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Review

Genetic, Epigenetic, and Metabolic Determinants of Disease Pathophysiology

Subham Mandal*[1], Suraj Mandal[2]

[1]*Department of Pharmacy, IIMT College of Medical Sciences, IIMT University, O-Pocket, Ganganagar, Meerut, U.P., 250001, India*

[2]*Sujata Research Laboratories, Global Sujata Ventures LLP, Vill-Mataiyalalpur, Post- Ramnagra, Dist-Pilibhit, U.P. 262122, India*

Corresponding Author:
Subham Mandal

Email:
sk8006721807@gmail.com

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Abstract:
The classical concept of genetic determinism in pathophysiology is changing to an integrative, systems-based concept. This model acknowledges that disease does not occur due to solitary genetic malformations but as a result of the interplay between genetic susceptibility, epigenetic control, and metabolic mediators and is complex and multidirectional. Genetic variants create a threshold of risk, but their implementation is dynamically considered by epigenome, or a malleable layer of chemical modifications, sensitive to environmental influences such as diet, stress, and toxins. This epigenetic control, in its turn, regulates metabolic pathways, whose metabolites (e.g., acetyl-CoA, SAM) are also fed back to power and control the epigenetic machinery. This leads to self-reinforcing loops that may entrapping cells in pathological states and this is where such phenomena as metabolic memory in diabetes and long-term effects of early-life programming can be explained. This triad has a clinical redefinition of diagnostics and therapeutics. It broadens the biomarker repertoire to encompass epigenetic and metabolic biomarkers and develops interventions-not to a single malfunction but to the reconstruction of the whole system-based on epigenetic drugs and metabolic modulators as well as lifestyle medicine. The model also gives a singular account of comorbidities (e.g., obesity, diabetes and depression) and how conditions such as cancer steal these interactions. Finally, it places pathophysiology as the new product of a disrupted conversation between genome, epigenome, and metabolome, providing new opportunities to prevent and cure it.

Keywords: Integrative Pathophysiology, Genetic Determinism, Genetic Predisposition, Epigenetic Regulation, Metabolic Intermediaries, Genome-Epigenome-Metabolome

Introduction

The classical paradigm of pathophysiology that has been dominated by a more or less linear and deterministic perception of the genotype-to-phenotype relationship is evolving radically and is in need of it. The central dogma of biology, which states that DNA is the genetic code of RNA, and that RNA is the genetic code of protein, has been the potent, yet never complete, model of disease. The paradigm frequently depicted genetic variants as direct and fixed blueprints to either health or disease, whereby the phenotype the apparent expression of disease was

perceived to be a comparatively direct expression of the genomic sequence. Nonetheless, the intricacies of mainstream, endemic diseases like diabetes, cardiovascular diseases, autoimmune diseases and cancer have always been hard to clarify in terms of this reductionist approach. The partial penetrance of risk variants, the inconsistent expression of the same mutations, and an enormous contribution of environmental and lifestyle factors have all raised an indication of a much more dynamic and intertwined reality. This has led to the change to an integrative pathophysiology, a systems-based approach, which has shifted its focus to a continuum in which the individual genome inherited is moderately expressed under the control of regulatory layers which in turn is influenced and shaped by the metabolic environment. This new model does not reject genetics but rather re-contextualizes it as a single important node in a very large network of biological processes, with predisposition being an imaginary possibility and not a fate but a potentiality determined by lifelong molecular dialogs [1].

The essential triad, which is in the core of this integrative model, consists of genetic predisposition, epigenetic regulation, and metabolic intermediaries. These three components do not follow one another but rather interacting aspects of physiological and pathological functioning. Genetic predisposition offers the script--the inherited nucleotides which give a minimum of risk or strength. This encompasses not just those mutations of high penetrance that directly result in monogenic disease but rather the huge numbers of single nucleotide polymorphisms (SNPs) and copy number changes that modulate protein function, receptor sensitivity or enzymatic activity in subtle ways. A mutation in BRCA1 gene, e.g., is a strong risk factor of breast cancer, whereas the genetic polymorphisms of e.g. TCF7L2 moderately affect the susceptibility of type 2 diabetes. However, this text is not read word-to-word. Its meaning is dynamically guided by the epigenetic regulating, the collection of heritable yet reversible chemical alterations to the DNA and its related histone proteins that change the levels of gene expression, yet do not change the sequence. DNA methylation, histone acetylation, and microRNA activity are molecular decoders that silence or activate parts of the genetic script depending on the developmental cues, cellular signals and most importantly environmental exposure. It can be diet, stress, toxins, physical activity, or psychosocial experiences that carve themselves into the epigenome to leave a biological memory of the past environments that influence the current and future physiological reactions. Therefore, the genetic predisposition of a subject to metabolic syndrome can be kept in the latent state without activating an obesogenic environment that causes an epigenetic modification that activates the expression of pro-inflammatory genes and disturbs the energy homeostasis [2].

