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Review

Epigenetics and Infectious Disease: State-of-the-Art and Perspectives in New Generation Therapies

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Abstract:

Infectious diseases are one of the most important causes of morbidity and mortality around the world and have a substantial impact on the health of communities. These diseases are caused by pathogenic microorganisms, such as bacteria, viruses, parasites and fungi. The antibiotics that are currently available are generally considered to be safe and well-tolerated. However antimicrobial resistance is an increasingly serious concern in the treatment of infectious diseases. An understanding of epigenetics now contributes significantly to the diagnosis and treatment of complex clinical disorders: epigenetics of the hosts can also explain the diversity in their responses to some infectious diseases due to microbes that escape the immunological system of the host. The new generation therapy with epigenetic drugs is here proposed as a useful tool in the fight against infective diseases.

Keywords
Epigenetics; infectious disease; epigenetic drugs

1. Introduction

Infectious diseases are one of the most important causes of morbidity and mortality around the world and have a substantial impact on the health of communities. These diseases are caused by pathogenic microorganisms, such as bacteria, viruses, parasites and fungi.

Given the high occurrence of infections, numerous studies have been conducted on pathogenic organisms and their capacity to develop drug resistance. The antibiotics that are currently available are generally considered to be safe and well-tolerated. These drugs have several targets, including the bacterial cell wall, cell membrane, essential enzymes, and protein synthesis inhibitors. However, in addition to the issues of toxicity and side-effects of antimicrobial drugs, antimicrobial resistance is an increasingly serious concern in the treatment of infectious diseases.

Recently, however, a light can be glimpsed at the end of the tunnel in the form of *epigenetics* (επίγεννετικός – "over the genetics", or rather the DNA code), a topic that has been commonly overlooked in the field of microbiology and has now become a significant focus of research in this area.

Epigenetics is the study of all inheritable changes that lead to variations in gene expression without altering the DNA sequence. In 1942 The term "epigenetics" was coined by Conrad Hal Waddington in 1942 to define "the branch of biology that studies the causal interactions between genes and their products and puts in place the phenotype".

The Human Genome Project has provided new opportunities to develop better diagnostic tools and target genes [1]. An understanding of epigenetics now contributes significantly to the diagnosis and treatment of complex clinical disorders.

2. Infection and Inflammation

The non-specific and innate defense mechanisms responsible for immunity and inflammation are triggered by chemical, physical and biological agents (viruses, bacteria, parasites). Inflammation is characterized by a series of events, made possible by the release of endogenous substances. The pivotal events of an inflammatory response are vasodilatation and increased vascular permeability combined with leukocyte infiltration in the damaged area. This defense mechanism, therefore, is a protective response that is mounted to eliminate the etiological agent and also to initiate the processes responsible for the repair and replacement of the damaged tissue (cellular and/or tissue repair) and is subdivided into *acute inflammation* and *chronic inflammation*.

Acute inflammation is a vascular and cellular reaction to tissue damage characterized by an immediate response to an injurious stimulus, while chronic inflammation is a long-lasting process involving active inflammation, tissue destruction and repair mechanisms. Chronic inflammation follows acute inflammation, which in turn leads to a series of responses of the infected organism. Infection can be considered as one of the causes of acute inflammation that is, in turn, related to an infectious disease. Infection is a pathological reaction that occurs after multiplication of invading pathogenic microorganisms, such as bacteria, viruses, fungi and parasites. The

pathological reaction may induce the onset of acute inflammation, which can progress to chronic inflammation if it is not completely resolved.

3. Epigenetics and Infections

Epigenetic processes arise from the need to respond to different internal and external stimuli, including infections. DNA is an interactive molecule and the epigenetics of the hosts can explain the diversity in their responses to some infectious diseases.

Internal stimuli have a moderate influence on the epigenetics of the various cells of an organism both during the differentiation phase and during embryogenesis and development. The British biologist Conrad Hal Waddington showed that the epigenetics of an organism is influenced by the interaction between various genes and the environment and that, in turn, this interaction can influence the survival and path to which a cell commits during the differentiation phase. The "epigenetic landscape" is a concept that represents embryonic development and was proposed by Conrad Hal Waddington to illustrate the various paths of development that a cell could follow from an undifferentiated to a completely differentiated tissue. This differentiation takes into account both the inductive (external stimuli) and genetic (internal stimuli) effects [2].

In the last decade, there has been an abundance of scientific studies on the epigenetic mechanisms by which microbes can escape the immunological system of the host. These mechanisms alter cellular functions to allow the pathogen to colonize, proliferate and permeate the host. Infection of a host with a pathogenic micro-organism stimulates the onset of a series of inflammatory responses aimed at eliminating both the molecules and toxins synthesized by the pathogenic organism, and the pathogenic organism itself [3]. Each pathogen, whether it is a virus, a bacterium, a fungus or a parasite, has developed an effective mechanism to evade the immune responses of the host. Infections activate genes involved in stress responses and inflammation. In broad terms, the different strategies can be divided into direct actions on DNA transcription (gene expression) and indirect actions as the chronic production of inflammatory cytokines and their consequences [4]. At the same time, however, there are various changes at the level of those genes able to activate and/or inhibit the various signal transduction pathways (programmed death-apoptosis, survival and motility) that may or may not favour the survival of the infecting pathogen [3]. Pathogenic microorganisms have, therefore, undergone a sort of evolution, an adaptation, which enables survival through the creation of an environment that allows their growth and replication. These pathogenic mechanisms include:

- Modifications of the transcription factors that are able to deregulate both the kinetics and the expression levels of the genes involved;
- Modifications that collaborate with various epigenetic changes;
- Modifications that facilitate epigenetic changes [5].

