Chapter 20
Epigenetics and Infectious Pathogens: Interactions, Ploy and Perspectives

Nitu Saha and Raghuvir Singh Tomar

Abstract Since the inception of life, organisms have enormously diversified, from simple unicellular to complex multicellular. As many life forms coexist in an environment, they constantly interact with each other via beneficial or harmful interactions. Humans, being part of the same environment, have confronted many hostile organisms partly comprising of disease-causing pathogens. Pathogens use humans as host for completion of their life cycle or nutrition. Regardless of their purpose, pathogens inflict profound harm to health and well-being of humankind. To name a few, millions of people have died due to the havoc caused by diseases such as plague, tuberculosis, cholera, Spanish flu, Ebola, etc. Revolution in the field of medicine has offered multiple drugs/medications and vaccinations against these pathogens, but owing to their misusage and the increasing anthropogenic rooted climate change, multidrug-resistant species have evolved, capable of attacking more smartly on the host. It has now been established that many such harmful organisms induce epigenetic modifications in the host to suppress host immunity, maintain their own latency, etc. in the course of establishing themselves. To curb this problem, epigenetic modifiers have now been formulated into drugs. These drugs have demonstrated promising results, paving way towards novel cure. This chapter is an attempt to introduce epigenetics and its modifications in host, mediated by pathogens, with an emphasis on bacteria and viruses. Finally, it gives an overview of different novel epigenetic approaches to combat these pathogens.

Keywords Epigenetics · Epigenetic drugs · Host · Interactions · Pathogen

N. Saha · R. S. Tomar (✉)
Laboratory of Chromatin Biology, Department of Biological Sciences, Indian Institute of Science Education and Research, IISER Bhopal, Bhopal, MP, India
e-mail: nitu16@iiserb.ac.in; rst@iiserb.ac.in

P. P. Singh (ed.), *Infectious Diseases and Your Health*,
https://doi.org/10.1007/978-981-13-1577-0_20

20.1 Introduction

The ever-increasing human population has led to the present scenario where earth is inhabited by more than seven billion people. Needless to say that such a growth has led to scarcity of resources for consumption by the humans. This demand has led to ruthless exploitation of environment, changing climate patterns, and more urbanization. These anthropogenic changes have caused an increase in the number of infectious diseases by creating opportunities for climate-dependent active infiltration of pathogens (Bloom 2011; Vitousek et al. 1997).

Infectious diseases have had dramatic influence on human population, and enough evidences depict that from time to time they have caused massive wipeout of individuals. For example, millions of people yielded to Spanish flu in the early twentieth century. Now, with increased facility of medications and lifestyle, the death trolls have decreased, but the pathogens are finding new ways to evade and re-emerge (Johnson and Mueller 2002).

The emerging diseases extend to a bigger geographical area, increasing the number of incidences and infecting new populations. Thus, these diseases pose major threat to humans. Of all the pathogens capable of causing infectious diseases, viruses have succeeded the most. They have evolved to exhibit high mutation and replication rates (Taylor et al. 2001; Medicine IO 2015). Next in the line are bacteria known to cause havoc and re-emerging episodes of disease in a given area, for example, the recurrence of plague and cholera in a country like India. Bacteria exhibit high mutation rates like viruses and are also capable of lateral transfer of genetic material (Lan and Reeves 1996; Ochman et al. 2000). Below is the description of different pathogens and the diseases they cause:

20.1.1 Bacteria

Bacteria [light micrograph of bacteria; refer to Fig. 20.1, source: (Dumler et al. 2005)] are known to inhabit some of the most diverse niches around the world. They appeared long back in the geological time scale. This long history is responsible for the diverse environment they have confronted over time. Thus, they have evolved with a remarkable capacity to respond as per the environmental needs (Persat et al. 2015). Bacteria are classified into at least two classes based on Gram's staining, viz. gram-positive bacteria and gram-negative bacteria. Gram-negative bacteria are particularly notorious and are known to cause variety of diseases (Anwar and Choi 2014).

A description of few bacteria and the associated diseases are as follows:

Mycobacterium tuberculosis: The bacterium is an obligate pathogen responsible for tuberculosis. Infection is manifested in the form of coughing of blood and severe wasting. It may also infect the central nervous system causing meningitis, the digestive tract, the urogenital tract, or the cutaneous region causing lupus vul-

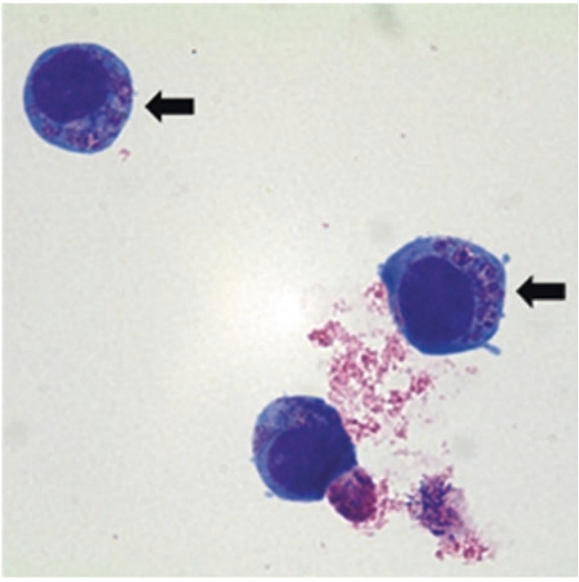

Fig. 20.1 An image of HL-60 (human promyelocytic) cell line containing A. phagocytophilum indicated via arrows © 2014 Kim KH. Published in Kim et al., 2014. Available from: https://dx.doi.org/10.3201/eid2010.131680 (Kim et al., 2014)

garis. The disease is still a major concern of different health organizations (Smith 2003).

Neisseria meningitidis: These are gram-negative, fastidious, and encapsulated bacteria. These organisms are responsible for septicaemia and meningitis in humans. Severity of disease is dependent on virulence of infecting organism, susceptibility factors of host, and the environmental conditions. The disease can lead to potent problems in hearing, behaviour, education, limb loss, and cognitive dysfunction. Disease may be asymptomatic or may cause local inflammation. Many reports of this disease have been reported in Asia, Latin America, Africa, etc. (Rouphael and Stephens 2012).

Salmonella enterica: These rod-shaped, gram-negative bacteria account for major infections in homeothermic organisms. One of the most distinguishing features is the abundance of different serovars within *S. enterica* which define the subspecies. These serovars exhibit different host specificity and virulence which is probably dependent upon their differential gene expression. They mainly infect the intestinal tract of host organisms such as humans. The infected organisms excrete out these bacteria in faeces which are then carried by insects to water sources and into the organisms drinking it. Severity of infection in humans is dependent on the microbial load and host immunity level. Collectively, these serovars are responsible for both typhoid and non-typhoidal infections causing millions of death across the globe, so many measures are being taken by scientists to understand the basis of these infections (Porwollik et al. 2004; Andino and Hanning 2015).

Helicobacter pylori: It is a gram-negative bacterium responsible for chronic gastritis infection, affecting a large number of people all over the world. It is also

involved in gastric cancer, mucosa-associated lymphoid tissue lymphoma, gastric ulcers, etc. Unique morphological features of these bacteria such as spiral shape and flagellar motility aid in quick movement towards the neutral pH area by penetration of thick mucus which provides favourable conditions for growth. *H. pylori* is known to be associated with acute and chronic gastritis. Acute gastritis generally marks the beginning of infection and is exhibited by symptoms related to indigestion such as vomiting, fullness, nausea, etc. and hypochlorhydria. However, after the incidence of acute gastritis, the bacterial colony might get cleared. In case the colony gets established in the host, it gives rise to chronic gastritis leading to augmentation of hypochlorhydria (Kusters et al. 2006; Garza-Gonzalez et al. 2014).

Legionella pneumophila: These bacteria are parasitic or commensal in nature and are found in association with soil or fresh water amoebae in nature. In the case of human-made aquatic habitats, they are found in the form of complex biofilms. These bacteria are responsible for atypical pneumonia known as Legionnaire's disease. This disease is clinically manifested in the form of headache, cough, diarrhoea, etc. Thus, the disease poses an important health problem (Fields et al. 2002).

Chlamydia trachomatis: These bacteria are ovoid or spherical in shape and are obligate intracellular pathogens. These are responsible for multiple inflammations like urethritis, cervicitis, and endometritis in both men and women. Additionally, it may also cause tubal factor infertility, pelvic inflammatory disease, ectopic pregnancy, etc. Though the disease is curable, it makes the infected person more prone to acquisition or transmission of HIV and contributes to the development of cancer in the cervix region. Varieties of symptoms are associated with the disease such as vaginal discharge, high fever, severe pain in the abdominal region, prolonged menstrual cycles, etc. (Malhotra et al. 2013).

Anaplasma phagocytophilum: It is the causal organism of human granulocytic anaplasmosis (HGA). The pathogen is known to employ many mechanisms and adaptations to infect its niche, the neutrophil cells present in human body. HGA is transmitted by infected ticks during their blood meal and is manifested by multiple symptoms such as leukopenia, myalgia, malaise, fever, headache, etc. The incidence of this disease is particularly high in the areas of Europe, California, New England, etc. *Anaplasma* is one of the few organisms which infect neutrophils, so understanding the mechanism of interactions between the two would aid in drug designing against this deadly disease (Dumler et al. 2005).

Ehrlichia chaffeensis: It causes human monocytic ehrlichiosis or human monocytotropic ehrlichiosis (HME). The bacterium is obligately intracellular in nature and exists in the form of two morphologically different reticulate and dense-cored forms. While the reticulate cells have nucleoid DNA fibrils and uniform distribution of ribosomes, the dense-cored cells have both their nucleoid DNA and ribosomes condensed in the centre. The bacterium is introduced into the human body as and when an infected tick bites. Though it mainly targets monocytes, there have been cases of infections in lymphocytes, segmented neutrophils, etc. Symptoms of the infection develop with time and include low back pain,

gastrointestinal symptoms, vomiting, abdominal pain, nausea, malaise, etc. The disease has been found in regions of Oklahoma, Georgia, Arkansas, Maryland, etc. raising concern among the people. Thus, development of potent drugs against the disease is important (Paddock and Childs 2003).