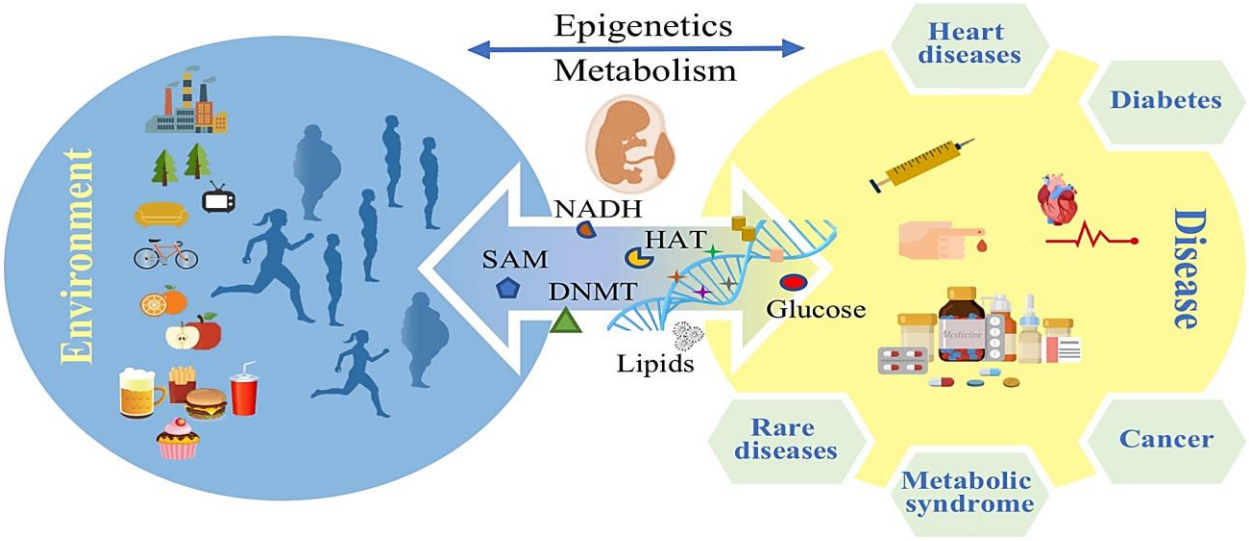

Fig: 1 Environmental factors affect epigenetics and metabolism and control disease predisposition in later life stages.

The interaction between the fixed genome and the malleable epigenome produces the functional output of the cell: a particular biochemical and metabolic set-up. This is where the metabolic intermediates are found the small molecules, substrates, fuels, and signaling compounds that make up the metabolome. These contain such nutrients as glucose and fatty acids, such hormones as insulin and cortisol, such inflammatory cytokines as tumor necrosis factor and interleukin-6, such oxidative stress markers as hydroxyl radicals, such gut microbiome-derived metabolites as short-chain fatty acids. Metabolism is not just a housekeeping activity; it is a language of state and a language of communication of cells. Metabolic pathways have direct effects on epigenetic machinery- e.g. metabolism of acetyl-CoA by nutrients determines histone acetylation, and the concentration of S-adenosylmethionine (SAM) determines the ability to methylate DNA. On the other hand, epigenetic modification can rearrange whole metabolic patterns, including silencing genes that control insulin response or antioxidant defense. This generates intense feedback loops. Inefficient lipid metabolism is more likely in a genetic predisposition combined with a high-fat diet and may result in changes in the metabolite profile (e.g., high free fatty acids and diacylglycerols). These metabolites have the capacity to cause epigenetic modifications that in turn suppress other metabolic oxidative genes, which creates a vicious cycle of metabolic dysfunction, inflammation and insulin resistance leading to the clinical manifestation of type 2 diabetes state. Oncogenic mutations reorganize cellular metabolism to facilitate rapid expansion (the Warburg effect) in cancer and this change in metabolic state itself can sustain the malignant phenotype by facilitating epigenetic modifications that silence tumor suppressor activities [3-6].

Thus, the integrative pathophysiological paradigm does not consider disease as a failure in a component of the system but rather as an emergent feature of a destabilized system such that a perturbation in one of the elements of the triad has a ripple effect on the other elements. The clinical implications are changing. Diagnostics moves to include epigenetic biomarkers (such as patterns of methylation of individual genes) and metabolic signatures (observable in a metabolomic profile of blood or urine), and provides a more dynamic picture of disease activity and progression. The therapeutics, in turn, do not just concentrate on the genetic defect itself or the end-stage symptom. They currently include epigenetic therapeutics (including histone deacetylase inhibitors in cancer), metabolic therapeutics (including specific diets or medications that modify important metabolic activities), and lifestyle medicine that is aimed at positively remodeling the epigenome and metabolome. The problem is the rebalancing of the system: pharmacological or behavioral means to divert the molecular dialogue to the pathological patterns and towards health. Other phenomena covered by this triad include metabolic memory in diabetes, in which previous hyperglycemia causes changes in epigenetics and metabolism, which predisposes to complications even in the case of glucose control, and transgenerational effects, in which parent diet or stress can affect offspring health by inheriting epigenetics through the germline [7].

Foundational Concepts and Interactions

The classical Central Dogma of molecular biology that there is a unidirectional flow of information starting in DNA to RNA to protein, is a key fact of the basic template of life. Nonetheless, the modern concept of integrative pathophysiology requires that it be revised significantly not in a denial form, but as a multi-layered structure of recursive information flow. In this sophisticated perspective, the genome is not a single executive that issues orders but instead is a dynamic store in a two-way, always-chatting interaction with its cellular and environmental surroundings. The instructions do not pass through, these are interpreted, edited and placed on a contextual level at each stage [8]. This restatement of the genome-environment interface involves the permeable boundary between lived experience, in the form of nutrients and toxins as well as social stress and physical exercise, and biochemical signals that directly converse with the genome. To a large extent, this interface is regulated by the epigenome, the ensemble of chemical modifications and chromatin states that are an interpreter in a manner of definition, are the ones that dictate which genetic instructions become available, audible, or silent, to the extent that they are present in any given cell at any given time. Here is where the genome is exposed to experience,