Pathogenic microorganisms regulate and act on the various epigenetic events, leading to alterations in chromatin and the normal signal transduction pathways. Thus, these organisms are considered to have the potential to reshape the epigenome.

When an infection occurs, there is a high probability of epigenetic reprogramming in the host cell. These modifications of the proteome and the transcriptome are mediated by molecules synthesized by the pathogen or by the RNA of the pathogen itself [6]. In response to infection, two sequential responses are activated by the host. The first is immediate and generic, whereas the

second is specific, but requires time to develop. In order to counteract host defenses adequately, some pathogens have developed systems that can influence host gene expression within a few minutes. Short-term changes are those that cease to exist when the infection and therefore, the pathogen, is eradicated, whereas the long-term changes can be inherited by the progeny of infected individuals and are therefore, a major concern [7]. Epigenetic modifications lead to various alterations as chromatin compaction, modification of gene expression, DNA ex-novo methylations, histone alterations, silencing of various physiological pathways of signal transduction.

They can be divided into various classes:

- Methylation of adenosine and cytosine residues by DNMTs (methylation that is not limited to symmetrical sites, such as in plants and in the fungus *Neurospora crassa*); in mammals, methylation is almost exclusively in the under-represented CpG dinucleotides, and most CpGs are methylated [1].
- Methylation of cytosines of CpG island leading to transcriptional silencing. This occurs on non-methylated genes that recruit protein complexes to alter the expression of genes involved in the condensation of chromatin and in silencing or recall of transcription factors that bind DNA to deregulate gene expression [8, 9]. Hypermethylation of CpG regions causes loss of function, whereas hypomethylation of the repeated sequences is the main mechanism of genomic instability. Except in some special cases, the methylation of CpG sites in the promoter of any gene induces silencing, thus inhibiting its expression, while hypomethylation events induce an increased expression of oncogenes, leading to greater genomic instability.

Recent studies have challenged the hypothesis, proposed in the 1970s, that gene silencing is mediated by changes in DNA methylation. This has been possible thanks to improvements in genome mapping, since DNA methylation at different sites that promote transcription, with or without CpG islands, regulatory elements and/or repeated sequences, can cause effects that differ from those that would normally be expected. Studies are still ongoing, but it is clear that the effects of DNA methylation can differ according to the various genomic contexts [10]. These modifications mediate the onset of a series of positive and negative feedback responses that regulate the homeostasis of the organism and, in extreme cases, can also lead to the onset of neoplasia. Methylation events and the changes derived from these modifications have been studied during differentiation and reprogramming of various mouse embryonic stem cells. This model facilitates investigation of such methylation events and dynamic changes in individual cells [11].

Chromosomal rearrangements that place heterochromatin next to euchromatin commonly lead to heterochromatin unfolding, and so induce silencing of nearby genes via the following mechanisms:

- Post-translational histone modifications, such as acetylation, methylation and/or phosphorylation, ADP ribosylation, ubiquitination (one in combination with the other), modify the histone tails to increase accessibility to the underlying DNA. These modifications are dynamic and occur in response to cell cycle progression and external stimuli, such as infections;
- RNA molecules, which have great plasticity and structural characteristics that provide catalytic properties as well as transport and storage of data. These molecules can direct DNA

methylation, post-translational modifications of histones and binding of chromatin remodeling complexes [7];

- Small non-coding RNAs (also known as interfering RNAs), which mediate DNA silencing, post-transcriptional regulation and genome maintenance by binding to mRNAs and either promoting their degradation or suppressing transcription via a negative feedback mechanism; some of these miRNAs are implicated as tumor suppressors or oncogenes [12].

In the context of infection, such alterations are exploited by pathogenic microorganisms to modulate the various nuclear and cytoplasmic processes acting on DNA, histones, and secreted and non-secreted effector proteins. Using these effector proteins, the various pathogenic microorganisms can act on an immense variety of target molecules including DNA, MAPK, guest chromatin, histones, STATs, tumor suppressors, nuclear factor kappa-light-chain-enhancers of activated B cells (NF-κB), and protein complexes. Many studies have focused on these mechanisms and a summary of the pathogens and their influence on host epigenetics is shown in Table 1.

Mechanism	**Pathogenic microorganisms**		**Target**
Interaction with DNA	*Anaplasma phagocytophilum*	Bacteria	DNA
	Theileria annulata	Parasite	
	HCV	Virus	
Binding on nuclear proteins	*Toxoplasma gondii*	Parasitic Protist	Deubiquitinating enzime HAUSP and phosphatase PP2A
	EBV	Virus	Polycomb, mSin3A, NCoR, istone deacetilase
	Shigella flexneri	Bacteria	Tumor suppressor proteinRb
	Anaplasma phagocytophilum	Bacteria	SHP-1
	Listeria monocytogenes	Bacteria	BAHD 1
Chromatin alteration	*Mycobacterium tuberculosis*	Bacteria	SWI / SNF e C / EBPβ
	Toxoplasma gondii	Parasitic Protist	NFKB, cJun, CREB
	Varicella zoster virus	Virus	ASF1
Phosphorylation	*Bacillus antraci*	Bacteria	Inhibition ofH3 phosphorylation, inactivation of MAPK
	Bacteroides vulgatus	Bacteria	H3, activation of inflammatory signaling cascade
	Epstein-Barr	Virus	Up regulation of methyltransferase DNA on Plasminogen activator promoter
	HBV	Virus	Up regulation of methyltransferase DNA on Plasminogen activator promoter
	Helicobacter pylori	Bacteria	H3, in monocytes
	Listeria monocytogenes	Bacteria	H3S10P/H3K14AC/H4K8AC and