Listeria monocytogenes: It is a gram-positive and facultative anaerobic bacterium causing a food-borne infection called listeriosis which might lead to meningitis and sepsis. Listeriosis is associated with the central nervous system leading to endocarditis, meningitis leading to malaise, vomiting, headache, etc. During pregnancy it has been shown to be associated with abortions. The bacterium is present in soil, water, air, sewage, faeces, etc. (Farber and Peterkin 1991).

Shigella flexneri: One of the most communicable bacterial dysenteries, shigellosis, is caused by the bacterium *S. flexneri*. The bacterium affects rectal and colonic epithelial cells and leads to chronic inflammation and destruction of the epithelia which is exhibited by severe pain in the abdomen and diarrhoea leading to bloody mucoid stool. The disease, if not treated, may further give rise to pneumonia, septicaemia, etc. The pathogen is very infectious, and the incidence of the disease increases due to malnutrition and poor sanitation in developing countries. Transmission of the disease is through faecal oral route and personal contact (Jennison and Verma 2004).

20.1.2 Viruses

These are simple, obligate intracellular parasites which are infectious in nature [electron micrograph of viruses, refer to Fig. 20.2a, b, source: (Barreto-Vieira and Barth 2015; Kawase 2013)]. The genome of viruses contains either RNA or

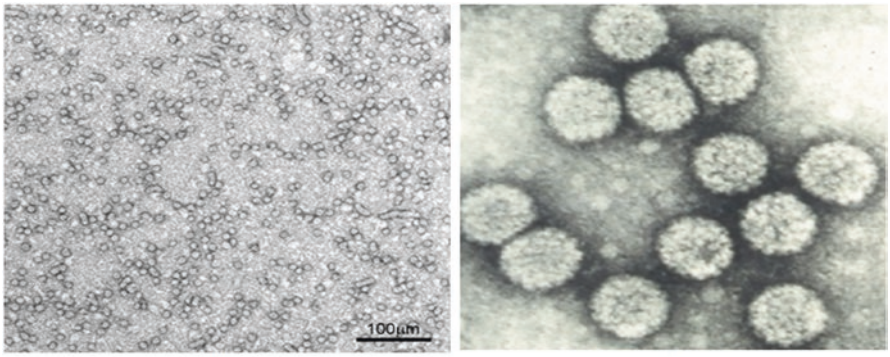

Fig. 20.2 HBV as seen under electron microscope © 2015 ferreira Barreto-Vieira D, Barth OM. Published in (Barreto-Vieira and Barth, 2015) under CC BY 3.0 license. Available from: http://dx.doi.org/10.5772/60511 (**a**) HPV5 virions as seen under electron microscope © 2013 Kawase M. Published in (Kawase, 2013) under CC BY 3.0 license. Available from: http://dx.doi.org/10.5772/55340 (**b**)

DNA. The main function of the genome is to hijack the host cellular machinery to synthesize viral components. Once the components form, viruses assemble to form the progeny viruses called virions which break open the host cells to release and repeat the process of infecting new cells. As the viruses cannot multiply on their own, they invade host cells to grow and flourish themselves and in the process give rise to multiple diseases (Flint et al. 2009).

Description of few viruses and the associated diseases are as under:

Cytomegalovirus (CMV): It is one of the most prevalent causes of congenial viral infection. The herpesvirus is ubiquitously found and is transmitted through interpersonal contact via blood, genital secretions, breast milk, or urine. Infection of this virus is generally mildly symptomatic or asymptomatic. However, in case of immunocompromised hosts, it leads to morbidity, and premature babies exhibit multiple symptoms associated with respiratory status, septic appearance, etc. (Swanson and Schleiss 2013).

Kaposi's sarcoma herpesvirus/human herpesvirus-8 (KSHV/HHV8): The virus causes Kaposi's sarcoma (KS), the most common cancer in HIV-positive untreated patients. KS is a type of vascular tumour which gives rise to lesions. These KS lesions have infiltration of inflammatory agents. Endothelial cells infected by the virus exhibit defective vascularization or angiogenesis and aberrant differentiation (Gramolelli and Schulz 2015; Mesri et al. 2010).

Epstein-Barr virus (EBV): It is ubiquitously found virus and infects mostly during early childhood or infancy. Though infection during early childhood leads to non-specific or no symptoms at all, infection in the adult stage is associated with sore throat, fever, lymphadenopathy, etc. Major concern lies in the fact that the virus is associated with multiple lymphomas, carcinoma, etc. Chronic active EBV is prevalent across continents of South America and Asia and is associated with NK cells or T-cells, while in the Unites States, it is associated with B-cells. Chronic active EBV is characterized by alarmingly elevated antibodies in response to EBV infection or elevated level of the viral DNA, infiltration of organs by EBV-infected cells, and the presence of viral nucleic acid or protein in tissues (Cohen 2009).

Hepatitis B virus (HBV): It is a DNA virus but exhibits properties of retroviruses. It is the causal organism of liver disease and liver cancer. Infection may not be manifested or may be exhibited in the form of hepatitis or liver inflammation. The virus may also lead to other liver diseases like cirrhosis, chronic hepatitis, etc. Proper and correct diagnosis of this disease requires multiple biochemical, serological, and histological tests (Liang 2009).

Human papillomavirus (HPV): These DNA tumour viruses are associated with anal cancer, cervix cancer, and genital warts. HPV causes one of the most common sexually transmitted infections. Within these viruses there are many subtypes each categorized into high-risk or oncogenic types and low-risk or non-oncogenic types. High-risk HPV has been shown to be involved in cervical cancer and dysplasia. The low-risk types are involved in the formation of genital warts which

generally cause morbidity or embarrassment among those who have it (Braaten and Laufer 2008).

Simian virus 40 (SV40): Originally the virus was isolated from rhesus monkey, but it gradually got introduced to the human system, and it is now suspected to be involved in causing cancer. Introduction of SV40 to humans occurred accidently during the administration of Salk and Sabin polio vaccines. These vaccine preparations were contaminated with the virus as they were obtained from primary kidney cell cultures of rhesus monkey which most of the time were SV40 infected. Thus, it could be possible that the viruses, over years, have become pathogen requiring humans as host (Garcea and Imperiale 2003; Vilchez and Butel 2004).

Foot-and-mouth disease virus (FMDV): The virus is from *Picornaviridae* family and is the causal agent for one of the most contagious diseases called the foot-and-mouth disease. Symptoms include the presence of vesicles on the foot and mouth of the cattle. This disease causes huge economic losses as the affected cattle and the ones nearby it are to be slaughtered to prevent any further infections in a given area. The virus is highly notorious as it exhibits high mutation rates and high levels of heterogeneity within a single host, so protection against one serotype does not confer resistance against all. Thus, drugs which can effectively eradicate the virus are to be designed using a novel approach (Salguero et al. 2005).

Thus, novel approaches are required to fight against these pathogens. A new ray of hope is now emerging with epigenetic studies of these pathogens and their interactions with different hosts thus paving way for novel drug designing.

In the 1950s, it was Conrad Waddington who had put forth meaning of the term ‘epigenetics’, but the history and idea of it dates back to the discovery of chromosomes by Flemming following which Muller performed experiments to produce a class of mutations in drosophila which depended on rearrangements in chromosomes (Berger et al. 2009; Holliday 2006). Now, decades later, we know that these epigenetic changes are responsible for regulating biological processes in a body. To sum up, epigenetics deals with the study of heritable changes in gene function without any change in actual DNA sequence. In other words, it supplies an additional layer of transcriptional regulation which aids in modulating the expression pattern of genes. Thus, it has multifaceted roles in gametogenesis, embryogenesis, reorganization of genome, and cell differentiation. Under the effect of non-coding RNAs (ncRNAs) and regulatory proteins, histone post-translational alteration and DNA methylation occur which aid in the rearrangement into heterochromatin, euchromatin, and compartmentalization of nucleus (Moosavi and Motevalizadeh Ardekani 2016). This burgeoning field has been providing greater insights into understanding of diseases or disorders associated with humans. Human genome has approximately 23,000 genes, the expression of which is tightly regulated based on the precise requirement of cells. Control over gene expression is achieved by wrapping of ~147 bp DNA around an octamer of histones containing two copies of H2A, H2B, H3, and H4 each. This unit is known as nucleosome, and many such units are packed