not passively as an imprint but as a force of regulation, and leaves behind a history of exposure to the environment and physiological reaction into the very machinery of gene expression. This is a deep dialogue between environment and genome which is mediated and displayed in a bidirectional crosstalk with metabolism. Metabolism is not an expression of genetic teaching, but a potent upstream controller and a chief medium of environmental interaction [9]. The epigenetic modification enzymatic machinery is powered by direct nutritional substrates and metabolic co-factors. Indicatively, metabolism via pathways such as glycolysis, tricarboxylic acid (TCA), and one-carbon produces vital metabolites of acetyl-CoA, a-ketoglutarate, ATP and S-adenosylmethionine (SAM). These molecules are required co-substrates of histone acetyltransferases, histone demethylases and DNA methyltransferases respectively. Therefore, high-fat nutrition or cellular hypoxia does not simply switch fueling; the supply of these co-factors of epigenetics can be reconfigured, reorganizing the chromatin topography and gene expression programs, to adjust to- or die of- the novel metabolic condition. On the other hand, epigenome manufactures a masterful control of metabolism. In cancer, epigenetic silence of tumor suppressor genes may open pro-growth metabolic pathways such as aerobic glycolysis (the Warburg effect) whereas epigenetic activation of inflammatory genes in immune cells can alter their metabolism to a pro-inflammatory state. This forms vicious cycles: a metabolic change occurs and transforms the epigenome, which in turn fixes and exacerbates the metabolic change. This interdependence relationship propels biology way beyond the linear Central Dogma into circular, self-referential network where cause and effect are both interwoven [10].

Clinical and pathological strength of this recursive system is dramatically demonstrated through a phenomenon of so-called metabolic memory a concept that is used to explain the continuation and further development of the disease even after the initial insult has been eliminated. Also referred to as legacy effects, metabolic memory is the persistent molecular record of a previous metabolic pathological condition. Long-term studies of diabetes are the most convincing, as they reveal that early history of low levels of glycemic control predisposes one to both vascular and neuropathic problems at old age, even when the latter glycemic control is very good. This memory is not encoded in the fixed DNA code but in this dynamic but obstinately inertial epigenetic and metabolic reprogramming elicited by the initial hyperglycemic environment. An increase in glucose such as that can cause sustained histone changes in promoters of pro-inflammatory and pro-fibrotic gene in endothelial cells and facilitate the accumulation of stable advanced glycation end-products (AGEs) that can permanently transform cellular function and cell-cell communication. The original metabolic imbalance (hyperglycemia) alters the epigenome which in turn sustains a pathophysiological pattern of gene expression that perpetuates oxidative stress and inflammation to create a new, stable disease-permissive condition that is independent of the triggering agent. This can be applied to more than diabetes, the long-term effects of early-life nutrition, transient hypertension, or transient inflammatory insults, all can be taught a maladaptive lesson by a cellular system that is long lasting [11-13].

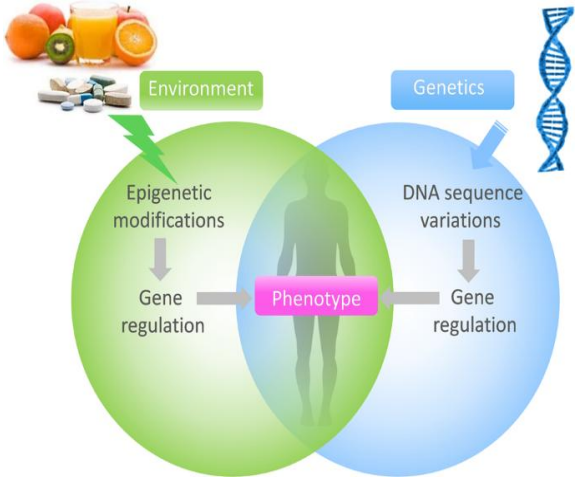

Fig: 2 Epigenetic and genetic dynamics regulate individual phenotypes. In addition to heritable Mendelian genetics, polygenic phenotypes, such as essential hypertension, are significantly affected by gene-environment interactions triggering epigenetic modifications

Genetic Determinants of Disease Susceptibility

The genetic impact on human disease is a wide and informative spectrum of landscape that essentially defines our perception of integrative pathophysiology. Monogenic disorders, e.g., cystic

fibrosis or Huntington, are located at one extreme, where a single, high-penetrance mutation in a particular gene is not only necessary but also sufficient to create disease, usually, by direct interference with a protein function [14]. This model is a forceful demonstration of the central dogma at work but is a minority percentage of the disease burden. Polygenic disorders such as type 2 diabetes, atherosclerosis and most psychiatric disorders are far more common and they involve the cumulative, minute effects contributions of hundreds or thousands of genetic variants spread across the entire genome, interrelating with one another and most importantly with the environment. This polygenic framework exposes the actual complexity of the genotype-phenotype interaction with genetic predisposition being probable rather than predetermined. The breakthrough that has made the difficult task of bridging these two extremes possible is the Genome-Wide Association Studies (GWAS), which have been able to identify thousands of shared genetic variants (single nucleotide polymorphisms, or SNP) significantly linked to complex diseases. Nevertheless, GWAS has come to reveal the deep problem of missing heritability a discovery that the total effect size of all the discovered common risk variants often only accounts for a small portion of the heritability of the disease estimated by family studies. This inconsistency indicates the weakness of a common-variant-centric model and indicates the significant roles of rare variants with stronger effects, structural changes, gene-gene (epistatic) interactions, and the very epigenetic and environmental context, which cannot be readily captured by GWAS, to support the importance of the integrative triad [15].

