are transferable from one cell to its daughter cell and inheritable from generation to generation. With ever growing advances in medical research, our life expectancy has improved considerably, however health span is still lagging behind. The modern treatment of diseases has reduced the mortality but has failed to prolong the disease free period. Our aging population continues to suffer for longer period with one or more chronic diseases. Thus, there is an urgent need to extend health span by arresting or delaying the aging process.[5]

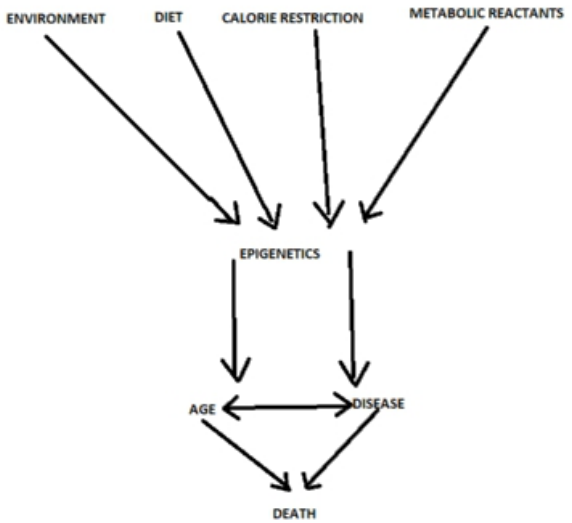
Environmental pollution including air, water and food along with various allergens, irradiation, tobacco use, excessive exposure to ultraviolet light and alcohol consumption etc are implicated in the aging and disease processes. The amalgamation of multiple factors and their interactions determine the final phenotypic appearance of a particular individual.

The best example to study role of epigenetic factors in modifying the phenotypic features and susceptibility to various diseases are monozygotic (MZ) twins. They are made up of the same genotype as they are formed by cell division of one zygote in to two. However, MZ twin siblings show observable phenotypic differences in various anthropomorphic features and their susceptibility to different diseases. Research using twin model and isogenic animal models indicate that environmental factors may cause phenotypic discordance between MZ twins through changes in epigenome.[6]Bisphenol A (BPA) is an endocrine disruptor found in polycarbonate plastic used in food and beverage containers, including baby bottles. Endocrine disruptors mimic or block action of hormones, thus interfering with endocrine system. Exposure to BPA is associated with high body weight, increased risk of breast and prostrate cancer and altered reproductive function.[7]It has been postulated that epigenome mediated phenotypic variations during development can be random, unpredictable and statistically measurable.

The study on calorie restriction (CR) in lower species infers that, CR influences epigenome resulting into delaying geriatric chronic diseases like atherosclerosis, diabetes, cardiovascular and neurodegenerative pathologies.[8] Nutritional interventions that promote longevity and health span could be able to attenuate age-associated epigenetic alterations and could have protective effect against various diseases. Under CR, the age related changes in epigenome are profoundly delayed, as CR promotes maintenance methylation and promotes epigenetic drift.[8]Whether

sustained calorie restriction or periods of fasting increases longevity in humans is not known.[9] The researches are channelizing their studies on understanding the mechanism of increased susceptibility to diseases by studying tissue biology, physiological phenomenon, and systemic homeostasis which are thought to be drivers of aging. Future studies incorporating specific targets attributed to aging and studying agents that lead to susceptibility of human beings to chronic non communicable diseases would potentially be used as therapeutic tool in the field of clinical medicine.[10] In milieu of these studies, it will be interesting to know how calorie restriction can affect the age related and epigenome mediated disease processes in human beings.

There is a direct relationship between dietary inflammatory markers and epigenetic expressions. Raised systemic inflammatory markers are implicated in the pathogenesis of aging. Glucose intolerance is closely linked with increased dietary inflammatory index. The adaptability of beta-cells decrease with advancing age, resulting in insulin resistance and is expressed as postprandial hyperglycemia in the geriatric population.[11] The incidence of type –II DM and incidental detection of hyperglycemia in the routine blood sugar analysis of aged population are on the rise. Demographic differences and clinical features of recently detected and incidentally detected DM, may lead to a better understanding of the pathogenesis of hyperglycemia in diabetes related to aging. Even the treatment recommendations will differ as per the age of the patient. Glycosylated hemoglobin is found to be relatively lower in geriatric onset diabetes there by reducing the insulin requirement. There is increased incidence of retinopathy in late onset DM than in adults with diabetes diagnosed in middle age but at the same time incidence of cardiovascular diseases and peripheral neuropathy do not differ in these two groups according to age at onset.[12]Cerebral ischemic events, lower extremity ischemia, myocardial infarction, impaired vision and end-stage renal diseases increase in adults with DM. Patients over the age of 75, are more prone to develop multisystem complications associated with DM, as compared to lower age groups. All the efforts, should be directed to improve patient care in complicated diabetes as most of the factors attributed to disease progression are modifiable.[13] These modifiable, age related, epigenome mediated risk factors should be our targets for directing the future treatment strategies.