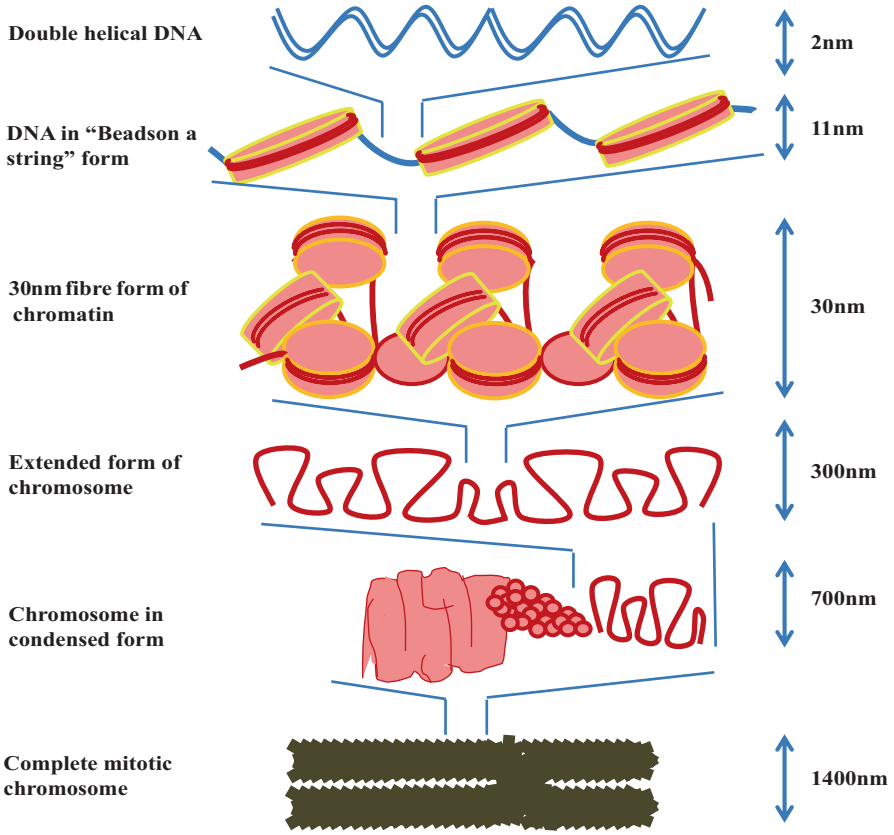

Fig. 20.3 Model depicting multiple levels of chromatin packing. Nucleosome forms the structural unit of chromatin which together gives an appearance of beads on a string. The nucleosomes associate together to form more compact solenoid structure via linker histones H1. The solenoid structure further compacts to frm looped dna alsp known as 700nm and ultimately 1400nm chromosome is formed. The DNA compresses about 10,000 times to form highly condensed structures

at multiple levels to form chromatin or chromosome. Nucleosome units arrange themselves in 'beads on a string fashion' which then form 30 nm chromatin and finally the condensed chromosome (Fig. 20.3; Kouzarides 2007; Alberts et al. 2013). Histone protein exhibits globular structure except the N-terminal tail of all and C-terminal tails of H2A and H2B which have undefined structure and protrude out of octamer to interact with DNA (Luger et al. 1997). Besides, the core histones, viz. H2A, H2B, H3, and H4, different variants of histones exist as well. These variants are involved in modulation of gene expression and are associated with particular chromatin forms (Buschbeck and Hake 2017; Brazel and Vernimmen 2016). For example, an H3 variant named CENP-A has been shown to be associated with a centromere-linked event during interphase (Figueroa et al. 1998). Another variant, H2A.Z, has been implicated in regulation of gene expression as it does not form

condensed chromatin under in vitro conditions (Fan et al. 2002). Also, previous studies have suggested that macroH2A, a histone variant, is involved in inactivated X chromosome of mammalian female (Costanzi et al. 2000). H2AX, another histone variant, plays a rather important role in repair of DNA damage (detailed under phosphorylation). Finally, H3.3, a variant of H3 has been shown to be involved in plausible exchange with H3 to enable activation of transcription (Ahmad and Henikoff 2002). There are at least 60 different residues on histones which are known to be modified. Different modifications may define an outcome dictated by signalling within the cell (Jenuwein and Allis 2001). Also, a given residue may show different levels of modifications. For example, methylation on a histone residue could be mono (one), di (two), tri (three), etc., based on which activation or repression of the associated gene occurs. Certain common histone modifications have come to light based on global analyses done in yeast. The actively transcribing genes have the following common characteristics:

Acetylation is found at the 5′-end of the coding region and the promoter region. Initiation site is flanked by a couple of nucleosomes enriched in Htz1, a variant of H2A, and also has few hypoacetylated lysine residues. Coding region exhibits enrichment of trimethylation and three widely known methylations, viz. H3K4, H3K36, and H3K79 show specific pattern. Thus, these all characteristics point to a basic pattern of modifications necessary for the functioning of a cell. An understanding of all the histone modifications is therefore required. There are, however, technical limitations to the studies in detail. For example, presently, a method like ChIP on CHIP is used, but it cannot give information about modifications on different histones at a given time, a major limitation. Another method which can be harnessed involves the use of mass spectrometry, but it also has a major limitation as the protein in question needs to be digested. So, a modified method comprising of knowledge about the protein following its digestion might provide better insights into the global histone modifications. Next challenge is to get a dynamic picture of histone modifications. The proposed method would provide a static idea of global histone modifications, but these modifications are known to rapidly change under different stimuli. Thus, examination of global histone modifications can only be partially done. Even so, there are problems associated with that too, like availability of specific antibodies, the absence of proper controls as it is almost impossible in mammalian cells to create a mutation that would render the residue completely inactive, and last the inhibition of the binding to a histone residue due to a neighbouring residue which would lead to misleading results. With mass spectrometry the problem lies in the non-uniform coverage of peptides in different sections of a protein which would result in inaccuracy.

It is also difficult to pinpoint the fact that a given histone modification caused by an enzyme leads to a specific function as the histone-modifying enzymes are known to have multiple substrates. So, a function shown may take place via an unknown different molecule. Also, redundant pathways may exist in cellular milieu, masking the effect of inactivation of enzyme so that the function remains unaltered. A double check, therefore, is required by mutating the residue and showing the same effect on the function though it is not possible in a mammalian system as they have multiple

genes for histone. Thus, it may be said that an absolute answer cannot be derived using present techniques but based on how rigorous experiments have been performed which a level of certainty can be reached.

Majority of histone modifications are deemed dynamic, i.e. modification on a residue by one enzyme is removed by another enzyme. However, for modifications of arginine methylation, any direct demethylating enzyme is not known; instead the removal of methylation seems to be tied with the deimination. It has also been found that specificity of a histone-modifying enzyme to a residue on nucleosome or free histones and the levels of modification of a residue as mono, di, and tri is dependent on other associated molecules or proteins (Kouzarides 2007; Steward et al. 2006).

20.2 Types of Epigenetic Modifications

Modification of histone leads to two things: First, it helps to 'open' the nucleosome by disrupting the interaction between histone and DNA. Second, it facilitates the binding of a group of molecules or occlusion of them from a chromatin. These molecules have varied enzymatic activities to bring about more changes in a chromatin according to an external or internal stimulus which in turn may result in gene activation due to an active chromatin or gene inactivation due to a condensed chromatin (Badeaux and Shi 2013). Thus, there is a need to bring different proteins in sequence of their involvement in multistep processes like transcription, repair, etc. (Kouzarides 2007).

The switch between condensed and active states of a chromatin requires epigenetic signatures like DNA methylation and histone modifications via enzymes called epigenetic modifiers. There are different classes of epigenetic modifiers which have been named on the basis of modifications they cause. These enzymes are as under:

20.2.1 DNA Methyltransferases (DNMT)

These enzymes are subdivided into de novo DNA methyltransferases which are enzymes involved in DNA methylation during embryogenesis there by establishing them, e.g. DNMT3A and DNMT3B, and maintenance DNA methyltransferases which are enzymes involved in copying methylation to newly replicated strand, e.g. DNMT1. DNMT1 is part of a complex which is involved in recognition of hemimethylated DNA followed by methyl group addition to the non-methylated daughter DNA strand during replication. Thus, methylation is maintained in a reciprocal manner during replication cycles (Bhutani et al. 2011; Chen and Riggs 2011; Bierne et al. 2012).

20.2.2 Histone Modifiers

It includes various enzymes involved in post-translational modification of multiple residues of histones (Fig. 20.4). Post-translational modifications and their importance are listed below:

20.2.3 Acetylation

Histone acetylation refers to addition of acetyl group to arginine (R) and lysine (K) residues of histone. Acetyl group is added to the ε-amino group of lysine residues. The acetyl group donor is charged CoA or acetylated CoA. Initially, it was shown that treatment of Friend erythroleukaemic cells by n-butyrate differentiated them into haemoglobin-synthesizing normoblast-like cells (Riggs et al. 1977). Later experiments confirmed that n-butyrate acts as histone deacetylase inhibitor or HDACi. Thus, the experiment uniquely defined the role of small molecule like n-butyrate leading to differentiation of cancer cells via inhibition of deacetylation on histone. Prescient experiments by Allfrey et al. laid the basis of histone

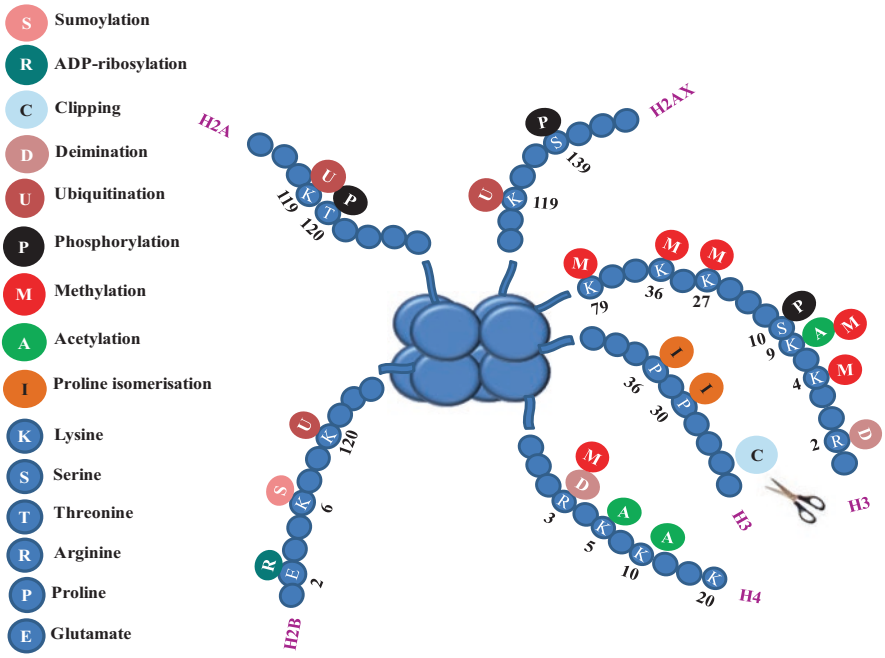

Fig. 20.4 Summary of different modifications on histone amino acid residues. Four types of core histones H2A, H2B, H3, H4, and histone variant H2AX are epigenetically modified through attachment of various chemical groups and/or proteins

acetylation and deacetylation governing the activated and inhibited RNA synthesis, respectively. Afterwards scientists could correlate the acetylation of core histone with the transcriptional activation of genes. It was thus shown that the modifications on histone could bring epigenetic changes. With the basis of an understanding of acetylation, scientists began to speed up the search of possible acetylating and/or deacetylating enzymes and their roles in histone modifications (Kouzarides 2007). Acetylation is associated mostly with activation of gene. So far, most of the acetylations have been described for residues on N-terminal tail of histone as it is the most accessible part. Although, recently, acetylation on H3K56 residue has also been reported which is localized at the core region. H3K56Ac is laid on newly formed histones during the S-phase of cell division. If there is no damage, then the modification is removed. In the presence of DNA damage, however, the modification is retained indicating its significance during DNA damage (Celic et al. 2006; Maas et al. 2006). Another enzyme called Hat1 has been shown to acetylate the lysine-12 on H4 (H4K12) at the sites of DNA repair. Studies suggest that acetylation of H4 has a role to play in the fixation of replication origins and initiation of S-phase (Qin and Parthun 2006; Kouzarides 2007).