However, the real worth of GWAS does not consist in simple cataloguing but in the biological information available at particular loci, which has shed some light on the previously unknown pathophysiological pathways. There are a number of major genes in metabolic disease. FTO (Fat Mass and Obesity-Associated) gene carries the most significant common genetic relation with obesity. Interestingly, the major molecular activity of FTO is that of an enzyme which removes the methyl group in nucleic acids, implying it may not directly change weight status, but does it by regulating of neuronal activity in physiological systems that control appetite and energy homeostasis via epigenetic or post-transcriptional regulations. In sharp contrast, mutations in MC4R (Melanocortin-4 Receptor) gene, although rather infrequent, are the most typical monogenic obesity of severe early-onset. MC4R is a hypothalamic G-protein-coupled receptor, which is a linkage in the leptin-melanocortin pathway, an essential circuit in satiety signaling. Both FTO and MC4R discoveries point towards the brain as the overall controller of energy relationships, which implies obesity genetic vulnerability is typically linked to the malfunction of the appetite and consumption regulation, rather than just active metabolism. In case of type 2 diabetes, TCF7L2 (Transcription Factor 7-Like 2) gene variant is the only most common genetic risk factor across populations. TCF7L2 is a transcription factor that participates in the Wnt pathway, but the diabetic impact has been greatly associated with a defected secretion of insulin, as opposed to insulin resistance. The variants of risks have been linked to impaired beta-cell functioning in the pancreas, such as impaired proglucagon processing and decreased incretin effect, which is shown to reveal how a genetic predisposition can cause a very specific node (beta-cell resilience) in a more extensive metabolic network. Although variations in the genes such as FTO and TCF7L2 participate in the subtle shift of population risk, the far end of the continuum of genetic effects provides the deep insight into the dire outcome of the rare mutations in the epigenetic machinery itself and creates the syndromic diseases that present a stark perspective of the need to control gene expression [16-20].

Monogenic tragedies of epigenetic dysregulation include disorders like Rett Syndrome (mostly due to mutations in MECP2 gene, a methyl-CpG-binding protein involved in the understanding of the DNA methylation state and silencing of transcription) or Kabuki Syndrome (mostly due to mutations in KMT2D or KDM6A, the histone-modifying enzymes). These syndrome-inducing mutations are in the very writers, readers and erasers of the epigenetic code themselves, in structural proteins or metabolic enzymes. The resultant worldwide mal-regulation of gene expression results in multi-system developmental diseases that display metabolic, neurological, and morphological specific features.

These syndromes are proof-of-concept evidence that the integrity of the epigenetic layer is a normal requirement in animal development and physiology as is the integrity of the genetic code itself. They provide an effective linkage between genetics and epigenetics demonstrating that a ruptured genetic teaching on epigenetic regulation can result in a disease as debilitating as any inherited error of metabolism [21].

The integrative model is therefore based on the genetic continuum between polygenic risk common and monogenic syndromes that are rare. It shows that genetic influences are not single but occur in sheets of effect size and biological mechanism. The missing heritability paradox compels us to consider something beyond the fixed genome sequence to the dynamic regulatory and metabolic contexts that provide a sense to genetic variants. The identification of loci such as FTO, MC4R, and TCF7L2 have effectively established the transition of genetics of statistical association to new biology to identify the central nervous system regulation of hunger and pancreatic beta-cell vulnerability as a foundation upon which metabolic illness is built. Last but not the least, the presence of syndromes such as Rett and Kabuki makes it clear that the epigenetic apparatus is not an additional modifier but a primary target of genetic disease, and so it is not a tentative partner of the triad. This genetic evidence combined forces one to think of pathophysiology in which the variation of DNA sequence preconditions the event, but the eventual clinical outcome is the result of a lifetime of epigenetic and metabolic conversation, which provides numerous sites of therapy intervention rather than the fixed code [22-25].

Epigenetic Mechanisms as Dynamic Regulators of Pathophysiology

Epigenetics is the basic control level that converts the fixed genetic code into a moving cellular performance and is the molecular panacea to connect the fixed DNA code with the dynamic environment. This system of heritable, reversible chemical additions governs the pattern of gene expression without changing the underlying genetic code, which in turn specifies cellular identity and regulates development as well as gives a means by which organisms respond to life challenges through biology. The fundamental epigenetic pathway consists of a number of inter-related processes: DNA methylation, histone modifications, non-coding RNA (ncRNA) regulation, and chromatin remodeling complexes. The most widely studied epigenetic mark is DNA methylation, which is the covalent addition of a methyl group to the cytosine base, mostly at CpG dinucleotides, to produce 5-methylcytosine (5mC). The chemical process is catalyzed by DNA methyltransferases (DNMTs) as writers, and by Ten-Eleven Translocation (TET) family enzymes as oxidizers of 5mC to become active, which are key erasers. DNA methylation is traditionally thought to be involved in transcriptional repression, particularly of gene promoters at CpG islands, but is now known to play context-dependent functions, including in genomic imprinting and X-chromosome inactivation. Newer oxidized derivatives of 5mC, including 5-hydroxymethylcytosine (5hmC), are not just fleeting demethylation intermediates, but are rather enriched at active enhancers and bodies of genes bearing indicators of specific regulatory roles and binding particular reader proteins [26].