			IL8 promoter, activation of MAPK
	Moraxella catarrhalis	Bacteria	H3, activation of inflammatory signaling cascade
	Toxoplasma gondii	Parasitic Protist	H3, sequester and deactivate several transcription factors
Acetilation	*Bacillus antracis*	Bacteria	Inhibition of H3 acetilation, inactivation of MAPK, downregulation of IL8 and KC genes
	Bacteroides vulgatus	Bacteria	H3, activation of inflammatory signaling cascade. Reclutation of HDAC on proinflammatory genes promoters
	Helicobacter pylori	Bacteria	H4 in epithelial cells
	Legionella pneumophila	Bacteria	H3, activation of IL-8
	Listeria monocytogenes	Bacteria	H3S10P/H3K14AC/H4K8AC and IL8 promoter, activation of MAPK
	Moraxella catarrhalis	Bacteria	H3, activation of inflammatory signaling cascade
Metilation	*Chlamydophila pneumoniae*	Bacteria	HC1/HC2
	Chlamydophila trachomatis	Bacteria	H2B/H3/H4
	Paramecium bursaria	Protista	H3K27
Deacetylation	*Aeromonas hydrophila*	Bacteria	H3/H4, formation of pores on plasmatic membrane and activation of a sensor for intracellular K^+
	Anaplasma phapocytophilum	Bacteria	H3, host defense genes
	Bacteroides vulgatus	Bacteria	H3, activation of antiinflammatory TGF β1 pathway
	Clostridium Perfiringens	Bacteria	H3/H4, formation of pores on plasmatic membrane and activation of a sensor for intracellular K^+
	Ehrlichia chaffeensis	Bacteria	H3
	Helicobacter pylori	Bacteria	H3K23 in epitelial cells; influence cell cycle, downregulation of hsp70 and upregulation of cJun
	Listeria monocytogenes	Bacteria	H3/H4, downregulation of CXCL2, MKP2 and IFIT3; formation of

			pores on plasmatic membrane and activation of a sensor for intracellular K^+
	Streptococcus	Bacteria	H3/H4, formation of pores on plasmatic membrane and activation of a sensor for intracellular K^+
Dephosphorylation	*Aeromonas hydrophila*	Bacteria	H3/H4, formation of pores on plasmatic membrane and activation of a sensor for intracellular K^+
	Clostridium Perfiringens	Bacteria	H3/H4, formation of pores on plasmatic membrane and activation of a sensor for intracellular K^+
	Helicobacter pylori	Bacteria	H3S10/H3T3 in epitelial cells
	Listeria monocytogenes	Bacteria	H3/H4, formation of pores on plasmatic membrane and activation of a sensor for intracellular K^+
	Shigella flexneri	Bacteria	H3S10, downregulation of MAPK
	Streptococcus	Bacteria	H3/H4, formation of pores on plasmatic membrane and activation of a sensor for intracellular K^+

Table 1 Pathogens and their influence on host epigenetics [3-5]. Changes in gene expression may vary depending on the life cycle stage of pathogen: ex. the slow-growing bradyzoite forms of Toxoplasma gondii, an obligate intracellular, parasitic alveolate that causes the disease toxoplasmosis, lead the dysregulation of few host genes, while his fast-growing form, the tachyzoite, go to alter the gene expression of several host genes. Plasmodium spp, agent of malaria, invade and replicate in liver cells where induce dysregulation of more than 1000 genes, some of which have different quantity of mRNA already after 30 minutes from infection; in a first phase an up-regulation of stress response genes and receptor-binding proteins genes it was observed, while later is detectable an alteration of genes of host's metabolism. This sequential program it was observed also in other organisms as Toxoplasma gondii, M.leprae and Cytomegalovirus.

4. DNA Methylation and Gene Silencing

DNA methylation alters gene expression, the transcriptome, and the proteome. The methylome, which is widely influenced by sex and differs among individuals, is characterized by a series of pre-defined modification during embryogenesis. These modifications are then transferred to the

daughter cells during mitosis. *Mycobacterium tuberculosi*s causes hypermethylation of CpG islands in the *HLA-DQB1* gene and the hypomethylation of the *HLA-F* gene. The *HLA-DQB1* gene encodes a class II HLA protein that plays a crucial role in the immune system and the reduced expression due to hypermethylation alters the antigen presentation process [12]. Some viruses mediate gene silencing by over-expressing methyltransferases that inhibit the transcription of key genes, such as the urokinase-type plasminogen activator in hepatocytes during hepatitis B infection. Methylation of histones by pathogen methyltransferases, such as nuclear effector E (NUE) secreted by *Chlamydia trachomatis*, are directed to the host nuclei. Other pathogens, such as *Legionella pneumophila*, affect methylation of histones. Dephosphorylation of histones is catalyzed by phosphatases secreted by pathogens and directed to the host nuclei (e.g., *Streptococcus pyogenes*). Pathogens, such as *Listeria monocytogenes*, secrete nuclear-targeted proteins that reverse the formation of heterochromatic regions, leading to over-expression of pro-survival and proliferation genes. *Cytomegalovirus* (CMV), and other pathogens produce proteins that affect the centromere during mitosis, interfering with correct chromatid pairing and subsequent segregation, leading to aberrant division. Another mechanism by which pathogens interfere with host gene expression is histone repositioning. This mechanism has been observed in bacteria (*Helicobacter pylori*) and viruses (*Varicella zoster*). Epigenetic modifications can be mediated by pathogens via several mechanisms: modulation of host nuclear signalling pathways, proteolysis of key proteins involved in host cytoplasmic signalling, secretion of proteins that target the host DNA or nuclear proteins, and sequestration or deactivation of host transcription factors. Virally-encoded transcription factors, are important proteins that direct gene expression from the host DNA. For example, the NS5A protein of the hepatitis C virus is crucial for viral replication, has been identified as a multifunctional protein that regulates host gene expression. Following cleavage of the C-terminus in cytoplasm, NS5A translocates to the nucleus and targets promoters of host genes to regulate genes expression. Other pathogens, such as *Toxoplasma gondii*, and Chlamydia spp., deregulate gene expression by deactivating transcription factors or sequestrating them from their transcription sites. The most interesting peculiarity of an epigenetic modification is that it can take place in response to external environmental stimuli, such as lifestyle (including nutrition) and health status. These epigenetic modifications are stable, but potentially reversible and can be transmitted to subsequent generations [13]. They can occur at different stages of life and not only at the embryonic stage (i.e., at the time when the cells start to differentiate), but also when the organism is already developed, leading to congenital disorders or predisposing people to pathological states, such as tumours and neurodegenerative disorders [1]. The epigenetic aetiology of some human diseases, the possibility of being influenced by external stimuli, and the "plasticity" of epigenetics, are all factors that have encouraged the development of a new therapeutic option described as "epigenetic therapy" [14, 15]. This approach is based mainly on the use of drugs that directly modulate epigenetic states by using specific molecules that restore normal conditions. Some of these drugs are central to ongoing clinical trials and there are high expectations, especially for haematological malignancies and soft tissue tumours. However, results obtained in the field of oncology indicate that other human disorders, including some neurodegenerative and cardiovascular diseases, may be suitable for this type of therapy [16].