20.2.4 Deacetylation

Deacetylation encompasses the reversal of acetylation. Histone deacetylation is involved in the regulation of multiple pathways, and they are part of multiple repression complexes. They are divided into different classes and are called as classical or nonclassical based on their dependence on Zn^{2+} or nicotinamide adenine dinucleotide (NAD^{+}), respectively. They are known for aiding in chromatin condensation. For example, in vitro studies have shown that sirtuin type2 (SirT2) exhibits specificity to acetylation of lysine-16 on H4 (H4K16Ac) and causes deacetylation to bring about chromatin condensation (Vaquero et al. 2006).

20.2.5 Phosphorylation

A relatively unexplored histone modification is phosphorylation which is known to occur on serine (S), tyrosine (Y), or threonine (T) residues on histone. The role of phosphorylation has mainly been explored in response to DNA damage wherein the serine-139 on H2AX is phosphorylated (in case of mammalian cells) (Celeste et al. 2003; Rogakou et al. 1998) and the modified histone variant is called as ϒH2AX. Yeast does not have H2AX, but parallel to mammalian cells, phosphorylation occurs at H2A serine-129 (Downs et al. 2000; Redon et al. 2003). In yeast, mutation of this residue to non-phosphorylatable alanine makes them hypersensitive to DNA-damaging agents such as methyl methanesulphonate (MMS), highlighting its importance in double-strand break repair (Downs et al. 2000). In

addition, this modification distributes over the broad region around the DNA damage probably creating a unique platform to recruit DNA damage repair proteins (Jungmichel and Stucki 2010; Stucki et al. 2005).

Phosphorylation of serine-1 in H4 (H4S1P) has been shown to be induced both in DNA damage repair by negatively regulating acetylation on H4 and during the transcriptional activation of genes. This seems to be contradictory as transcription generally requires hyperacetylation. One hypothesis derived from studies point that phosphorylation of this residue helps to stabilize nucleosome after the ribosome moves in order to prevent inappropriate initiation of transcription within coding sequence of genes which are active (Utley et al. 2005; Cheung et al. 2008; Li et al. 2007). Another phosphorylation is found on serine-47 of H4 (H4S47) which is shown to help in incorporating H3.3-H4 into the nucleosome by associating with a chaperone histone cell cycle regulation defective homolog A (HIRA) specific for H3.3 (Kang et al. 2011).

20.2.6 Dephosphorylation

Like phosphorylation, dephosphorylation also plays a significant role in the regulation of cell functioning and is brought about by class of enzymes known as phosphatase. Studies show that a phosphatase complex, viz. HTP-C, helps in the recovery from DNA damage checkpoint by dephosphorylating phoshorylated serine-129 of H2A (H2AS129P). Similarly, defect in H2AXY142 dephosphorylation recruits pro-apoptotic molecule instead of repair setup to ϒH2AX (Rossetto et al. 2012; Kouzarides 2007).

20.2.7 Methylation

It occurs on various amino acid residues of histone as lysine, arginine, and histidine (Byvoet et al. 1972; Murray 1964; Fischle et al. 2008). Lysine residues get methylated on their ε-amine group, and it can either be mono-, di-, or trimethylation (Murray 1964; Hempel et al. 1968). Arginine residues get methylated on their guanidinyl group, and it can be mono- or dissymmetric or asymmetric dimethylation. Histidine residues are known to be monomethylated (Borun et al. 1972; Gershey et al. 1969). Few types of methylation on H3 and H4 have been studied extensively, viz. H3K4, H3K9, H3K27, H3K36, H3K79, and H4K20. Arginine methylations which include H3R2, H3R8, H3R17, H3R26, and H4R3 have also been reported. Recent studies using mass spectrometry have revealed the presence of methylated basic residues (Greer and Shi 2012).

Histone methyltransferases use methyl groups from S-adenosylmethionine to methylate the histone residues. They belong to three different families: SET domain

containing proteins (Rea et al. 2000), Dot1-like proteins (Feng et al. 2002), and ariginine N-methyltransferase (PRMT) proteins (Bannister and Kouzarides 2011).

H3K4 trimethylation (H3K4me3) in general is linked to active transcription or with poised genes which are ready for activation. H3K4 monomethylation (H3K4me) is often linked to function of enhancer. On the contrary, H3K27 trimethylation (H3K27me3) is a mark of repressed form of chromatin. Cell cycle is regulated by H3K79 dimethylation (H3K79me2) (Bernstein et al. 2002; Santos-Rosa et al. 2002; Heintzman et al. 2007; Schulze et al. 2009). Though methylation on specific residues, in general, is associated with a state of chromatin, it is not always the case. For instance, H3K4 di- and trimethylation (H3K4me2 and H3K4me3) are deemed to be activation marks, but they may be involved in repression. H3K4 di- and trimethylation associate with an inhibitor of growth family member 2 (ING2) protein and help in repression via stabilization of histone deacetylase complex (Shi et al. 2006). Histone methylation has been implicated in the transcriptional regulation, ageing, and intellectual disability (Bernstein et al. 2002; Santos-Rosa et al. 2002; Noma et al. 2001; Pollina and Brunet 2011). Aberrant methylation pattern is found in many types of cancer (Chi et al. 2010).

20.2.8 Demethylation

Methylation mark on histone residues is removed by enzymes called demethylases which are categorized into one of the two families, viz. jumonji-C (JmjC) domain-containing dioxygenases which depend on iron and amine oxidases (Shi et al. 2004; Tsukada et al. 2006; Whetstine et al. 2006; Cloos et al. 2006; Klose et al. 2006a).

One of the lysine demethylases, lysine-specific histone demethylase 1 (LSD1), acts to demethylate H3K4 and repress transcription, but when it combines with androgen receptor, it helps in demethylation of H3K9 and activates transcription (Shi et al. 2006; Metzger et al. 2005). Jumonji-C (JMJC) domain-containing histone demethylases 1,3A, i.e. JHDM1, JMJC domain protein 2A (JMJD2A)/JHDM3A, and JMJC domain protein 2C (JMJD2C)/GASC1, have been reported to be involved in the removal of H3K36 methylation (Tsukada et al. 2006; Whetstine et al. 2006; Klose et al. 2006b; Cloos et al. 2006). Thus, like methyltransferases, demethylases are important to bring about changes in chromatin state (Kouzarides 2007).

20.2.9 Ubiquitination

It is defined as addition of one or more ubiquitin molecule to histone residues. Most abundantly ubiquitinated histones are H2A and H2B. Monoubiquitinated H2A and H2B are the most widespread and take place on Lys-119 for H2A and Lys-123 for H2B. Enzymes which help in the ubiquitination of histone are known as histone ubiquitin ligases (Goldknopf et al. 1975; West and Bonner 1980). For example,

H2AK119 ubiquitination is catalysed by ring finger protein1B (RING1B) (Wang et al. 2004; Cao et al. 2005). Polyubiquitination of H2A and H2AX, a histone variant at K63, has been shown to play an important role in DNA damage repair (Stewart et al. 2009).

20.2.10 Deubiquitination

Like other histone modifications, ubiquitination is also reversible. Enzymes that aid in the removal of ubiquitin from histones are known as deubiquitinating enzymes. Different deubiquitinases as ubiquitin-specific peptidase 16 (USP16), BRCA1-associated protein 1 (BAP1), Myb like, SWIRM and MPN domains 1 (MYSM1) alias 2A-DUB, and USP21 are specific for H2A. They have been shown to play roles in transcription, DNA damage response, etc. (Joo et al. 2007; Shanbhag et al. 2010; Cao and Yan 2012).

20.2.11 Proline Isomerization

Proline (P) isomerization encompasses a non-covalent histone modification which converts peptidyl-proline residues in between *cis* and *trans* form. This causes changes in polypeptide secondary structure which in turn affects histone methylation and therefore gene expression. An enzyme involved in proline isomerization is known as proline isomerase, peptidylprolyl isomerase FPR4 (Fpr4). Studies have implicated a crosstalk in between H3P38 isomerization and H3K36 methylation. It has been shown that H3P38 isomerization to its *cis* form changes the secondary structure of H3 tail so that H3K36 does not fit into Set2 methyltransferase active site. In case of active transcription, the movement of RNA polymerase through genes disturbs the nucleosome and reveals H3K36 to be modified by Set2. The modified H3K36 trimethylation inhibits activity of Fpr4 and maintains an active chromatin state (Nelson et al. 2006).

