

Different Prevalence of Chronic-Non-Infectious Diseases

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Abstract

Inflammatory bowel disease, coronary artery disease, cerebrovascular disease, hypertension, diabetes, tumours, are examples of chronic degenerative diseases that have a high prevalence in developed nations. These chronic-non-communicable diseases have multifactorial aetiologies that considered to be caused by the interaction of environmental risk factors with multiple predisposing genes. Genetic researches on these diseases have traditionally focused on investigation aimed at identifying disease-susceptibility genes. Recent evidence suggests that somatically acquired DNA mutations may also contribute significantly to the pathogenesis of these disease states such as coronary artery disease indicating a similarity between the atherosclerotic and carcinogenic processes. The high incidences and prevalence of these chronic diseases in the Western World in comparison with the East and changing trends in disease incidence (seen in many countries) provide strong evidence that those environmental factors as playing a major influence in disease-expression. There is an ample reason to believe that environmental factors have contributed to inducing alterations in genetic code in precedent generations, which were subsequently inherited and further modified by modern life style activities. Consequently, we now see the appearance of chronic degenerative diseases and their higher incidences in the Western nations as compared with the Eastern ones.

Keywords: *Hypertension, Coronary artery diseases, Stroke, Diabetes, Bowel diseases, Genetic code, Genetic mutation, Inheritance*

Introduction

A single genotype may give rise to many different phenotypes under varying circumstances of environment. In turn, one environmental factor may act to elicit various responses depending on the genotype of the organism, which determines the threshold of the responses (1).

The concept about the ability of environmental factors in introducing changes in genetic codes has been accepted recently (2-6).

Communications of free radicals such as superoxide, nitric oxide (NO), and peroxynitrite have been established to be important in the pathogenesis of conditions such as hypertension, atherosclerosis, diabetes and the resulting cardiovascular diseases (7-9) and to induce myocardium reperfusion injury following coronary artery bypass grafting (10). Excessive levels of superoxide during oxidative stress caused a reduction in NO bioavailability by forming peroxynitrite and

resulting in endothelial dysfunction. In addition, the existence of antioxidants, such as, Superoxide dismutase (SOD) was necessary to compete with NO for superoxide, and to reduce the formation of peroxynitrite (7).

The question is whether the lifestyle and the consequently resulted overproduction of Free radicals play a role in inducing these recorded significant discrepancies of the incidences of different chronic diseases in different areas across the globe.

Hypothesis

We propose that environmental factors induced alterations in the genetic codes in the preceding generations, which were inherited and were further modified by our modern life style and lead to the appearance of chronic degenerative disease. We believe that this process is a possible explanation for the variety in the incidences and

prevalence of these diseases in different regions of the World.

Evidence: The role of Free Radicals in causing genetic mutations

When we analysed the traditional English Menus over the last 500 yr since the Tudor times and compared the results with the required dietary standards, we found that lack of afforded antioxidants in diets was significant in the majority of the examined menus (Table 1-4). Deficiency of vegetables & fruits was also remarkably significant. However, how can lack of antioxidants and over production of Reactive Oxygen Species induce somatic mutations, which presumably form the grounds for the development of chronic non-infectious diseases?

One example of possible changes in genetic expression is that the single electron reduction of molecular oxygen to superoxide initiates the formation of a family of ROS that pose a constant and insidious threat to aerobic organisms (11-13).

The released superoxide can specifically liberate Fe^{++} from cellular iron-sulphur clusters $\{4 Fe-4S\}^{++} + O^{--} + 2 H^{+} \rightarrow \{3 Fe-4S\}^{++} + H_2O_2 + Fe^{++}$.

The hydroxyl radical which generated from the superoxide and hydrogen peroxide through transition-metal-catalyzed Fenton chemistry ($Fe^{++} + H_2O_2 \rightarrow OH^{\bullet} + OH^{-}$) is reactive & generating numerous radical adducts and their derivatives. This condition is similar to what usually occurs in case of radiation.

Moreover, the negative charge of DNA facilitates the local generation of hydroxyl radical through the binding transition metals.

The overall consequences is that ROS can generate oxidatively modified bases as well as single and double strand breaks if un-repaired, such oxidative damage can lead to mutation that can range from single nucleotide substitution to gross chromosomal rearrangement which in a metazoans can have somatic as well as germ line consequences (14).