5. Action of Microorganisms on the Host Epigenome

5.1. Bacteria and Viruses

Pathogenic microorganisms, such as bacteria and viruses, induce multiple epigenomic alterations, which positively or negatively influence the transcription of genes. Many studies are underway to identify the mechanisms of action that exploit this principle. *Legionella pneumophilia*, H*. pylori* and *L. monocytogenes*, are examples of bacteria capable of altering the epigenome of the host cell by means of histone post-translational modifications [17-19]. H3S10 dephosphorylation and decreased H3K23ac acetylation are observed following contact of *H. pylori* with gastric cells[18]. H3S10 dephosphorylation is associated increased IL-6 transcription, while H3K23 deacetylation is presumed to be involved in downregulation of IL-8 transcription [20]. *Legionella pneumophila* mediates trimethylation of H3K14 and a reduction in H3K14 acetylation, leading to an alteration of the levels of cytokines, such as TNFα and IL-6, and pattern-recognition receptors [19]. After translocation of a class 3 histone deacetylase (HDAC) to the nucleus, *L. monocytogenes* induces deacetylation of H3K18, which causes a decrease in the expression of genes involved in DNA binding and a decrease in the immune response to the pathogen [21]. Furthermore, this bacterium secretes a toxin that forms pores (listeriolysin O), which cause the H3S10 dephosphorylation and decreased acetylation levels of histone H4 [17]. Mycobacteria inhibit the changes in histones induced by INF-γ. Epigenetic changes are also found following infections by viruses, such as human adenovirus [22], influenza A [23] and HIV [24]. CMV replication in primary fibroblasts involves various alterations in histones at the post-translational modification (PTM) level, including H3K79 dimethylation, H3K27 methylation, H3K36 dimethylation and decreased H4K16 acetylation [25].

5.2. Parasites

Parasites hijack host cell signaling pathways to orchestrate stable and sustainable changes in host genome activity in the absence of changes in DNA sequence. Parasites are seen as pathogens capable of diverting the various intracellular mechanisms of the host, to induce the occurrence of various changes both in the chromatin status and gene expression [26]. Intracellular pathogens can mimic altered environmental states from inside the cell and can mediate extensive alterations in the regulation of the host transcriptome [27-29] that induce stress and inflammatory responses. To achieve this, the pathogen acts through the "epigenerator" [26], the link between environmental triggers and intracellular signaling pathways that include parasite-encoded effector molecules and initiation of host cell signaling cascades that lead to nuclear readouts of the parasite signals [30].

Many studies have shown that parasitic infection involves extensive changes in gene expression profiles and that the parasite-induced signaling pathways can lead to stable changes in the chromatin structure and in the epigenetic mechanisms underlying cellular phenotypes [28-30]. For this reason, parasites can be called epigenerators that lead to innumerable changes in both the transcriptome of the host and also at the level of the subsequent responses [27-29]. *Toxoplasma gondii* is an example of this type of parasite, which has undergone evolutionary processes resulting in the development of a series of strategies to influence the host cell to promote the growth, persistence and transmission of the parasite. In fact, this parasite is able to induce

epigenetic changes that clearly influence the behavior of parasitic host cells [31]. Intracellular parasites manipulate host gene expression directly by leaving epigenetic signs on the host epigenome [30]. Both *Theileria* and *Toxoplasma* exploit a direct chromatin initiator strategy to guide the proliferation of host cells [30]. However, there is another intriguing possibility that the intracellular parasite secretes proteins that are capable of translocating to the host nucleus, binding to the DNA and perhaps, even initiating gene regulation programs [30].

5.3. Fungi

Methylation is very poor or totally absent in several model eukaryotes, such as *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Caenorhabditis elegans* and *Drosophila melanogaster*, while in plants most cytosines are methylated. In mammals and *Neurospora*, methylation is moderate [32]. *Neurospora* is a common model organism used in biology since DNA methylation is dispensable. For this reason, *Neurospora* was chosen as a model to study the control of DNA methylation in eukaryotes [33]. In vegetative cells, several regions are subject to methylation [32] and a molecular mechanism is in place to protect endogenous genes from aberrant silencing by the DNA methylation machinery. In *S. pombe*, boundary elements prevent the spreading of heterochromatin into neighboring euchromatin [34]. It is well-known that transposons inactivate the genes in which they are to be inserted and impact neighbouring genes. In eukaryotes, transposable elements are critically controlled by DNA methylation [32, 35-37]. Loss of DNA methylation reactivates transposons in *Neurospora*, indicating that methylation is a checkpoint in the control of proliferation of transposons, in conjunction with repeat-induced point (RIP) mutations, which are products of the genome defense system in fungi [32]. Various pathogenic fungi and plant models, such as *Magnaporthe grisea* and *Neurospora crassa* have been used to investigate the effects of DNA methylation in their development. This reprogramming obtained by DNA methylation events is global and occurs both at the transposon level and at the level of non-transposable elements. The effects of these methylation events are multiple, inducing both transcriptional silencing of the transposable elements, and fungal development that result, above all, in more specific and effective defense of the genome. Further studies on fungal species are required to fully clarify these processes [32-37].