20.2.12 ADP-Ribosylation

It is a reversible post-translational modification of proteins (Hottiger et al. 2010). Like other modifications, proteins can be both mono- or poly-ADP-ribosylated. During the modification, there is transfer of one ADP-ribose moiety from NAD^+ to acceptor protein amino acid, and thus mono-ADP-ribosylation occurs. The ADP-ribosylated protein may further be ADP-ribosylated (Messner and Hottiger 2011). In general, residues like lysine, glutamate (E), cysteine (C), asparagines (N), phosphor-serine, aspartate (D), and arginine have been shown to undergo this

modification. ADP-ribosylation is catalysed by enzymes called ADP-ribosyltransferases (ARTs) belonging to three different classes, viz. ARTDs (where D stands for diphtheria toxin-like), ARTCs (where C stands for clostridial toxin-like), and NAD^+-dependent protein deacetylases called sirtuins (Hottiger et al. 2010; Hassa et al. 2006; Koch-Nolte et al. 2008; Milne and Denu 2008). This modification has been shown to mediate nucleosome structure dynamics by interacting with 'super beads' made of eight to ten nucleosomes. When NAD^+ is absent, binding of ARTD1 to nucleosome encourages compaction of chromatin, whereas in the presence of NAD^+, automodification of ARTD1 takes place leading to a relax state of chromatin. Poly-ADP-ribosylated chromatin shows a distinct structure and is more sensitive and accessible to treatment of nuclease. It has also been shown that increased levels of mono- and poly-ADP-ribosylated proteins are found in case of DNA damage induction. Besides, ADP-ribosylation level is shown to increase in case of regions which are transcriptionally active. ARTD1 and histone H1 show a reciprocal pattern with respect to chromatin binding. ARTD1 is found to be enriched at transcriptionally active gene promoter (Messner and Hottiger 2011).

20.2.13 ADP-Ribosylation Removal

Poly-ADP-ribosylation of histone is reversible in nature, and the enzymes responsible for removal of this modification are categorized into two classes, viz. PAR glycohydrolases (PARGs) and ADP-ribosylhydrolases (ARHs). The importance of these enzymes lies in their role of primary ADP-ribosyl group removal and maintenance of PAR groups in a cell (Messner and Hottiger 2011).

20.2.14 Histone Clipping

Histone clipping is defined as cleavage of histones. Unlike other histone modifications, this modification is irreversible. All the core histones can undergo cleavage, but H3 clipping has been of great interest because of abundant cleavage sites on the tail, and also it has been found to be cleaved during sporulation, infection, differentiation, ageing, and spermatogenesis (Mandal et al. 2014). Besides, clipping of histone H3 has been found to be involved in alleviation of cytotoxicity or in increasing it. Thus, targeting the clipping of H3 histone might enable improved survival by controlling inflammation. Various enzymes have been shown to be associated with H3 clipping. For example, cathepsin L has been shown to cleave H3 at specific sites Ala21-Thr22 and Lys27-Ser28. Similarly, glutamate dehydrogenase GDH has been shown to target H3 on two sites Lys23-Ala24 and Lys27-Ser28 (Adams-Cioaba et al. 2011; Mandal et al. 2012, 2013; Zhou et al. 2014).

20.2.15 Deimination

It is a modification involving arginine conversion to citrulline. Deamination might play a role in antagonizing the arginine methylation-induced activation as its conversion to citrulline essentially prevents the methylation**.** One of the enzymes required for this conversion is peptidylarginine deiminase 4 (PADI4), and it has been shown that deimination is specific to monomethylated arginine (Kouzarides 2007).

20.2.16 Sumoylation

Sumoylation involves addition of small ubiquitin-related modifier (SUMO) proteins to lysine residues on proteins. Sumoylation occurs through multistep reactions which involves conversion of precursor SUMO protein into its active form via hydrolysis. Activation leads to exposed gly-gly motif in the SUMO protein following which it gets conjugated to SUMO-activating enzyme E1 via thioester bond. Finally, ubiquitin-conjugating enzyme 9 (UBC9) covalently attaches SUMO to lysine residues. Studies have shown that the modification results in repression as both ubiquitination and acetylation are oppressed by it (Maejima and Sadoshima 2014; Kouzarides 2007).

20.3 Epigenetics and Pathogenic Interactions

Once pathogens invade their host, they cause a variety of epigenetic modifications which enable them to thrive and evade the host defence measures (Chen et al. 2014).

20.3.1 Role of Epigenetics in Bacterial Pathogenicity

Bacterial invasion on host triggers changes in epigenetic marks such as DNA methylation, microRNAs (miRNAs), and histone post-translational modifications (Table 20.1). Bacterial lipopolysaccharide (LPS) has been shown to induce miRNA levels. Different bacterial strains bring about different epigenetic modifications in host (Yaseen et al. 2015) (Fig. 20.5).

M. tuberculosis has been one of the most notorious strains of bacteria causing havoc in wide population. Because of its evasion mechanisms, it has become difficult to tackle. Evidence from recent studies suggest that it secretes a protein named Rv1988, a methyltransferase which methylates the histone H3 arginine 42, i.e.

Table 20.1 Summary of epigenetic modifications induced by bacterial pathogens

Organism	Epigenetic modification	Effector (E); target (T)	Functional consequence	Refs.
Bacteria				
Chlamydia	Methylation of histones	NUE (E); histones in mammals (T)	Target genes unknown	Pennini et al. (2010)
Plasma phagocyophilum	Deacetylation of H3 at CYBB locus	AnkA (E); CYBB locus (T)	Repression of CYBB which affects survival of organism	Garcia-Garcia et al. (2009)
Ehrlichia chaffeensis	NA	P200 (E); Alu-Sx elements (T)	Possibly involved in global gene transcription	Zhu et al. (2009)
Lysteria monocytogenes	Histone acetylation	LntA (E); BAHD1 (T)	Enhancement of ISG expression	Bierne et al. (2009)
Shigella	Prevention of phosphorylation	OspF (E); H3 (T)	Inhibition of MAPK	Arbibe et al. (2007)
Shigella	Ubiquitinylation	IpaH9.8 (E); U2AF (T)	Degradation of splicing factor U2AF	Bierne et al. (2012)
Listeria monocytogenes	H3 dephosphorylation, H4 deacetylation	Listeriolysin O (E); H3, H4 (T)	Reduced transcriptional activity of key immunity genes and helps the bacteria to survive in host	Hamon et al. (2007)
Helicobacter pylori	Aberrant methylation of DNA	NA (E); tumour suppressor genes, DNA repair genes (T)	Hypermethylation at tumour suppressor genes, DNA repair genes	Bierne et al. (2012)

H3R42, and thus aids in the repression of defence mechanism employed by the host against *Mycobacteria* (Yaseen et al. 2015).

One of the causal organisms for bacterial meningitidis is *N. meningitidis*. Two potent virulence factors secreted by this organism are meningococcal serine protease A (MspA) and adhesion and penetration protein (App). These two factors cause death of dendritic cells by caspase-dependent apoptosis following proteolytic cleavage of H3 (Khairalla et al. 2015).

Pathogens also employ epigenetics to maintain varied levels of gene transcription. For example, serovars of *S. enterica* have varied levels of DNA methylation which may lead to difference in virulence. Another example is furnished by *H. pylori*, which, after infecting the gastric cells, causes the dephosphorylation of H3S10 and decrease in H3K23ac. H3S10 dephosphorylation is possibly associated with cytotoxin-associated gene A pathogenicity island (cagPAI), as cagPAI deletion leads to restoration of phosphorylation in H3S10. Furthermore, it has also been shown that these changes lead to upregulation of c-Jun, an oncogene, and

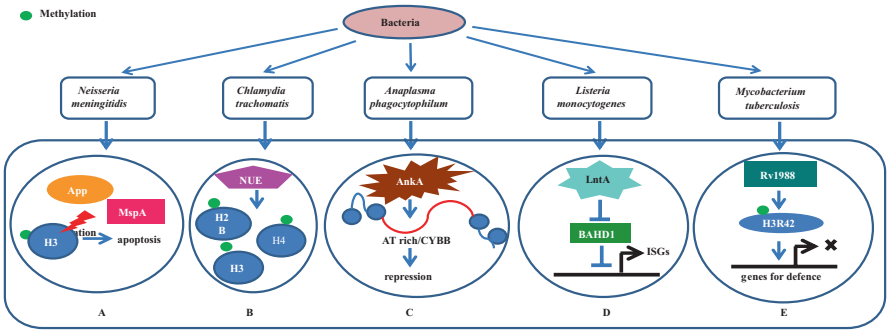

Fig. 20.5 Schematic of epigenetic modifications in bacterial infections. Neisseria meningitides releases App and MspA into the host cells which enter the nucleus to cleave H3 histone and trigger apoptosis (**a**); Chlamydia trachomatis releases NUE which enters inside host cell and methylate the histones (**b**); Anaplasma phagocytophilum secretes AnkA which recognizes AT rich sequence in chromatin and specifically downregulates CYBB which affects survival of the bacteria (**c**); Listeria monocytogenes release LntA which alleviate the interaction of repressor BAHD1 from ISG gene in an attempt to open the chromatin (**d**); Mycobacterium tuberculosis methylates the H3R42 residue which suppresses the expression of genes involved in defence against the bacteria (**e**)

downregulation of heat shock protein 70 (Hsp 70), implicating the possibility of tumour development besides inflammation.

L. pneumophilia employs a regulator of methylation A (Rom A), type 4 secretion system effector, Suvar3-9, enhancer of zeste, and trithorax (SET) domain inhabiting methyltransferase involved in H3K14me3 increase and H3K14ac reduction leading to switching off of gene transcription.

C. trachomatis secretes a nuclear effector (NUE) which enters inside the host cell nuclei and gets associated to the chromatin. NUE methylates histones H2B, H3, and H4 though the advantage of this modification is still not clear**.**

A. phagocytophilum encodes Ank-containing (AnkA) protein which shows preference for AT-rich chromatin region. AnkA is known to repress CYBB which encodes cytochrome b-245, part of phagocyte oxidase, and is known to play a crucial role in survival of the bacteria.