The Role of Antioxidants

Besides functioning as an electron donor in the enzymatic removal of hydrogen peroxide catalyzed by ascorbate peroxidase, water-soluble can be oxidized non-enzymatically by superoxide or hydroxyl radicals to yield the monohydroascorbate radical (MDA). In this sense, ascorbate can act directly as a scavenger of superoxide or hydroxyl radicals. Vitamin C is required in the diet of primates (including humans). This is due to the lack of a gene that encodes one of the enzymes required for ascorbate synthesis from glucose (15, 16).

One of the major cellular targets for attack by oxygen-derived free radicals species is the polyunsaturated fatty acid components of phospholipids cell membranes. This can lead to the propagation, in chain reactions, of extensive peroxidative damage. However, the presence in the membranes of a lipid-chain-breaking antioxidant such as α -tocopherol can quench this propagation.

My response to this is explanation is that oxidation of α -tocopherol to α -tocopheroxy radicals occurs during this process when lipid peroxy radicals are quenched. Then the resultant products accept hydrogen to regenerate the original α -tocopherol molecules (17).

Can the genetic mutations in the precedent generations be inherited to their successors?

It is likely that altered Reactive Oxygen Intermediates (ROI) metabolism is involved in inherited phenotype. For example, the derived SW620-IR1 cell line from SW620 human colon cells was found surviving to ionizing radiations and showed an increased radio sensitivity and a higher yield of spontaneous chromosomal aberrations.

This was obviously clear at comparing the two cell lines for their radiation-induced modifications at the level of ROI production, antioxidant activities, and chromosomal aberrations (18). Compared to SW620, SW620IR1 cells exhibit a higher and more persistent ROI induction after various doses of ionizing radiations and a higher yield of dicentric chromosomes. They are also characterized by lower basal activities of glutathione per-

oxidase and manganese-containing superoxide dismutase, and lower ability to induce these antioxidant defences after irradiation. Resumption of cell growth after irradiation coincides with maximal induction of antioxidant activities and normalization of ROI concentration.

However, at that time radiation-induced chromosomal aberrations are eliminated, leading to the proliferation of genetically unstable cells. These results indicate that the inherited sensitivity of SW620IR1 cells is associated with altered antioxidant activities resulting in higher and more prolonged oxidative stress after radiation exposure. They also suggest that the normalization of ROI levels allows these p53 mutant cells to resume proliferation although high levels of DNA damages are persisting, thereby explaining the chromosomal instability observed as a delayed effect of radiation exposure.

Again, researchers have noted a high incidence of obesity among the Pima, a Native American tribe whose ancestral homeland is along the Gila and Salt rivers in Arizona. The Pima tend to eat a similar diet to the average Americans, which usually consists of chips, bologna, ice cream, and all the other high-calorie, low-nutrient foods. However, whereas the average American is overweight, the average Pima is more dramatically so. This suggests that long ago, when the ancestors of the Pima had to face repeated periods of famine in the dry lands of the American Southwest, survival favoured the individual or individuals who had a mutation for fat storage. It so happens that today, there is more than enough food at the local supermarket, but by now the Pima as a group has the fat-storage gene. Therefore, many members of the tribe have to undergo strict dietary and exercise regimens so as not to become grossly overweight and susceptible to heart disease and other ailments.

Certainly, the confirmation of this theory will increase our awareness of the mechanisms of these chronic degenerative diseases, will create new era for management of these groups of patients, and will assist in designing new strategy for the prevention of these diseases in the future.

Table 1: Peasant (15th Century)¹⁹

Nutrient	Units	Intake	Per 100 Grams	R.N.I
Selenium (Se)	ugm	+20	1	75
Vitamin C	mgm	mgm	1	40

Table 2: Meat eaters (15th Century's Diet)

Nutrient	Units	Intake	Per 100 Grams	R.N.I
Vitamin C	mgm	0	0	40

Table 3: Sailors (Robert Hitchcock in 1580)

Nutrient	Units	Intake	Per 100 Grams	R.N.I
Selenium (Se)	ugm	+32	1	75
Vitamin C	mgm	1	0	40

Table 4: Hospital (St. Bartholomew's Hospital in April 1687)

Nutrient	Units	Intake	Per 100 Grams	R.N.I
Vitamin C	mgm	34	1	40

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