6. Molecular Pathological Epidemiology

Epigenetic modifications are a hallmark of complex multifactorial diseases, including neoplastic and non-neoplastic disorders (cardiovascular disease, hypertension, diabetes mellitus, autoimmune diseases and some infectious diseases) and epigenetics itself acts as an interface between environmental and exogenous factors in addition to cellular and pathological processes [38]. Every disease, regardless of the cause, is associated with some type of dysfunction of a specific type of cells or multiple types of cells (in an organ or multi-organ system). Therefore, the optimal approach to understanding the mechanisms underlying these disease processes is to analyze the molecular changes in the specific cell types that are affected [38, 39].

Neoplastic diseases are characterized by uncontrolled cell proliferation, which can provide abundant amounts of diseased cells for epigenetic analysis. However, a tumour consists of many different cell types (transformed neoplastic cells and various non-transformed cells, such as fibroblasts, endothelial cells, smooth muscle cells and inflammatory cells) and the cells are

heterogeneous even within a single tumour [40]. To examine the complex relationships between etiological factors, molecular alterations and disease evolution, the disciplines of molecular pathology and epidemiology have recently been integrated to generate the interdisciplinary field of molecular pathological epidemiology (MPE) [41, 42]. Conventional epidemiology is the study of the frequency with which diseases occur and the conditions that favour or hinder their development in population cohorts. This conventional approach assumes that patients with similar symptoms or manifestations of disease represent a homogeneous group (i.e. a single pathological entity) and share similar etiologies [43]. MPE, on the other hand, is based on the "unique disease principle" and "the disease continuum theory". The first states that patients with the same pathology share some similarities, but each individual has a unique pathological process guided by a complex interaction between molecular alterations in cells and the surrounding microenvironment. At the same time, "the disease continuum theory" states that patients with different diseases may have overlapping etiologies and pathogenesis [38, 43, 44]. Through MPE, a disease is divided into two or more subgroups, established on the basis of molecular pathological characteristics. This subdivision process allows more specific and accurate detection of the relationship between exposure and risk of a single subgroup of patients, with the same pathology. However, approach not only provides estimates of risk, incidence, recurrence or progression, but also insights into different pathogenic pathways [38]. In addition, for individuals classified in a specific sub-group of a given disease, appropriate preventive measures can be implemented (such as avoiding identified risk factors), or early diagnosis can be attempted. Over the past decade, many germline genetic variants associated with numerous multifactorial diseases have been identified in genome-wide association studies (GWAS) [45]. The main shortcomings of existing GWAS include insufficient consideration of the heterogeneity of the disease, and the relative lack of functional follow-up analysis of the risk variants [46-48]. MPE represents a logical evolution of GWAS, known as the GWAS-MPE approach. Although the association of germline genetic variants with disease is receiving increasing attention, this is limited by the fundamental problem that every cell within an individual has a unique epigenome that varies over time [38]. Nevertheless, the GWAS-MPE approach has some advantages, such as providing a possible causal link between the risk variant and the molecular signatures in the diseased cells as well as a more accurate and refined risk estimate for each molecular subtype, which will eventually lead to the identification of new variant-subtype relationships that could be obscured in conventional GWAS because this approach addresses only the overall risk of disease. Thus, in contrast to traditional epidemiological research that includes GWAS, MPE is based on the unique disease principle; that is, every pathological process derives from univocal profiles of exposures, epigenomes, transcripts, proteomes, metabolites, microbes and interactions in relation to the macro-environment and the tissue micro-environment [38]. Recently, MPE has emerged as an evolving transdisciplinary science that integrates molecular pathology and epidemiology in an attempt to decipher the disease at the molecular, cellular, organ, individual and population levels. Epigenetic research is promising strategy for drug development because epigenetic mechanisms play a fundamental role in regulating cell growth, differentiation and behavior, and epigenetic changes are potential targets that can be modified for therapy and chemo-prevention.