E. chaffeensis encodes p200 protein which binds to chromatin at specific elements called Alu-Sx. Thus, it might have a role in affecting global gene transcription.

Listeria monocytogenes codes for listeria nuclear targeted protein A (LntA), a nuclear targeted factor. LntA has been shown to interact with BAH domain-containing protein 1 (BAHD1), a factor involved in formation of heterochromatin. BAHD1 forms a complex along with other chromatin factors, viz. heterochromatin protein 1 (HP1), SETDB1, KRAB-associated protein 1 (KAP1), histone deacetylases (HDACs), and methyl-CpG-binding domain protein (MBD1) all of which help in silencing expression of genes. Depending on the signal in the cell and the cell types, the BAHD1 complex represses the expression of genes. BAHD1 is involved in the interferon-stimulated gene (ISG) repression in epithelial cells. An unknown

signal triggers expression of *lntA* gene which then enters the nucleus and releases binding of BAHD1 to ISG promoters thus helping in upregulation of ISG expression. LntA most probably facilitates unwinding of chromatin by restricting BAHD1 recruitment to ISG promoters. Thus, the interplay of LntA and BAHD1 helps in modulation of interferon response.

In another example, bacteria *S. flexneri* have been shown to target the chromatin via modulation of transcription factor activity. OspF of *S. flexneri* is a phosphothreonine lyase which converts the phosphothreonine residue of MAPK into dehydrobutyrine. Dehydrobutyrine cannot be phosphorylated, so the MAPK remains in inactive form, resulting in MAPK signalling inhibition. Inhibition of MAPK signalling deters phosphorylation of H3 at promoters regulated by nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-*k*B) and ultimately blocks pro-inflammatory gene expression. Studies show that OspF and OspB interact with Rb, a human retinoblastoma protein which binds to many chromatin remodelling factors. Thus, *Shigella* uses both OspF and OspB to suppress host immunity via alteration of specific genes. Another factor which aids in pathogenesis of *Shigella* is IpaH9.8, an E3 ubiquitin ligase which binds to host proteins and channels them for proteasomal degradation. IpaH9.8 affects activity of U2A, an mRNA splicing factor and NF-*k*B pathway, and therefore modulates the host response (Bierne et al. 2012; Kaul et al. 1997).

20.3.2 Role of Epigenetics in Viral Pathogenicity

Viruses have developed numerous ways to attack the host cells, and using epigenetic modifications to disarm host has not remained untouched (Fig. 20.6) (Table 20.2). For example, cytomegalovirus (CMV) replication induces H3K79 dimethylation (H3K79me2) which is associated with disruptor of telomeric silencing (DOT1). The absence of DOT1L leads to decreased CMV replication. Also, CMV replication is associated with an increase in H3K27 monomethylation (H3K27me) and H3K36 dimethylation (H3K36me2) and a decrease in H4K16 acetylation (H4K16ac). Like with other epigenetic modifications, sirtuin 1 (SIRT1) aids in latency of human herpes-8 virus via H3K27me3, a repressive mark on the viral replication and transcription activator**.** Thus, these epigenetic modifications limit the spread of the virus. Knockdown of SIRT1 led to a decrease of H3K27me3 and an increase in the H3K4me3 resulting in lytic *infection* (Cole et al. 2016).

KSHV is involved in B-cell lymphoma. It encodes a protein named latency-associated nuclear antigen (LANA) which interacts with DNMTs in the cell. Studies have implicated an association of LANA with H-cadherin (CDH13), a tumour suppressor gene which is methylated in variety of cancers. Also, it has been shown that LANA binds to DNMT1, DNMT3A, and DNMT3B. Thus, it is likely that LANA helps in de novo DNA methylation via recruitment of DNMT3A in B-cell lymphomagenesis. Besides, LANA is shown to bind to transforming growth factor (TGF)-β type II receptor (TGF-βRII) gene promoter and inhibiting its transcription. TGF

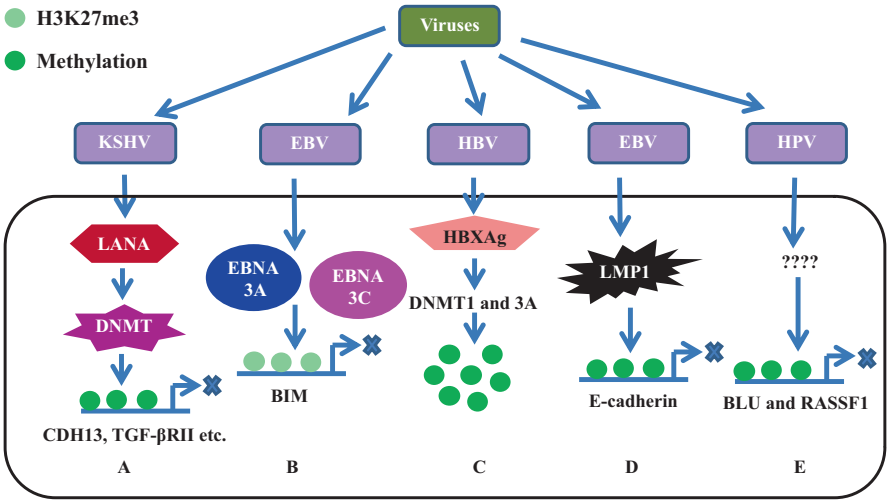

Fig. 20.6 KSHV employs LANA which interact with DNMT to methylate H-cadherin, TGF-βRII in cancerous cells (**a**); EBV uses latency associated molecules to negativelyregulate BIM, a tumor suppressor by methylation of its gene in associated cancer (**b**); HBV codes for HBV X antigen and induce DNMT1 and 3A to methylate E-cadherin and p16INK4A tumor suppressor in cancer (**c**); EBV encodes LMP1 to negatively regulate E-cadherin via methylation (**d**); HPV induces tumor formation by negatively regulating BLU and RASSF1, where RASSF1 is a tumor suppressor (**e**)

Table 20.2 Summary of epigenetic modifications induced by viral pathogens

Organism	Epigenetic modification	Effector (E); target (T)	Functional consequence	Refs.
Kaposi's sarcoma associated virus	Methylation of promoter region of genes	Latency-associated nuclear antigen (E); transforming growth factor (TGF)-β type II receptor (TGF-βRII) (T)	Downregulation of transcription of TGF- βRII and possibly aiding maintenance of latency of virus and lymphoma development	Di Bartolo et al. (2008)
Simian vacuolating virus	Methylation of gene promoter	Large T-antigen (Tag) (E); RASSF1 (T)	Methylation of promoter RASSF1 and associated with pathogenesis of cancer	Paschos and Allday (2010)
Human immunodeficiency virus	Gene promoter methylation	NA (E); GNE (T)	Methylation of GNE gene	Paschos and Allday (2010)
Human adenovirus	Blockage of H2B monoubiquitination	HAdV E1A (E); hBre1 complex (T)	Evasion of interferon (IFN) response	Fonseca et al. (2014)

pathway has pro-apoptotic and/or anti-proliferative role in B-cells, so its inhibition would lead to increased survival of cells**.**

EBV has been found to be associated with B-cell, T-cell, and some forms of Hodgkin's lymphoma. EBV mediates BCL-2-interacting mediator (*BIM*) transcription repression via H3K27me3 epigenetic modification. *BIM* is crucially involved in apoptosis and is therefore important for survival of lymphocytes. Another way by which EBV aids in tumour formation is by latency membrane protein LMP1-assisted methylation of E-cadherin (CDH1) promoter. E-cadherin is an adhesion molecule which controls tumour invasiveness and is found to be epigenetically repressed in many carcinomas. Thus, EBV induces lymphomagenesis via different epigenetic modifications**.**

HBV is reported to be associated with hepatocellular carcinoma. Many studies indicate the involvement of HBV in aberrant DNA methylation during hepatocellular carcinoma. A protein named HBV X antigen (HBVXAg) may mediate methylation as it has been shown to induce DNMT1 and DNMT3A. Thus, EBV triggers aberrant methylation via induction of epigenetic modifiers (Paschos and Allday 2010).

HPV like other viruses has been implicated to DNA methylation in cervical carcinoma cells. Studies show that HPV is linked to enhanced DNA methylation of putative RAS association domain family protein 1 (RASSF1) and BLU (tumour suppressor) gene promoter (Lai et al. 2007; Dammann et al. 2000).

SV40 has similarly been shown to enhance the level of DNMTs and promoter DNA methylation of tumour suppressor gene like RASSF1. Adenoviruses have been reported to block H3K18Ac globally via an oncoprotein e1a thereby repressing transcription of many genes. Human immunodeficiency virus has been shown to enable promoter methylation of glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (*GNE*) gene and repress its transcription. This may lead to disruption of sialylation of cell surface required for cell-cell recognition and may have effects on lymphocyte trafficking (Paschos and Allday 2010).

Studies have shown that FMDV cleaves H3 in a process known as H3 clipping. This modification is irreversible and is catalysed by FMDV 3C protease. Thus, FMDV causes epigenetic modulation of the host resulting in a change of transcriptional regulation of several genes (Falk et al. 1990).

20.4 Future Perspectives

Over several decades now, scientific community has been facing problems with the tackling of bacterial, viral, and other infectious diseases. These organisms exhibit high mutation rates and are capable of lateral gene transfer, rendering them resistant to multiple drugs. The field of epigenetics has given a new scope for fending off these pathogens.

