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Mini Review

Environmental Stressors Potentiate Metabolic Disease: Prediction to Prevention by Curating Multilayer Omics

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Abstract

By accelerating industrial activity or adjusting the new era from manufacturing to Information technology, many hazardous intoxicant filtrates into our lifestyles. Of these, several environmental factors such as stress (i.e., work related stressor, anxiety, depression, etc.), chemicals, and food ingredients also contribute to metabolic diseases. It is fundamental to understand the role of the environment factors (i.e., internal and external factor to imbalance in body metabolism). Compelling evidence support that interruption of neural circuit could affect metabolic dysfunction by oxidative stress includes ER stress, mitochondria dysfunction, and generation of misfolding proteins in several disease models. In addition, stress could alter connectivity between neural circuits to metabolism through CNS and PNS, or reward deficiency system in limbic system. To define the stress chain in disease development, several studies including ours have demonstrated that oxidative stress is a critical risk to impair molecular network system in homeostasis of adipocyte and balance interaction by mitigating stress reflects molecular alteration. Dual concepts of such prevention and prediction in metabolic disease using significant animal data, we propose that translational or transitional medicine such as lab to clinic could be an advantage to achieve prevention of metabolic disease to prediction of secondary disease using multilayer of molecular detection system, Omics under personalized molecule dependent architecture. To better understand socio-economic burden of diseases like Diabetics represented a metabolic disorder, we try to define the impact of stressors. We also try recognize the symptomatic pattern following malfunction of crosstalk due to modify molecular key features include expression, functional alteration, as well as intervene stability to extend signaling cascade. Upon exposure time and redundancy, stress driven oxidative stress could attribute to secondary disease progression in the elderly or young population.

Introduction

Metabolic disease is characterized by obesity, hyperlipidemia, hypertension, dyslipidemia, and progressive autoimmune alteration caused by beta-cell mass include dysfunctionality like increased beta-cell apoptosis, and impaired insulin secretion [1-6].This characteristic reflects oxidative stress mediated inflammation, mitochondria dysfunction and generation of unfolded protein [7-12].

According to the World Health Organization (WHO) in 2014, the incidence of diabetes was 422 million [13]. The average medical expenditure of a diabetic person is about $13,700 per year.The burden in terms of cost in diabetes is staggering.In 2012, it was estimated that both the direct and indirect estimated cost of diagnosed diabetes in the United States was $245 billion. This burden cuts across society broadly but disproportionately affects the people in the low and middle socio-economic class.

An estimated 30.3 million people (9.4%) of the US population have diabetes.Additionally, 84.1 million have prediabetes, a condition that, if not attended to within five years, could result in type 2 diabetes. Therefore, there are more than 100 million Americans living with diabetes or prediabetes making it a health priority [14]. It is projected that the prevalence of diabetes will be 12% by 2050. This indicates a significant increase from its current rate of 9.4%. Due to the correlation between increase in age and the risk of developing chronic diseases like diabetes, insufficient attention to the disease will lead to significant strain on the economy and the nation due to the loss of productivity (American Diabetes Association [ADA]) [15].

It arises from the body's failure to maintain normal glucose homeostasis, which results from the change in the action of insulin – the hormone responsible for the uptake of glucose in the body [16].

Type 1 Diabetes Mellitus (T1DM) and type 2 Diabetes Mellitus (T2DM) are the main types of this disease. Type 1 diabetes is due to the body's inability to produce insulin because of the autoimmune destruction of the beta cells in the pancreas [17,18].Featured symptoms are represented as polyuria, polydipsia, polyphagia, and unexplained weight loss. It is irreversible and requires lifelong insulin replacement alongside multidimensional approach that involves a dietician, physician, and family support. Although it is a disease of all ages, it is most prevalent in the juvenile years. People with this disease are not usually obese.Unlike T1DM, T2DM is present in adults. In this case, there is no auto-destruction of beta cells. Familial disposition, obesity, and sedentary lifestyle predispose individuals to this disease. In this situation, insulin is produced and the body is either resistant to its action or the body's production doesn't equate the carbohydrates

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ingested. Complications of diabetes include secondary health complications such as retinal and renal pathologies [4]. Additionally, uncontrolled diabetes in pregnancy can be fatal to both mother and child with increased risk of complication and possible fetal loss.

Previously diabetes was only linked with diet and exercise. It is increasingly clear that several environmental factors such as stress (i.e., work, anxiety, sickness, etc.), chemicals, and food ingredients also contribute to the disease. It is fundamental to understand the role of the environment factors (i.e., internal and external factor in body metabolism). Interestingly, Fonseca et al. demonstrated various ER stressor (i.e., Protein overload, protein trafficking defects, mutant proteins, environmental toxins, viral infection, and ageing) produce Unfolding Protein Response (UPR) and its lead to dysfunction/cell apoptosis of beta cells. In T2DM case,activation of ER stress under pre-diabetic condition such asinsulin resistance and Hyperinsulinemia could affect consequential outcomes by cross-talking down-stream molecular pathways, for examples, c-Jun N-terminal Kinase (JNK) phosphorylation, C/EBP homologous protein (CHOP), Akt and GSK3b phosphorylation by which it may cause cell death or dysfunction of beta cell [19].

Impact of Stress on Metabolic Disease

Physiological response to stress

Dallman et al.[20] postulated that the response to stress signaling (i.e., corticosterone and insulin) against energy balance which could be regulated by sympathetic nervous system in the neuroendocrine axis (HPA).The sympathetic nervous system activates a quick response, while HPA axis response activates a delayed response.