6.1. *"Epigenetic Drugs"*

In recent years, several agents have been discovered that alter DNA methylation or induce histones modification. For example, nucleoside analogs, intercalating agents and drugs with demethylating action. Once incorporated into the DNA, these agents interact with methyl-transferases and inhibit cytosine methylation. However, the use of nucleoside analogs is limited due to their toxicity. In addition, some of these agents are non-specific inhibitors and inhibit DNA methylation throughout the genome, causing possible activation of genes that are not otherwise expressed in specific tissues [49]. There are five types of nucleoside analogs: 5-azacitidine, 5-aza-2-deoxycytidine or decitabine, 5-fluro-2-deoxycycidin and zebularine [50]. Azacytidine blocks the growth of tumor cells by inhibiting the synthesis of DNA and RNA. Furthermore, its incorporation into the newly synthesized DNA inactivates DNA methyltransferase and leads to DNA hypomethylation, which can restore normal expression of genes that play a critical role in cell differentiation. 5-Aza-2-deoxycytidine or decitabine inhibits the activity of DNA methyltransferase, leading to hypomethylation and subsequent gene activation through remodeling of "open" chromatin. Genes are reactivated synergistically when demethylation is combined with histone hyperacetylation. Furthermore, low doses of azacytidine and decitabine cause demethylation due to inactivation of DNA methyltransferase-1 (DNMT-1) [51]. 5-Fluoro-2-deoxycytidine is a fluorinated pyrimidine analog antimetabolite with potential antineoplastic activity. As a pro-drug, 5-fluoro-2-deoxycytidine is converted from intracellular deaminase to cytotoxic 5-fluorouracil (5-FU), which is subsequently metabolized into active metabolites comprising 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). Zebularin is a nucleoside analog of cytidine. It reactivates the gene that is silenced and inhibits DNA methylation and is less toxic than other DNMT inhibitors in particular breast cancer cell lines [50]. Although rare, epigenetic drugs also include non-nucleoside analogs that inhibit DNA methylation. These agents do not incorporate into DNA, but link directly to the catalytic region of DNMT. Finally, another class of epigenetic drugs is represented by the inhibitors of histone deacetylation. Since HDACs remove acetyl groups from histones, their overall effect is to leave exposed and potentially vulnerable regions of DNA. On the other hand, these drugs inhibit the enzyme HDAC, thus preventing deacetylation of histones and protecting the DNA. HDACs are widely used to treat HIV and many clinical trials have been conducted to date. A study carried out by San Raffaele of Milan highlighted the role of the enzyme HDAC4 in the epigenetic regulation of gene expression. Suppression of this enzyme leads to a surprising reactivation of viral sequences that are extraneous to the genome[52]. Although the currently available antiviral therapy is very efficient in blocking an activated virus, it is not as effective against the latent or extinguished virus. One possible solution would be to use HDAC4 inhibitors concurrently with classic antiviral therapy, thus allowing the reactivation of the virus (latent or extinct) and its eradication. In humans, there are 18 different types of HDACs, which are divided into four classes based on their homology with yeast HDACs. All have proved useful in resolving inflammation, but also involve changes in the antibacterial capacity of macrophages [53]. Recent studies have elucidated the molecular mechanism by which primary response genes can be induced in a stimulus-dependent manner, despite their constitutive assembly into a chromatin structure resembling that found at active genes. Although low levels of precursor transcripts are constitutively produced at these genes, NF-κB, and possibly other inducible factors, are needed to enhance the efficiency of transcription,

elongation and pre-mRNA processing, in addition to enhancing the frequency of transcriptional initiation [54, 55]. These inducible factors promote acetylation of histones H4K5, K8, and K12. The acetyl lysines are then recognized by the bromodomain-containing adaptor protein Brd4, which recruits P-TEFb to promotes elongation and pre-mRNA processing through its ability to phosphorylate the C-terminal domain of RNA polymerase II [55]. A bromodomain consists of approximately 110 amino acids and recognizes acetylated lysine residues, such as those on N-terminal histone tails. Bromodomains, or "readers" of lysine acetylation, are responsible for transduction of the signal transported by acetylated lysine residues and production of various normal or abnormal phenotypes. Proteins containing bromodomains have a wide variety of functions, ranging from histone acetyltransferase activity to chromatin remodeling, transcriptional mediation, and co-activation. A well-known example of bromodomain-containing proteins is the BET (bromodomain and extra-terminal domain) family, members of which include BRD2, BRD3, BRD4 and BRDT [56]. Bromodomain inhibitors act at the low density promoters of CpG islands and allow modulation of some of the most powerful lipopolysaccharide (LPS) responses leading to the induction of IL-6, IL-12 and NO, which could have advantages in downregulation of systemic inflammation [57].

CRISPR (clustered regularly intersected short palindromic repeats) is the name of a family of DNA segments containing short repeated sequences (of phage or plasmidic origin) from viruses that have previously attacked the bacterium. These sequences were previously known as short regularly spaced repeats (SRSRs). These short repetitions are exploited by the bacterium to recognize and destroy the genome from viruses similar to those of the original CRISPR and therefore, represent a form of acquired immunity of prokaryotes. CRISPR is one of the basic elements of the CRISPR/Cas system, which is also involved in the acquired immunity of prokaryotes. A simplified version of this system, CRISPR/Cas9, has been modified to provide a very powerful and precise genetic editing tool that is much easier, and at the same time cheaper, than pre-existing technologies. Thanks to the CRISPR/Cas9 system, it has been possible to permanently modify the genes of multiple organisms. The CRISPR/Cas system is also gradually supplanting more obsolete methods to study the genetic causes and the course of diseases, such as various types of cancer (in cellular and animal models), as well as the efficacy of drugs. The greatest probabilities of success are expected for the treatment of diseases of the immune system. In fact, the immune cells can be isolated, modified in vitro and reintroduced in the patient once they have been "corrected". This strategy has already been used successfully to generate HIV-resistant T lymphocytes in vitro [58, 59]. This pioneering development paves the way for a reversible modification of the epigenome and therefore, a specific approach to modifying cellular function by influencing gene expression without altering the underlying DNA. This could lead to the targeted resolution of inflammatory processes or the manipulation of individual epigenomes to reduce susceptibility to disease or prevent the relapse of malignant tumours [53]. In conclusion, the development of HDAC inhibitors, bromodomain inhibitors and CRISPR technology offers powerful tools with the potential to modulate the PTM of histones that regulates gene transcription for the management of infectious diseases. Finally, the same pathogens can express enzymes that modify histone PTM and regulate gene transcription; therefore, modulation of histone PTM could offer a range of therapeutic options in the future.