Initially, a number of epigenome modulators were designed to alter the modifications imposed by the pathogens or to let pathogens come out of their latent states so that drugs can act on them and prevent further chances of recurrence from reactivation of their latent forms. The designed drugs span from the generic bromodomain inhibitors and HDAC inhibitors (HDACis) to specific clustered regularly interspersed palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) coupled to acetylases and methyltransferases (Heerboth et al. 2014; Hilton et al. 2015). The most extensively used class of epigenetic drug are HDAC inhibitors (HDACis). In humans there are approximately 18 different kinds of HDACis and have been classified into 4 classes on the basis of their homology with that of yeast HDACis. The major concern of these drugs is their off-target effects. They have been shown to alleviate problem associated with infections but at the same time have disturbed the normal functioning of immune system, for example, by impairing macrophage function. To overcome this disadvantage, several site-specific modifiers have been designed such as tubastatin A, HDAC6 inhibitor, etc. (Vishwakarma et al. 2013). When taken for trial, these HDAC6 inhibitors which target more specifically yielded more positive results. Thus these drugs could be used to target epigenetic pathways individually.

Another class of bromodomain inhibitors are known to inhibit bromodomain and extraterminal domain (BET) proteins. These BET proteins are involved in associating the histone acetylation with transcription (Smale et al. 2014). They recognize the acetyl group on chromatin and then help in its association with RNA polymerase II for transcription. Also, the ET domains of BET proteins interact with several proteins which can possibly influence remodelling of chromatin. Thus, the specific BET inhibitors could modulate the response to lipopolysaccharide to alter levels of interleukins IL-6 and IL-12 and nitric oxide (NO) which in turn be utilized for bringing down pathological inflammation while maintaining the robust immune response during chronic infections (Smale et al. 2014). A bromodomain inhibitor, JQ1, has been used to alter the c-Myc (a transcription factor) functioning in myeloma (Delmore et al. 2011).

A more targeted approach has been under an intensive research which exploits the use of CRISPR technology to specifically modulate epigenetic changes (Ledford 2015). Cas9, a DNA endonuclease enzyme, is used in general for specificity to a particular site. In one of the studies, scientists used an inactive Cas-9 and acetyltransferase (p300) fusion construct to acetylate H3K27 at specific sites leading to targeted gene activation (Hilton et al. 2015). In another instance, inactivated Cas9 was fused with LSD1 to activate specific genes which resulted in a map of 'enhancer' sequences at genetic level, giving insight of their locations (Kearns et al. 2015).

In one study, it has been shown that bromodomain inhibitor could act as a potential therapeutic candidate for diseases associated with human T-cell leukaemia virus 1 (HTLV-1). The viral infection causes prolonged activation of NF-*k*B and its targeted gene expression. Acetylation of NF-*k*B subunit and RelA and recruitment of Brd4 are required following which expression of NF-*k*B targeted genes occur. The

acetylation of RelA and the binding of Brd4 to acetylated RelA are induced by Tax molecule. The presence of JQ1, a BET inhibitor, disrupts the interaction between bromodomain-containing protein 4 (Brd4) and acetylated REL-associated protein (RelA) and thus suppresses Tax, an oncogenic protein-mediated tumorigenesis of HTLV-1-infected cells. Thus, such inhibitors can be utilized for cancer treatment (Wu et al. 2013). JQ1 has also been shown to be effective in the reactivation of latent HIV-1 and aiding in the suppression of T-cell activation gene C-X-C chemokine receptor type 4 (CXCR4) and cluster of differentiation CD3 and CD28 thereby minimizing the T-cell proliferation. Thus, it can be of therapeutic use for treatment of viral infection (Banerjee et al. 2012).

Bacterial and viral infections have long been known to be associated with cancer of different types such as head and neck, liver, cervical, and gastric cancers. One of the common characteristics of these cancers is the presence of aberrant methylation of DNA. An interesting fact about DNA methylation is that the level of aberrant methylation pattern correlates with cancer development risk. Bacterial or viral infections are known to cause severe inflammatory response which gives rise to abnormal pattern of DNA methylation and which culminates in cancer. Now, according to one study, administration of 5-aza-2′-deoxycytidine (5-aza-dC), a demethylating agent, has been shown to decrease the incidence of gastric cancers (Niwa et al. 2013).

Influenza virus infections have become difficult to deal with as they have evolved to multiple antigenic variants and drug-resistant varieties. Researchers have developed C646, a histone acetyltransferase (HAT) inhibitor which binds to p300/cAMP response element-binding protein (CREB) and affects multiple stages of virus life cycle thus helping in suppression of influenza A virus infection (Zhao et al. 2015). Furthermore, it has been proposed that the combined highly active antiretroviral therapy (HAART) and inhibitor of histone methyltransferase (HMT) could be used for inducing HIV-1 recovery. It was shown earlier that H3K9 methylation was required for the HIV-1 promoter. Thus, it can lead to powerful remedy towards the cure of HIV (Bouchat et al. 2012).

HDACis have been shown to aid in the clearance of intracellular bacteria like *E.coli* and *Salmonella typhimurium* of macrophage by increasing the production of mitochondrial reactive oxygen species generated by these cells. HDACis have also been known to inhibit hypoxia-inducible factor, HIF-1α, thereby abrogating the pro-inflammatory cytokine secretion (Ariffin et al. 2015).

Thus, a combination of different epigenetic modifiers can be employed to eradicate different multidrug-resistant pathogenic species.

Acknowledgements We thank all the members of our lab for their immense patience, discussions, and repeated corrections which helped us in writing the chapter. NS acknowledges IISER Bhopal for her fellowship support. SERB and DBT are acknowledged for the funding support to RST.

References

Adams-Cioaba MA, Krupa JC, Xu C, Mort JS, Min J (2011) Structural basis for the recognition and cleavage of histone H3 by cathepsin L. Nat Commun 2:197

Ahmad K, Henikoff S (2002) The histone variant H3.3 marks active chromatin by replication-independent nucleosome assembly. Mol Cell 9:1191–1200

Alberts B, Bray D, Hopkin K, Johnson A, Lewis J, Raff M et al (2013) Essential cell biology. Garland Science, New York

Andino A, Hanning I (2015) Salmonella enterica: survival, colonization, and virulence differences among serovars. Sci World J 2015:520179

Anwar MA, Choi S (2014) Gram-negative marine bacteria: structural features of lipopolysaccharides and their relevance for economically important diseases. Mar Drugs 12:2485–2514

Arbibe L, Kim DW, Batsche E, Pedron T, Mateescu B, Muchardt C et al (2007) An injected bacterial effector targets chromatin access for transcription factor NF-kappaB to alter transcription of host genes involved in immune responses. Nat Immunol 8:47–56

Ariffin JK, Das Gupta K, Kapetanovic R, Iyer A, Reid RC, Fairlie DP et al (2015) Histone deacetylase inhibitors promote mitochondrial reactive oxygen species production and bacterial clearance by human macrophages. Antimicrob Agents Chemother 60:1521–1529

Badeaux AI, Shi Y (2013) Emerging roles for chromatin as a signal integration and storage platform. Nat Rev Mol Cell Biol 14:211–224

Banerjee C, Archin N, Michaels D, Belkina AC, Denis GV, Bradner J et al (2012) BET bromodomain inhibition as a novel strategy for reactivation of HIV-1. J Leukoc Biol 92:1147–1154

Bannister AJ, Kouzarides T (2011) Regulation of chromatin by histone modifications. Cell Res 21:381–395

Barreto-Vieira DF, Barth OM (2015) In: Shah MM (ed) Negative and positive staining in transmission electron microscopy for virus diagnosis. InTech, Rijeka

Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A (2009) An operational definition of epigenetics. Genes Dev 23:781–783

Bernstein BE, Humphrey EL, Erlich RL, Schneider R, Bouman P, Liu JS et al (2002) Methylation of histone H3 Lys 4 in coding regions of active genes. Proc Natl Acad Sci U S A 99:8695–8700

Bhutani N, Burns DM, Blau HM (2011) DNA demethylation dynamics. Cell 146:866–872

Bierne H, Tham TN, Batsche E, Dumay A, Leguillou M, Kerneis-Golsteyn S et al (2009) Human BAHD1 promotes heterochromatic gene silencing. Proc Natl Acad Sci U S A 106:13826–13831

Bierne H, Hamon M, Cossart P (2012) Epigenetics and bacterial infections. Cold Spring Harb Perspect Med 2:a010272

Bloom DE (2011) 7 billion and counting. Science 333:562–569

Borun TW, Pearson D, Paik WK (1972) Studies of histone methylation during the HeLa S-3 cell cycle. J Biol Chem 247:4288–4298

Bouchat S, Gatot JS, Kabeya K, Cardona C, Colin L, Herbein G et al (2012) Histone methyltransferase inhibitors induce HIV-1 recovery in resting CD4(+) T cells from HIV-1-infected HAART-treated patients. AIDS 26:1473–1482

Braaten KP, Laufer MR (2008) Human papillomavirus (HPV), HPV-related disease, and the HPV vaccine. Rev Obstet Gynecol 1:2–10

Brazel AJ, Vernimmen D (2016) The complexity of epigenetic diseases. J Pathol 238:333–344

Buschbeck M, Hake SB (2017) Variants of core histones and their roles in cell fate decisions, development and cancer. Nat Rev Mol Cell Biol 18:299–314

Byvoet P, Shepherd GR, Hardin JM, Noland BJ (1972) The distribution and turnover of labeled methyl groups in histone fractions of cultured mammalian cells. Arch Biochem Biophys 148:558–567

Cao J, Yan Q (2012) Histone ubiquitination and deubiquitination in transcription, DNA damage response, and cancer. Front Oncol 2:26

Cao R, Tsukada Y, Zhang Y (2005) Role of Bmi-1 and Ring1A in H2A ubiquitylation and Hox gene silencing. Mol Cell 20:845–854

Celeste A, Fernandez-Capetillo O, Kruhlak MJ, Pilch DR, Staudt DW, Lee A et al (2003) Histone H2AX phosphorylation is dispensable for the initial recognition of DNA breaks. Nat Cell Biol 5:675–679

Celic I, Masumoto H, Griffith WP, Meluh P, Cotter RJ, Boeke JD et al (2006) The sirtuins hst3 and Hst4p preserve genome integrity by controlling histone h3 lysine 56 deacetylation. Curr Biol CB 16:1280–1289