Operating in unison with DNA methylation, histone changes make up a complex histone code which regulates accessibility of chromatin. The protein tails around which DNA is coiled are called histones, and the tails are subject to various post-translational modifications- such as acetylation, methylation, phosphorylation and ubiquitination. These marks are actively added by enzymes such as the histone acetyltransferases (HATs) and histone methyltransferases (HMTs) and are removed by the histone deacetylases (HDACs) and histone demethylases (HDMs). The functional consequence is very precise: euchromatin with an open, transcriptionally active state is strongly associated with the acetylation of histone H3 lysine 9 (H3K9ac) or H3 lysine 27 (H3K27ac), whereas condensed and repressive heterochromatin is greatly favored by trimethylation of histone H3 lysine 9 (H3K9me3) or histone H3 lysine 27 (H3K27me3). Most importantly, these systems are not independent; they have a wide crosstalk [27]. Histone modulations have the potential to directly regulate DNA methylation patterns; in vivo, H3 lysine 36 trimethylation (H3K36me3) of gene bodies is recruited by DNMT3A, whereas H3 lysine 4 trimethylation (H3K4me3) on active promoters prevents de novo

methylation. On the contrary, proteins that prefer repressive histone modifications can be recruited by DNA methylation creating a self-reinforcing loop of gene suppression. This conversation is also adjusted by ATP-dependent chromatin remodelling complexes (e.g. SWI/SNF) which slide or evict nucleosomes to regulate access to DNA, as well as a very extensive repertoire of non-coding RNAs. An example of how RNA component is woven into the epigenetic regulatory network is the post-transcriptional gene silencing mediated by MicroRNAs (miRNAs), and the scaffolding of chromatin-modifying complexes to genomic loci by long non-coding RNAs (lncRNAs) [28].

This complex epigenetic system is the main molecular system by which environmental influences, such as nutrients and toxins, stress, and behavior, have long-term effects on physiology and risk of disease. The natural experiment of the Dutch Hunger Winter (1944-1945), a season of critical famine, being illustrated with great power, has given seminal information on in utero and early-life programming. Epidemiological follow-ups of those who were conceived or gestated during this famine indicated that the prenatal under nutrition resulted in organ-specific health outcomes in adulthood such as increased incidences of obesity, type 2 diabetes, coronary heart disease and even poor cognitive functions. Importantly, these effects were also dependent on the timing of exposure during gestation: exposure during early gestation was associated with subsequent obesity and coronary heart disease, exposure during mid-gestation with impaired renal function and lung disease and exposure during late-gestation with glucose intolerance. This shows that environmental affronts at sensitive periods of development may permanently program organ structure and metabolic set points, presumably via stable epigenetic modifications set up as the key genes pass between the active and repressed states. Notably, these long-term effects could manifest themselves frequently without low birth weight and make the epigenetics the most important mediator [29].

The effects of the environment on the epigenome are much broader that extreme famine. Epigenetic landscapes can be reformulated by common diet, lifestyle, and toxic exposures throughout the lifespan. As an example, the dietary elements such as folate and other methyl donors furnish the substrates of the DNA methylation reactions, relating nutrition outright to the epigenetic apparatus. On the other hand, natural toxins like bisphenol A (BPA) and air pollution have the capacity to alter normal epigenetic patterning. Hormonal and neuronal pathways triggered by psychological and physical stressors result in long-term epigenetic modifications in brain areas of emotion and stress response, which offer a molecular explanation of how life experiences are acquired as a risk factor to mental health. This is the ecologically sensitive quality of the epigenome that forms the basis of the pathophysiology of significant non-communicable disease. Persistent hyperglycemia in type 2 diabetes causes changes in episodic hyperglycemia-related epigenetics of pancreatic beta-cells and insulin-target tissues, which cause changes in the expression of insulin-related genes involved in secretion and sensitivity. These adaptations may result in a kind of metabolic memory, in which the damaging consequences of inappropriate glucose regulation remains even after glycemic regulation is restored, which can be used to explain the pathogenesis of diabetic complications over time. Likewise in cancer, silencing of tumor suppressor genes through promoter hypermethylation is an established hallmark which is frequently a result of a complex interaction between genetic predisposition and carcinogenic environmental factors [30-33].

The most provocative form of what epigenetic plasticity suggests is the possibility of transgenerational epigenetic inheritance, or the transcription of learned epigenetic changes and related phenotypes by parents to offspring, via the germline, even in the absence of immediate environmental influence. This idea contradicts rigid Mendelian genetics, and the idea that the risk of disease may be shaped by the experience of the previous generations. There is strong evidence in animal models: When gestating female rats are exposed to environmental toxins or extreme stress, abnormalities in behavior and metabolism can be generated in not only the directly exposed F1 generation, but also in the next, unexposed F2 and F3. In mammals, evidence of intergenerational impact is given by data of the Dutch Hunger Winter cohort that indicated that the children and even

grandchildren of famine-exposed individuals might have changed birth weights and health characteristics. Nevertheless, determining unequivocal evidence of germline transmission in humans is a very significant scientific problem since it needs the separation of genuine epigenetic inheritance by sperm or egg cells and confounding variables such as shared postnatal environment, cultural transmission or in utero effects on the fetal germline (which would technically affect the F2 generation). The suggested mechanisms of such inheritance are the incomplete loss of DNA methylation marks during development of primordial germ cells, transmission of small non-coding RNAs carried by sperm, and consistent histone modifications in sperm chromatin. Although it is an extremely important area of research, with immense potential implications to our current knowledge of how disease etiology and evolution work, it is a topic of contention and study and represents the edge in how we currently understand the possibility of a molecular echo of the lived experiences of our ancestors in offspring. In this way, epigenetics fulfills the integrative triad of pathophysiology, as it stands as the responsive, dynamic translator that is at the cross-section of genetic predisposition and metabolic activity, which interprets the lifetime of environmental discourse into a final biological repercussion and, possibly, a legacy to future generations [34-36].