A) Stress induced diabetes: Epidemiological studies show that severe stress often precedes the development of Th1-mediated autoimmune diseases. Among these, type 1 diabetes mellitus is characterized by the development of antibodies against islet cells in the pancreas and autoantibodies against insulin. The effect of stress on the individual depends on a lot of factors such as physical and mental resilience, and the presence social support.Metabolic syndrome is a pre-clinical condition and predisposes people to type 2 diabetes, and stress is one of the triggers. The reaction to a stressor, in some cases, may lead to the development of an unhealthy lifestyle: sedentary lifestyle, poor nutrition, neglect of physical well-being, and often using food as coping mechanism to the underlying stressor. These factors indirectly affect the risk of developing the disease. Also, the physiological changes, triggered by stress, affect the endocrine and immune systems.Young children, who are exposed to sustained and constant stress, are particularly vulnerable to develop hyper-vigilance in face of constant danger and display low propensity to seek help. This emotion further exacerbates the propensity to develop stress. This physiological stress can affect diabetes by altering their immune system, changing the normal activity of the antigens GAD65, HSP60 and Insulinoma Antigen-2(IA-2), responsible for diabetes-related autoimmunity [20-23].Stress hormones (i.e., cortisol) are responsible for the body's fight or flight mechanism. Cortisol raises the blood glucose levels by stimulating hepatic gluconeogenesis, and blocking the action of insulin. This defense mechanism is not entirely suited for modern stressors rooted from internal or external environment. These stressors are not based on acute response. In this case, the stressors are subtle, persistent, and sometimes go unnoticed.

B) Disease as a source of stress: Diseases, such as obesity and diabetes, can equally be the source of stress. The constant worry and disruption in daily activities can lead to conflicts between one identity and their goals and objectives in life. The complex and daily regimen of treating diabetic diseases (the daily use of insulin or hypoglycemic treatment, regular checking of blood glucose, inflammation from injection sites, and dietary constraints) may increase the stress level on an individual. The need to control the daily and normal part of life can lead to frustrations and anxiety. This requirement to pay attention to aspects of life or routine that usually go unmonitored is a consequence of dealing with chronic diseases. This can have impact on the individual's behavior and mood and can lead to other diseases such as depression and hypertension.

For younger adults and children, some of these diseases coincide with puberty, making it more difficult to cope with. Coping with image and identity issues can lead to social isolation, which limits physical activity and interaction. Therefore, the propensity to seek help is diminished. In the elderly, stress has a vital role in the development of complications such as neuropathy, nephropathy, and retinopathy. In addition, this unpleasant emotion may reduce the willingness to comply with treatment and diet. Thus, a circle of nervousness, poor compliance, poor glycemic control and physical vulnerability is instituted. The sudden need to change and adapt to a disease can bring about serious discomfort; the need to learn new techniques and medications can bring about mental fatigue. Therefore, the adherence to treatment regimen will be inadequate.

Stress and disease progression

The impact of stress can also play a role in the progression of diseases like obesity and diabetes. Blood glucose level is affected by neuroendocrine processes that release cortisol and IL-6, or Growth Hormone (GH), such as stimulator (i.e., GH-Releasing Peptide 6 (GHRP-6)that are activated by physiological diabetic metabolic condition [24-26]. The response to external stimuli has an effect in both normal and diseased patients. Of note, this cortisol and growth hormone response can exacerbate the diseased patients. Therefore, the environmental stimuli can affect the severity of a disease, especially in young people, where there is an adaptation of the endocrine system.

The use of omics technologies include systemic biology approach can provide important information on genetic susceptibility, new biomarkers, better understating of pathogenesis and treatment. New venue from omics, especially using metabolomics, provides more knowledge into the pathology, prediction of disease onset, and developing new biomarkers to improve diagnosis of the disease. In previous studies,utilize Proteomic techniques like Mass Spectrometry (MS), and Nuclear Magnetic Resonance (NMR) spectroscopy to monitor metabolite profiles,itwas demonstrated that pre-diabetes and type 2 diabetes are associated with many metabolites, including Branched-Chain Amino Acids (BCAAs), aromatic amino acids, hexoses, phospholipids, and triglycerides. Moreover, BCAAs isoleucine, leucine, valine, tyrosine and phenylalanine are positively associated with the risk of type 2 diabetes, and glycine and glutamine are inversely associated with diabetes [27,28].

In additions, Nutrigenomics combines nutrition and genetics platform; it explores how food interacts with genes at a molecular level. A study led by Berna et al. [28] indicate that Human Leukocyte

Antigen (HLA) is the single most important genetic determinant of type 1 diabetes, which is responsible for60% of the genetic influence of the disease. Aside from the impact of vitamin D, intake of cow milk and gluten, the impact of early breastfeeding, role of gut microbes, specific food that triggers β cell autoimmunity, environmental factors like diet-related issues contribute to this disease.

The application of omics technologies provides a deeper understanding of the individual at the molecular level and leads to avenues for identification of better biomarkers and diagnostic mechanisms. Also, it provides ways by which we can prevent diseases like diabetes and obesity, by understanding food nutrients, additives, and other environmental factors. Identifying genes that are influenced by diet could result in the development of diagnostic tools and personalized intervention.Converting this research to be applicable to clinic innovation such an everyday patients promises contributions to the growth of personalized medicine or systemic health surveillance that includes nutritional as well as drug interventions in translation medicine include neurogenetics and/or nutrigenomics with reward circuit in the brain. The combination with other genomic categories like pharmacogenomics, glycomics, cellomics, proteomics, transcriptomics, along with other important clinical data will generate big data, which can be used in the research of metabolic diseases and identify biological networks to understand its link with various environmental and genetic factors to aid in personalized disease and aging related secondary disease prevention, for example, Cardiovascular Disease (CVD), hypertension, mental illness.

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