Metformin and other Oral hypoglymemic pharmaceutical agents are postulated to have antiaging properties. [14] In geriatric patients, metformin is chosen as the first line of treatment for DM. The anti-aging property of metformin is attributed to its ability of decreasing the glucose availability in extracellular space. It also lowers cardiovascular events combined with lower tendency of the hypoglycemic episodes in aged patients. The important drawback of the metformin treatment is, it cannot be started in patients with decreased GFR < 30millilitre/minute. The full dose (2000 mg/day) metformin is advocated in patients with GFR > 60 milliliter/minute and a half dose (1000 mg/day) in patients with GFR 30-60 millilitre/minute. Metformin induced weight loss can act asa potential benefit when used in obese patients. The acid peptic disorder associated with metformin can be minimized by administering initial dose of 500 mg/day and gradually increasing the dose within next few weeks.[15]

In older population, obesity may be induced by dietary inflammatory agents through interactions of inflammatory markers and slowing of metabolic function. A study by Alam I et al, have investigated the role of dietary factors in immunological modulation. The Immune biomarkers may be useful in the future for studying the inflammatory potential of nutritional factors leading to aging. Extensive research is required in the gut-brain metabolic axis and dietary modifications to prevent apoptosis of the cells. Dietary interventions like high fat-low carbohydrate diet, dark green leafy vegetables and broccoli can retard, control or reverse low grade inflammation, therefore, can control the aging process and chronic epigenomic diseases. This approach can extend the lifespan of an individual.[16]

The Skin is most voluminous organ in the body, exposed to both intrinsic and extrinsic aging factors. Wrinkles, loss of skin tone, loss of elasticity, roughening of the skin texture are attributes of skin aging. Functional and structural modifications in extracellular collagen and elastin matrix in combination with altered expressions in cells of the skin are all involved in the process of aging skin. Extrinsic factors such as dehydration, ultraviolet radiation, cigarette smoking and heavy alcohol consumption are implicated in premature apoptosis of cutaneous cells. While, Intrinsic factors are genetic mutations and epigenetic processes. These two pathways acting in tandem modify phenotypic appearances in the form of graying and fraying of hairs, coarse textured and wrinkled skin.[17] [18]

Smoking damages repair mechanisms and decreases extracellular matrix turnover (collagen and elastin synthesis), leading to premature signs of aging.[19][20] Alcohol consumption decreases dermal carotenoid concentrations by impairing antioxidant defense system of skin[20] and causes peripheral vasodilation.[21][22] A recent study proved that smokers had more severe signs of aging like increased forehead and glabellar lines, infraorbital puffiness, nasolabial folds, oral commissaries and reduced lip fullness than non-smokers. The same study also showed that infraorbital puffiness, mid face volume loss and blood vessels on cheeks were more severe in heavy alcohol drinkers than non-alcoholics.[23]

Biological byproducts have bearing on expression of epigenetic cascade. Free radicals are generated during intrinsic metabolic processes and extrinsic factors as infections (bacteria,Viruses , fungi or parasites) and allergens. Free radicals are produced by chemical accidents during utilization of glucose and proteins by mitochondria and these oxygen, nitrogen radicals and cytokines are required by the body as defense against pathogens but our body needs to maintain fine balance between these free radicals and antioxidant agents like glutathione or superoxide dismutase. If there is overproduction of free radicals, they will cause damage to our own cells through epigenetic mediators. Increased oxidative stress is implicated in the development of many diseases like heart diseases, stroke, dementia, parkinson's disease, lung fibrosis and

malignancies, arthritis.[24] Dietary trace elements like Vitamin A,E,C and zinc exhibit antioxidant properties and should be maintained adequately in our daily diet. Glutathione is a newer molecule used in rejuvenation of skin and body as a whole.

Emerging studies have shown physical activity (PA) modulate mechanisms associated with epigenetics of variety of chronic human diseases including cancer, metabolic disease, cardiovascular disease and neurodegenerative disease. Brain derived neurotrophic factor (BDNF) is a protein involved in neurogenesis, brain development and learning.[25] Exercise is known to promote BDNF production.[26] lack of physical inactivity increases in DNA methylation of peroxiding proliferator-activated receptor-gamma, co activator 1-alpha, promoter region and increase insulin resistance.[27]

This systematic review underlines that environmental factors, diet, calorie restriction and biological reactants contribute to the epigenetic changes which in-turn have effects on aging and disease processes. Aging and disease processes are also interlinked and together they lead to apoptosis of cell and death as final event. (Fig.1)

We need to take preventive as well as curative measures to arrest the premature aging of skin and hairs. Primary prevention measures include those taken prior to initiation of the aging process. Secondary interventions encompass procedures when the first sign of aging already set in. Tertiary measures are timed at negating established signs of aging. Photo protection and abstinence from smoking and alcohol consumption are the main stay of primary prevention. Photo protective agents, hair growth factors and anti-aging measures play pivotal role in aesthetic dermatology. Skin resurfacing peels, Microdermaabrasion, laser for facial rejuvenation, hyaluronic acid fillers, radiofrequency techniques, botulinum neuromodulators, injections of platelet rich plasma to promote the hair growth, cell replacement therapy with stem cells and corrective surgical procedure like autologous hair transplant are promising interventions with ever growing demand.

CONCLUSION

In the present literature review, we observed that environmental factors, calorie restriction, dietary supplements and metabolic reactions modify epigenetics. However, there is significant scope for better understanding of various environmental factors and their precise pathology in aging. Though caloric restriction is known to reduce chronic illnesses in lower animals, precise mechanisms for the same and longevity due to disease free period needs to clearly elucidated. The role of metformin in reducing disease free period and prolonging life is well established. Antioxidants like vitamins and minerals reduce free radical oxidation and prolong disease free period and delay aging. Newer generation tertiary interventional anti-aging procedures like use of chemicals, Laser, Radiofrequency, inoculation of growth factors, stem cell transplant and organ transplants help in restructuring and rejuvenating skin and hair. But do these measures will ultimately result in modulating epigenetic markers attributed to the aging process and thus, this parameter must be given utmost importance.

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