Metabolic Determinants: Fuels, Signals, and Dysregulation

Having long been seen mainly through the prism of bioenergetics and ATP production, metabolism has since been taken as a dynamic and ubiquitous signaling network, and metabolites themselves are now considered as fundamental messengers that guide cellular fate, function and adaptation. This paradigm shift not only gives a new perspective to physiology and disease but it goes beyond the simplistic approach to metabolic pathways as fuel providers to a view of a complete regulatory circuit. Lactate, succinate and beta-hydroxybutyrate are not just passive intermediates, but can act by binding to certain receptors on cell surfaces or inside the cell, and thus have a direct effect on gene expression, post-translational changes, and cell-cell communication. This signaling capacity situates metabolism in the center of reaction to environmental signals, such as nutrient availability, oxygen, and physiological requirements, and their transformation to specific cell reactions, allowing the coordination of all processes, including immune cell activation, to neuronal plasticity [37].

The importance of this metabolic signaling network is highly evident in the etiology of significant diseases, in which impairment of important pathways causes a hospitable environment to malfunctioning. A good example is the insulin signaling and glucose homeostasis axis. The secondary characteristic of metabolic syndrome is insulin resistance, which is a failure of metabolic communication, in which the cells are no longer responsive to the command of insulin to absorb glucose. It leads to chronic hyperglycemia, which in turn is a pathogenic signal, and hyperproduction of harmful end-products of advanced glycation (AGEs) and oxidative stress facilitation. In the same way, the metabolism of lipids is closely connected to the inflammatory signaling. Saturated fatty acids are able to stimulate pro-inflammatory cascade via toll-like receptor 4 (TLR4) activation on immune cells that resembles a bacterial infection, whereas omega-3 fatty acid-derived specialized pro-resolving lipid mediators play a pro-inflammatory role in quenching inflammation. This pathological conversation of lipids and immune system is one of the pillars of atherosclerosis, non-alcoholic fatty liver disease and insulin resistance itself. Moreover, the functions of mitochondria are far more than its use as the powerhouse of the cell. Mitochondria play important roles in the production of reactive oxygen species (ROS) and metabolic processing of intermediates to produce signaling. In disease contexts including neurodegeneration and cancer, mitochondrial impairment causes abnormal ROS signaling and bioenergetic crisis which interferes with calcium homeostasis and causes apoptotic signaling. Importantly, this metabolic conversation directly forms the epigenetic space, forming an influential mechanistic connection of the cellular milieu and the long-term pattern of gene expression. This is the substrate-enzyme nexus: the same enzymes that add or remove epigenetic marks, e.g. DNA methyltransferases (DNMTs), histone acetyltransferases (HATs), ten-eleven translocation (TET) demethylases, are highly sensitive to the presence of important metabolites. The universal

methyl donor of DNMTs and histone methyltransferases is S-adenosylmethionine (SAM), the product of the folate and methionine pathways. Changes in the SAM levels, which are brought about by diet or disease, may directly modify global and gene-specific patterns of DNA methylation. Likewise, the central metabolite of glycolysis, fatty acid oxidation and the citrate cycle, acetyl-CoA, is the cofactor of HATs. The nuclear acetyl-CoA pool in turn directly links the metabolic condition of the cell to histone acetylation and transcriptional activation. On the other hand, alpha-ketoglutarate (a-KG), a TCA cycle byproduct is a key cofactor with the TET enzymes and JmjC-domain histone demethylases, leading to an open chromatin state. Its rival, succinate, also builds up in certain cancers and in ischemic diseases, and suppresses these same enzymes resulting in a hypermethylated, repressive chromatin environment [38-40].

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Therefore, the epigenetic machinery is powered by the metabolites, which are the instructions for them, and the memory of metabolic experience is encoded into the genome. This complex crosstalk implies that systemic metabolic disorders cause and result in (epi)genetic dysfunction and form vicious cycles, which perpetuate illness. As an example, the metabolic disequilibrium of obesity, hyperglycemia, dyslipidemia, and inflammation causes a changed milieu of metabolites (e.g., elevated acetyl-CoA, SAM, and succinate), which reprograms the epigenome in hepatocytes, adipocytes, and pancreatic beta-cells. Such reprogramming may silence genes controlling insulin sensitivity and activate pro-fibrotic or pro-inflammatory pathways and fix cells in a pathological condition. This then acquired (epi) genetic dysfunction propagates and exacerbates the metabolic disorder. Notably, such epigenomic alterations may occasionally be inherited by the daughter cells, which further contributes to the persistence of the disease and it is even suggested that they can even be inherited by germ cells, impacting the metabolic wellbeing of the future generations. Hence, it is possible to consider conditions such as diabetes, cardiovascular disease, and cancer as disorders of metabolic signaling failure, in which early physiological attacks are encoded in the cell regulatory system, via metabolite-contained epigenetic modifications. This combined viewpoint shows that metabolism is not just a

sideline actor, but a leading conductor of cellular identity and destiny with new therapeutic opportunities to adjust metabolic-epigenetic axes to healthy cellular communication and functioning [42].

