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Epigenetics Effects of Stress Influence the Genomics, Proteomics, Metabolomics of Addiction and Cancer Pathways

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Introduction

The metabolic and genetic changes instigated by the Stress pathways are involved in the pathogenesis of Addiction and subsequently Cancer through a cascade involving Genomics, Transcriptomics, Proteonomic and finally Metabolomic (Figure 1).

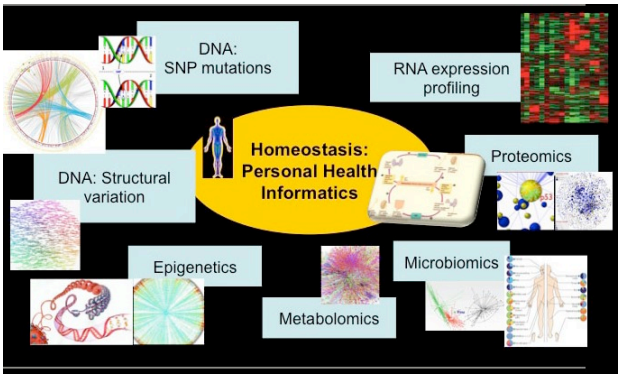

Figure 1: Homeostasis the Genomics-Metabolomics Governor.

Metabolic homeostasis is crucial for human survival. Hence ultimate health depends on proper functioning of the pathways that are involved in sensing and management of homeostasis. These metabolic systems are cohesively coupled and influenced by evolutionarily conserved pathways involving the stress signal pathways, pathogen -sensing and immune responses. This close functional and molecular integration of the stress, immune and metabolic systems are emerging as a crucial homeostatic mechanism, the dysfunction of which underlies many chronic metabolic diseases, including and not limited to addiction, cancer, type 2 diabetes and atherosclerosis. In this Review we provide an overview of several important networks that sense and manage nutrients and discuss how they integrate with the immune and inflammatory pathways to influence the physiological and pathological metabolic states in the body (Figure 2).

Sizeable scientific research suggests that stress acts as a fertilizer that fuels addiction and cancer in humans. In recent years an emerging growing body of knowledge identifies and details the relationship between the stress signaling pathways and the changes they induce in the biology of metabolic homeostasis and of the immune system inadvertently promoting the development of and the spread of cancer to distant organs rendering cancer much harder to treat. Stress signaling pathways change the makeup of cells in particular immune cells — causing them to become agents of harm as opposed to agents of healing and protection.

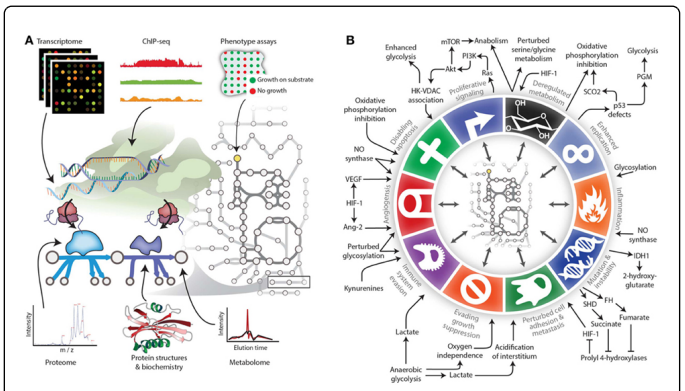

Figure 2: Influence the physiological and pathological metabolic states in the body.

Genotoxic stress and other adverse environmental conditions elicit a variety of stress-related signals that lead to the altered expression of multiple genes involved in cell-cycle control, programmed cell death, and DNA repair. Chronic stress causes cancer cells to escape from the primary tumor and colonize in distant organs. Many of the genes that promote cancer metastasis get turned on during the immune response by macrophages. Stress signaling from the sympathetic nervous system enhances the recruitment of macrophages into the primary tumor, and increases their expression of immune response genes that inadvertently facilitate the escape of cancer cells into other parts of the body.

I here illustrate several of these pathways in my presentations such as the important pathway involving the P53 network.

P53 Pathway and Network

P53 is situated at the crossroads of a network of signaling pathways that are essential for cell growth, regulation and apoptosis induced by genotoxic and non-genotoxic stresses [1-3].

In normal unstressed cells, the level of p53 protein is down-regulated via the binding of proteins such as MDM2, COP1, PIRH2 or JNK that promote p53 degradation via the ubiquitin/proteasome pathway. As most of these genes are up regulated by p53, this lead to a regulation loop that will keep p53 level very low in a normal cells. After genotoxic or non-genotoxic stresses, activation of p53 is a two steps process. First p53 protein level is increased via the inibition of its interaction with mdm2 and the other negative regulators.

Overtranslation of p53 RNA is a complementary that will also ensure p53 accumulation. Second, a series of modulator (kinases, acetylases) will activates p53 transcriptional activity. A plethora of proteins have been found to bind various regions of p53 in order to regulate the specificity of its activity. Downstream signalling includes a large series of genes that are activated by the transactivating properties ofp53. This occurs via specific DNA binding of the p53 protein to a p53 response element (p53 RE) that is found either in the promoter or in the intron of target genes [4-6].

I hope that this presentation helped to unveil new insight into the roadmap of cancer prevention, cancer regression and perhaps cancer cure. Specially that there is even more exciting research demonstrating that not only the effects of stress on cancer progression and metastasis.

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