6.2. Immunity

Epigenetic mechanisms regulate the expression of genes and are essential for correct translation of the information contained in DNA into proteins. Alterations in these mechanisms may lead to the onset of various diseases because the immune system does not work as it should. This is demonstrated in a study published in *Frontiers in Immunology* by Anne Corcoran et al. from the Babraham Institute in Cambridge, UK. The object of the study was the production of antibodies, proteins that allow the body to fight infections, by the immune system. Each antibody is synthesized in a process known as V(D)J recombination from different elementary units produced by a limited number of gene groups. This incredibly complex system allows the production of thousands of different antibodies from a handful of genes.

Epigenetic markers, which play a crucial role in the process of V(D)J recombination, regulate the expression of genes, basically via the methylation process by which methyl groups are added to DNA. One of the great mysteries of this process is that some genes are much more commonly used than others for the synthesis of antigens. Corcoran and colleagues focused their investigations on a single region of the mouse genome that, as in humans, contains approximately 140 genes that encode the basic units of antibodies. Precisely for this reason, the authors are convinced that the study of mice can provide useful information on the same genetic and epigenetic mechanisms in humans. Researchers discovered that the genes encoding the most common antibodies are marked by a specific methylation of the histones that coat the DNA.

It has been proposed that this methylation of histones contributes to weakening of the immune system under particular conditions throughout life or in old age, favouring infections or other diseases, such as leukaemia. Some of the crucial factors that allow the activation and inactivation of the genes necessary for antibody synthesis have been identified, which provides fundamental information required to understand the protective mechanisms of the immune system, and what goes wrong when the system is weakened. In the last instance, this information could be useful for the development of new diagnostic tests for recurrent infections as well as novel therapies that stimulate the response to these infections, as well as the onset of other pathologies [60]. Since the beginning of 2000, it was believed that only three pathologies were unquestionably linked to epigenetics: Rett syndrome, Fragile X syndrome and ICF centromere instability syndrome. It is now believed that many pathologies with multifactorial etiopathogenesis such as tumors, neurodegenerative syndromes, and psychiatric disorders, could be induced by epigenetic alterations [51].

6.3. Epigenetic Therapy in Other Diseases

Neoplasms. Cancer is a multistep process in which genetic and epigenetic errors accumulate and transform a normal cell into an invasive or metastatic tumor cell [1]. The alteration of DNA methylation patterns changes the expression of genes associated with cancer. There are three ways in which DNA methylation leads to neoplastic development: hypomethylation of proto-oncogenes that are activated in oncogenes, hypermethylation of oncosuppressor genes with consequent loss of function, and direct mutagenesis [49]. *Helicobacter pylori* infection cause the chronic inflammation and, after 5–10 weeks, hypermethylation of several genes in the gastric mucosa leading to silencing of tumor suppressor genes that trigger cancer [13]. The potential reversibility of DNA methylation patterns suggests that epigenetic therapy may be practicable for

cancer treatment; in fact, one of the specific goals of therapy is to restore normal DNA methylation patterns and prevent cells from acquiring further DNA methylation, which could lead to silencing of genes crucial for normal cell function[61]. The connection between DNA methylation and histone modifications makes it possible to use a combination therapy consisting of DNMT and HDAC inhibitors. Furthermore, as previously mentioned, high doses of DNMT inhibitors are cytotoxic, although lower doses can be administered when they are combined with HDAC inhibitors. A different approach is to use epigenetic therapy first on tumor cells and then traditional chemotherapy, radiotherapy or interferon [50]. Treatment of tumor cells with demethylating agents can reactivate a group of genes, such as p16, MLH1 and retinoblastoma (RB), which are often crucial in the control of cell proliferation, differentiation, apoptosis and other key homeostatic mechanisms [61]. There are discordant opinions among those who prescribe these drugs. Some believe that they can lead to unintended consequences or side-effects [62], while others are more positive based on the findings of microarray studies indicating the target genes in malignant cells are targeted preferentially by this treatment [63, 64]. In cancer cells, changes in acetylation and histone lysine methylation have been observed, suggesting that the general pattern regulating the genome is disturbed [65]. Histone modification patterns are not the same in the various types of cancer or in the various stages of progression, so epigenetic models could be useful in differentiating different types of tumor. Studies have shown that lysine deacetylation, rather than increased histone methylation, is the first step in gene silencing. Furthermore, HDACs, which are responsible for removing acetyl groups from histones, have become the main goal of therapy. However, lysine acetylation can also reduce DNA repair, thus accelerating the molecular events that lead to cancer development [61]. Myelodysplastic syndromes (SMD) are a heterogeneous group of rare haematological diseases characterized by a deficit in the production of normal blood cells (erythrocytes, leukocytes and platelets) and an increased percentage of bone marrow blasts, associated with the risk of progression to acute myeloid leukaemia. A study by Thathia et al. suggests that epigenetic inactivation of the TWIST2 gene in acute lymphoblastic leukaemia has a dual role in disease progression. Initially, in fact, it favours cell growth and alters its survival properties that subsequently increase resistance to chemotherapy [66]. In the patients with SMD and LMA, the nucleoside analogue azacytidine and others have been very widely used with excellent results. Epigenetic therapy could also be useful for chemo-preventive approaches, especially for those diagnosed with aberrant epigenetic changes but who have not yet acquired neoplastic lesions[61].