Integrative Pathophysiology: Case Studies of the Triad in Action

This complex interplay between metabolism, genetics and epigenetics is most deeply and clinically meaningfully expressed in complex human diseases in which these levels of regulation interact to establish susceptibility, progression and persistence. The most important and significant example of such interaction is obesity and Type 2 Diabetes (T2D). They are not a result of a single genetic defect but a polygenic risk landscape - hundreds of common genetic variants each of minute effect but leading to a cumulative bias in an individual towards weight gain and insulin resistance. But this genetic predisposition is latent, and does not show itself except in the presence of the permissive conditions of caloric extravagance and an inactive life. The environment can do this via epigenetic regulation, in which the components of the diet (e.g., saturated fats, simple sugars) and the resultant metabolites (e.g., acetyl-CoA, SAM) change the epigenetic environment of the specific tissues. Chronic overnutrition, in adipocytes, may result in histone alterations that facilitate pro-inflammatory genes, whereas in the liver and skeletal muscle, the DNA methylation alterations may silence insulin signaling genes, including the insulin receptor substrate. This sets up a positive feedback between genetic risk and environmental pressure, where dysfunctional metabolism makes an environmentally stressed individual more prone to metabolic dysfunction, and interfering with metabolism leaves behind a pathogenic epigenetic signature that is impervious to reversal. This is one of the reasons why T2D is chronic and weight loss is not usually enough to completely normalize metabolic performance-the epigenetic memory of excess persists [43].

The scope of such a metabolic-epigenetic axis stretches potently into the brain, and it forms the basis of the pathogenesis and comorbidity of neuropsychiatric and neurodevelopmental diseases. Depression, schizophrenia, as well as autism spectrum disorders are gradually being associated with metabolic imbalances no longer as side effects but as part of their etiology. At the core of this connection is Brain-Derived Neurotrophic Factor (BDNF), which is critical in the survival of neurons, synaptic plasticity and cognitive processes. BDNF expression is highly maintained by epigenetic processes involving histone acetylation and DNA methylation of the prompts. Most importantly, these epigenetic controls are sensitive to metabolites. As an example, a ketone body formed during starvation or a ketogenic diet, beta-hydroxybutyrate has the potential to be an endogenous histone deacetylase (HDAC) inhibitor and increase BDNF expression. On the other hand, the repressive epigenetic marks of the BDNF gene can be induced by the inflammatory and oxidative stress environment of the metabolic syndrome to suppress its expression. This decrease is involved in depression in hippocampal atrophy and in neurodevelopmental conditions in impaired cortical connectivity. Moreover, the metabolic programming of hypothalamic circuits, which control both appetite and stress, in early-life can potentially have lifelong effects. Maternal obesity or malnutrition has the potential to interfere with the epigenetic programming of fetal hypothalamic neurons, including those synthesizing pro-opiomelanocortin (POMC) or agouti-related peptide (AgRP), to program the body weight set-point and stress response axis in a manner that predisposes them to metabolic and mental health disorders in adulthood. This common pathway is what accounts for such high co-occurrence rates of obesity, diabetes and other disorders such as depression, and makes the use of these disorders not contingent comorbidities but rather different manifestations of a similar underlying perturbation of metabolic-epigenetic-neural integration [44].

Unlike these polygenic illnesses, imprinting disorders like the Prader-Willi and the Angelman Syndromes have an inherently starkly clear image of where a definitive genetic lesion determines an epigenetic disaster. The loss of the functionality of the genes on chromosome 15q11-13 within the locus of expression that is expressed in a parent of origin specific fashion causes these syndromes- a process directed by epigenetic marks formed during gametogenesis. Prader-Willi Syndrome is caused by the loss of the paternally expressed genes (e.g., SNRPN), which is usually caused by a paternal deletion, whereas

Angelman Syndrome is caused by the loss of maternally expressed gene UBE3A. More importantly, the silent allele on the second chromosome is epigenetically silenced with the help of DNA methylation and histone modifications.

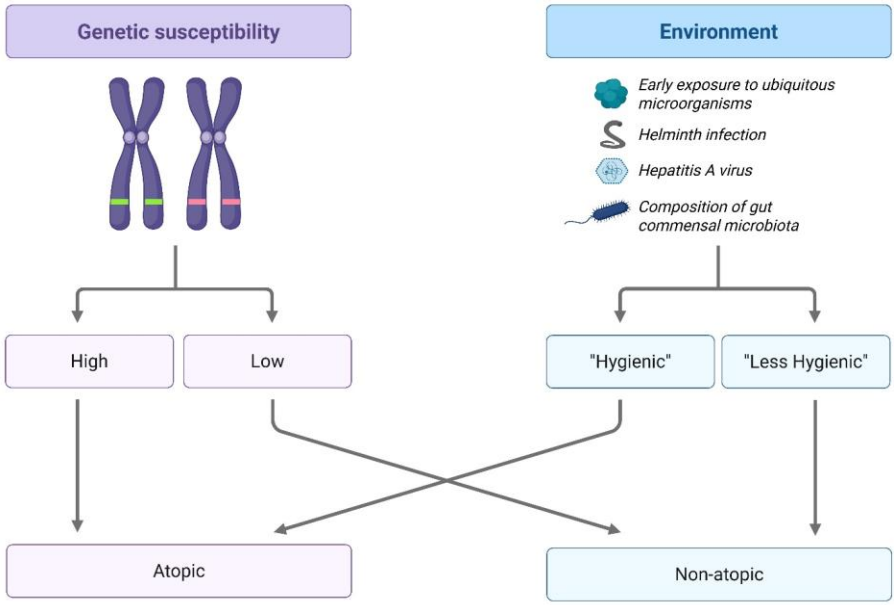

Fig: 3 Influence of Genetic Susceptibility and Environment on Atopy

The hijacking of the metabolic-epigenetic nexus is perhaps no better illustrated and exhibited in cancer. The prototypical "Warburg effect" or aerobic glycolysis, in which the cancer cells use glucose to lactate over glucose to phosphoglycerate in the face of oxygen, is no longer seen as a simple bioenergetic adaptation but as a re-programming to favour rapid propagation. This changed metabolism inundates the cell with acetyl-CoA produced by glycolysis and citrate, which promotes the acetylation of histones and expression of pro-growth genes. At the same time, it produces sufficient alpha-ketoglutarate and succinate that is capable of controlling the activity of TET and JmjC demethylases and results in extensive epigenetic changes. Moreover, these pathways are directly overlapped by common driver mutations in cancer. Isocitrate dehydrogenase (IDH) mutations give rise to the oncometabolite 2-hydroxyglutarate that is a potent inhibitor of a-KG-dependent dioxins, including the TET enzymes and histone demethylases. This leads to a world-wide hypermethylation phenotype (the CpG island methylator phenotype, or CIMP) which inactivates tumor suppressor genes and inhibits differentiation of cells. Equally, alterations in the activity of the epigenetic regulators, including EZH2 or DNMTs, can be regarded as frequent oncogenic alterations. Accordingly, genetic mutations, altered metabolism, and epigenetic silencing become inseparably combined in self-perpetuating triad in cancer to support unchecked proliferation, immune resistance, and resistance to therapy.

This whole symphony of peripheral and central cues needs a master orchestrator, a place of union, in which metabolic condition, epigenetic knowledge, and genetic predisposition are integrated into harmonious physiological instructions. This node is the neuroendocrine system, which is focused on the hypothalamus. The hypothalamus is the central metabolic/(epi)genetic signal processor that takes into account the nutrients and (epi)genetic signals circulating in the blood (glucose, fatty acids, hormones such as leptin and insulin), GIT peptides, and stress signals. These signals are converted into appetitive and autonomic responses by specialized groups of neurons in the arcuate nucleus, e.g., the anorexigenic POMC neurons and the orexigenic AgRP neurons. Importantly, these neurons also experience dynamic epigenetic reprogramming according to the metabolic state. This have been observed in obesity and metabolic syndrome, where chronic exposure of high leptin and insulin may

result in leptin and insulin resistance of these neurons, a phenomenon linked with particular histone modifications and changes in DNA methylation which silence key signaling genes such as Lepr or Insr. This is the epigenetic locking of hypothalamic set-point of body weight and is the root cause of unsuccessful weight loss since the brain defended weight does not decrease. This is a deep embodiment of systemic metabolic disease leading to epigenetic dysfunction on the central nervous system which in turn perpetuates the peripheral one [45].

The key to this hypothalamic integration is the Brain-Derived neurotrophic factor (BDNF) especially in the ventromedial hypothalamus. BDNF in this case is not a typical neurotrophin but an essential anorexigenous signal, whose expression is stimulated by these two hormones, leptin, and insulin. Hypothalamic decrease in BDNF results in hyperphagia and severe obesity. The whole theme is summarized in its regulation: BDNF expression is regulated by genetic factors, altered by lesions of epigenetic markers in reaction to metabolic hormones, and its malfunction results in systemic metabolic disease. In addition to this, BDNF is a molecular integrator outside the hypothalamus, involving a connection of energy metabolism and neural plasticity in the hippocampus and cortex. This integrative molecule deficiency through genetic variation or stress-related epigenetic silencing and or a metabolic regulation-depleting process, gives a common pathway of vulnerability, which is simultaneously revealed as metabolic imbalance (obesity) and cognitive or affective maladjustment, and this is a biological reason uniting the two conditions into one common pattern. To sum up, on one side, due to the polygenic nature of obesity, to the single genetic defects of imprinting disorders, to the malignant usurping of cancer, to the central reprogramming of the hypothalamus, the pathogenesis of diseases is most accurately viewed as a failure in smooth communication between our genome, our epigenome, and our metabolome. Identifying this triad is not merely an academic game but a requisite model that needs to be used in formulating therapies that can re-set this dialogue with a focus on not only the symptoms, but on the core regulatory dialogues which have gone astray.

Conclusion

The advent of integrative pathophysiology is a decisive departure of a reductionist, gene-oriented perception of illness to a dynamic systems model. The paradigm redefines disease as an emergent characteristic of a biological network that is undergoing a state of destabilization, with the ongoing and multidirectional conversation between the genetic predisposition of an individual, epigenetic control, and metabolic intermediaries falling apart.

The demonstration is persuasive and cuts across the spectrum of human disease. The triad is never at rest and this is the case, whether in the polygenic complexity of obesity and type 2 diabetes, in which the environmental cues activate epigenetic and metabolic feedback loops which entrench the pathology, or in the case of imprinting disorders in which the pathology is caused by single genetic lesions triggering epigenetic catastrophe. It describes the manner in which the mechanism of cancer hijacking this network occurs, through metabolic reprogramming, inducing epigenetic alterations that secure the survival of cancer, and that the brain, especially the hypothalamus, is a central integrator, the epigenetic state of which may be trapped in a maladaptive set-point. More importantly, this framework de-mystifies comorbidities and demonstrates common mechanisms the epigenetic regulation of BDNF, which is metabolically sensitive, to unite disorders of metabolism, affect, and cognition.

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