Diabetic retinopathy. The World Health Organization estimates that there are 422 million people with diabetes worldwide. Diabetic retinopathy is a consequence of diabetes and is the leading cause of blindness in patients who have had the condition for at least 20 years. If not controlled, diabetes leads to the development of alterations of blood vessels to create microaneurysms and transudation of the liquid part of the blood near the retinal center, which in turn, can lead to macular edema. At the onset, symptoms are reversible, but if not treated early, the condition is incurable. Diabetic retinopathy is a multifactorial disease and a number of metabolic abnormalities have been associated with its development. Numerous studies demonstrate the role of epigenetics in the development of diabetic retinopathy and the correlation between histone changes and onset of the pathology. *In vivo* and *in vitro* models have shown that HDAC activities are increased and histone acetyltransferase (HAT) activity is decreased, both in the retina and in its capillary cells, and overall histone acetylation is decreased. Moreover,

during the course of pathology, the mitochondria of the retinal cells become dysfunctional due to alterations in the enzyme superoxide dismutase manganese-dependent (MnSOD) caused by epigenetic modification on the SOD2 gene, leading to increased levels of superoxide radicals. All this evidence indicates the potential of therapeutic modalities aimed at regulation of the histone methylation status in preventing the inhibition of MnSOD and protecting against mitochondrial damage. Diabetes also increases some of the major reactive miRNAs of NF-κB. Thus, these diabetes-induced alterations in miRNAs are implicated as biomarkers of the early stages of disease progression [14]. However, the role of epigenetic modifications in diabetic retinopathy is an emerging area and still under investigation. A better understanding of epigenetic regulators would facilitate identification of new targets to combat this pathology. Kowluru et al. showed that curcumin improves post-retinal metabolic abnormalities thought to be important in the development of diabetic retinopathy [67], as it modulates a number of histone and miRNA modifying enzymes. This finding indicates that natural compounds may have potential benefits in inhibiting the development of retinopathy in diabetic patients throughout their ability to modulate both metabolic alterations and epigenetic modifications [14].

Neuropsychiatric disorders. Epigenetic alterations also affect many syndromes that alter the physio-neurological development associated with gene and chromosomal mutations. Studies have shown that there is a correlation between histone methyltransferases and numerous human congenital diseases associated with defects in the development of the nervous and cardiac systems. Abnormal DNA methylation is associated with numerous other human diseases, such as psychiatric and immune system disorders[49].

Autism and autism spectrum disorders (ASD) are complex neurological disorders characterized by dysfunctions in social interactions, in communications, in restricted interests and in repetitive stereotyped behaviors [68]. Several reports have associated schizophrenia and mood disorders with DNA rearrangements that include DNMT genes [1]. Autism has been related to the region of chromosome 15, which is also responsible for Prader–Willi syndrome and Angelman's syndrome. The results of autopsy of brain tissue of patients with autism revealed a deficit in the expression of MECP2 that seems to confirm a reduced expression of several relevant genes. These results suggest that MECP2 deficiency plays a role in the organization of chromosomes in the developing brain in autism, Rett syndrome and many other neurodevelopmental disorders [69]. Epigenetic drugs, such as the DNA methyltransferase inhibitors azacytidine and decitabine, have mainly been studied as anti-cancer drugs. However, they also show other properties; in fact, low doses of these drugs could be useful in ASD therapy. HDAC inhibitors could be used as neuroprotective drugs. It is noteworthy that no pre-clinical or clinical trials have yet been conducted to evaluate the use of epigenetic drugs for the treatment of ASD [68].

Muscular dystrophy. Muscular dystrophy is a genetic disease, often hereditary, that leads to loss of motor capacity and weakening of muscles. It is a progressive disease that worsens over time and is triggered by one or more gene mutations. There are several types of dystrophy, but the Duchenne form is the most common and well-characterized. In Duchenne muscular dystrophy, the absence of dystrophin in the muscles give rise to a compensatory response controlled by epigenetic mechanisms that can also influence therapeutic treatments. This response can lead to the creation of muscular or fibrotic tissue, different from the normal contractile form. In healthy individuals, dystrophin regulates the activity of HDAC, whereas in patients with Huntington's disease, HDACs are deregulated and the muscles are repaired with fibrotic scars and fat deposition

instead of contractile tissue. DNMT inhibitors that act as an epigenetic factor to reintegrate dystrophin have been shown to block the disease in the early stages of development.

7. Conclusions

The epigenetic profile varies between cells of the same organism and is reversible, dynamic and inheritable. Epigenetic alterations are, therefore, modifications that do not alter the nucleotide sequence but instead, regulate the structure of the chromatin and the gene expression associated with the events deriving from the various genetic factors. Studies on the transcriptome, the proteome and methylome could explain, both the checkpoints of gene regulation (upstream) and the biological response mechanisms (downstream) that are modified epigenetically [3]. The important processes in the regulation of gene expression and therefore, in the regulation of cellular activity, may undergo a reorganization imposed by the various epigenetic changes derived from the inflammatory response to infection by a pathogenic agent (bacterium and/or virus) [12]. Drugs capable of modulating DNA expression could activate or inactivate genes with functions that are closely linked to the pathogenesis of a specific disease. “Epigenetic” therapy aims to modulate the activity of genes mainly involved in the pathogenetic mechanism of the disease itself (methylation or deacetylation) or of myelo-lymphoproliferative diseases. The potential of these new forms of treatment are considerable, with the possibility of application both in the field of oncology and in disease with an autoimmune etiopathogenesis. It is evident that we are only just beginning to understand the substantial contributions of epigenetics to human diseases, and the full impact remains to be discovered. Understanding the mechanisms of epigenetic represents an interesting challenge for the scientific community that will lead to a clearer understanding of the development of human disease as well as highlighting new therapeutic concepts. Since epigenetic changes are modifiable but reversible events, the new frontiers of pharmacology can be used to design drugs that can transiently modify epigenetics in order to reduce access and proliferation of the pathogen.

Author Contributions

Valeria Maddaloni had the idea for this work, designed the review scheme, collaborated in the writing and correction of the manuscript. Daniela D'Arco collaborated in the writing and correction of the manuscript, designed the Table1. Francesca Morano wrote about the epigenetic drugs and therapy and collaborated to the correction. Nicola Pepe is the coordinator of the group, he collaborated to the correction. Luigi Atripaldi is the head of the labs, he collaborated to the correction.

Competing Interests

The authors have declared that no competing interests exist.

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