Chen ZX, Riggs AD (2011) DNA methylation and demethylation in mammals. J Biol Chem 286:18347–18353

Chen R, Kang R, Fan XG, Tang D (2014) Release and activity of histone in diseases. Cell Death Dis 5:e1370

Cheung V, Chua G, Batada NN, Landry CR, Michnick SW, Hughes TR et al (2008) Chromatin- and transcription-related factors repress transcription from within coding regions throughout the *Saccharomyces cerevisiae* genome. PLoS Biol 6:e277

Chi P, Allis CD, Wang GG (2010) Covalent histone modifications – miswritten, misinterpreted and mis-erased in human cancers. Nat Rev Cancer 10:457–469

Cloos PA, Christensen J, Agger K, Maiolica A, Rappsilber J, Antal T et al (2006) The putative oncogene GASC1 demethylates tri- and dimethylated lysine 9 on histone H3. Nature 442:307–311

Cohen JI (2009) Optimal treatment for chronic active Epstein-Barr virus disease. Pediatr Transplant 13:393–396

Cole J, Morris P, Dickman MJ, Dockrell DH (2016) The therapeutic potential of epigenetic manipulation during infectious diseases. Pharmacol Ther 167:85–99

Costanzi C, Stein P, Worrad DM, Schultz RM, Pehrson JR (2000) Histone macroH2A1 is concentrated in the inactive X chromosome of female preimplantation mouse embryos. Development 127:2283–2289

Dammann R, Li C, Yoon JH, Chin PL, Bates S, Pfeifer GP (2000) Epigenetic inactivation of a RAS association domain family protein from the lung tumour suppressor locus 3p21.3. Nat Genet 25:315–319

Delmore JE, Issa GC, Lemieux ME, Rahl PB, Shi J, Jacobs HM et al (2011) BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell 146:904–917

Di Bartolo DL, Cannon M, Liu YF, Renne R, Chadburn A, Boshoff C et al (2008) KSHV LANA inhibits TGF-beta signaling through epigenetic silencing of the TGF-beta type II receptor. Blood 111:4731–4740

Downs JA, Lowndes NF, Jackson SP (2000) A role for *Saccharomyces cerevisiae* histone H2A in DNA repair. Nature 408:1001–1004

Dumler JS, Choi KS, Garcia-Garcia JC, Barat NS, Scorpio DG, Garyu JW et al (2005) Human granulocytic anaplasmosis and Anaplasma phagocytophilum. Emerg Infect Dis 11:1828–1834

Falk MM, Grigera PR, Bergmann IE, Zibert A, Multhaup G, Beck E (1990) Foot-and-mouth disease virus protease 3C induces specific proteolytic cleavage of host cell histone H3. J Virol 64:748–756

Fan JY, Gordon F, Luger K, Hansen JC, Tremethick DJ (2002) The essential histone variant H2A.Z regulates the equilibrium between different chromatin conformational states. Nat Struct Biol 9:172–176

Farber JM, Peterkin PI (1991) *Listeria monocytogenes*, a food-borne pathogen. Microbiol Rev 55:476–511

Feng Q, Wang H, Ng HH, Erdjument-Bromage H, Tempst P, Struhl K et al (2002) Methylation of H3-lysine 79 is mediated by a new family of HMTases without a SET domain. Curr Biol CB 12:1052–1058

Fields BS, Benson RF, Besser RE (2002) Legionella and Legionnaires' disease: 25 years of investigation. Clin Microbiol Rev 15:506–526

Figueroa J, Saffrich R, Ansorge W, Valdivia MM (1998) Microinjection of antibodies to centromere protein CENP-A arrests cells in interphase but does not prevent mitosis. Chromosoma 107:397–405

Fischle W, Franz H, Jacobs SA, Allis CD, Khorasanizadeh S (2008) Specificity of the chromodomain Y chromosome family of chromodomains for lysine-methylated ARK(S/T) motifs. J Biol Chem 283:19626–19635
Flint SJ, Racaniello VR, Enquist LW, Skalka AM (2009) Principles of virology, volume 2: pathogenesis and control. ASM press, Washington, DC
Fonseca GJ, Cohen MJ, Mymryk JS (2014) Adenovirus E1A recruits the human Paf1 complex to enhance transcriptional elongation. J Virol 88:5630–5637
Garcea RL, Imperiale MJ (2003) Simian virus 40 infection of humans. J Virol 77:5039–5045
Garcia-Garcia JC, Rennoll-Bankert KE, Pelly S, Milstone AM, Dumler JS (2009) Silencing of host cell CYBB gene expression by the nuclear effector AnkA of the intracellular pathogen Anaplasma phagocytophilum. Infect Immun 77:2385–2391
Garza-Gonzalez E, Perez-Perez GI, Maldonado-Garza HJ, Bosques-Padilla FJ (2014) A review of Helicobacter pylori diagnosis, treatment, and methods to detect eradication. World J Gastroenterol 20:1438–1449
Gershey EL, Haslett GW, Vidali G, Allfrey VG (1969) Chemical studies of histone methylation. Evidence for the occurrence of 3-methylhistidine in avian erythrocyte histone fractions. J Biol Chem 244:4871–4877
Goldknopf IL, Taylor CW, Baum RM, Yeoman LC, Olson MO, Prestayko AW et al (1975) Isolation and characterization of protein A24, a "histone-like" non-histone chromosomal protein. J Biol Chem 250:7182–7187
Gramolelli S, Schulz TF (2015) The role of Kaposi sarcoma-associated herpesvirus in the pathogenesis of Kaposi sarcoma. J Pathol 235:368–380
Greer EL, Shi Y (2012) Histone methylation: a dynamic mark in health, disease and inheritance. Nat Rev Genet 13:343–357
Hamon MA, Batsche E, Regnault B, Tham TN, Seveau S, Muchardt C et al (2007) Histone modifications induced by a family of bacterial toxins. Proc Natl Acad Sci U S A 104:13467–13472
Hassa PO, Haenni SS, Elser M, Hottiger MO (2006) Nuclear ADP-ribosylation reactions in mammalian cells: where are we today and where are we going? Microbiol Mol Biol Rev 70:789–829
Heerboth S, Lapinska K, Snyder N, Leary M, Rollinson S, Sarkar S (2014) Use of epigenetic drugs in disease: an overview. Genet Epigenet 6:9–19
Heintzman ND, Stuart RK, Hon G, Fu Y, Ching CW, Hawkins RD et al (2007) Distinct and predictive chromatin signatures of transcriptional promoters and enhancers in the human genome. Nat Genet 39:311–318
Hempel K, Lange HW, Birkofer L (1968) Epsilon-N-trimethyllysine, a new amino acid in histones. Naturwissenschaften 55:37
Hilton IB, D'Ippolito AM, Vockley CM, Thakore PI, Crawford GE, Reddy TE et al (2015) Epigenome editing by a CRISPR-Cas9-based acetyltransferase activates genes from promoters and enhancers. Nat Biotechnol 33:510–517
Holliday R (2006) Epigenetics: a historical overview. Epigenetics 1:76–80
Hottiger MO, Hassa PO, Luscher B, Schuler H, Koch-Nolte F (2010) Toward a unified nomenclature for mammalian ADP-ribosyltransferases. Trends Biochem Sci 35:208–219
Jennison AV, Verma NK (2004) Shigella flexneri infection: pathogenesis and vaccine development. FEMS Microbiol Rev 28:43–58
Jenuwein T, Allis CD (2001) Translating the histone code. Science 293:1074–1080
Johnson NP, Mueller J (2002) Updating the accounts: global mortality of the 1918–1920 "Spanish" influenza pandemic. Bull Hist Med 76:105–115
Joo HY, Zhai L, Yang C, Nie S, Erdjument-Bromage H, Tempst P et al (2007) Regulation of cell cycle progression and gene expression by H2A deubiquitination. Nature 449:1068–1072
Jungmichel S, Stucki M (2010) MDC1: the art of keeping things in focus. Chromosoma 119:337–349
Kang B, Pu M, Hu G, Wen W, Dong Z, Zhao K et al (2011) Phosphorylation of H4 Ser 47 promotes HIRA-mediated nucleosome assembly. Genes Dev 25:1359–1364

Kaul R, Hoang A, Yau P, Bradbury EM, Wenman WM (1997) The chlamydial EUO gene encodes a histone H1-specific protease. J Bacteriol 179:5928–5934
Kawase M (2013) Genetics of epidermodysplasia verruciformis. InTech, Rijeka
Kearns NA, Pham H, Tabak B, Genga RM, Silverstein NJ, Garber M et al (2015) Functional annotation of native enhancers with a Cas9-histone demethylase fusion. Nat Methods 12:401–403
Khairalla AS, Omer SA, Mahdavi J, Aslam A, Dufailu OA, Self T et al (2015) Nuclear trafficking, histone cleavage and induction of apoptosis by the meningococcal App and MspA autotransporters. Cell Microbiol 17:1008–1020
Kim K-H, Yi J, Won Sup O, Kim N-H, Choi SJ, Choe PG, Kim N-J, Lee J-K, Myoung-don O (2014) Human granulocytic Anaplasmosis, South Korea, 2013. Emerg Infect Dis 20(10):1708–1711
Klose RJ, Kallin EM, Zhang Y (2006a) JmjC-domain-containing proteins and histone demethylation. Nat Rev Genet 7:715–727
Klose RJ, Yamane K, Bae Y, Zhang D, Erdjument-Bromage H, Tempst P et al (2006b) The transcriptional repressor JHDM3A demethylates trimethyl histone H3 lysine 9 and lysine 36. Nature 442:312–316
Koch-Nolte F, Kernstock S, Mueller-Dieckmann C, Weiss MS, Haag F (2008) Mammalian ADP-ribosyltransferases and ADP-ribosylhydrolases. Front Biosci 13:6716–6729
Kouzarides T (2007) Chromatin modifications and their function. Cell 128:693–705
Kusters JG, Van Vliet AH, Kuipers EJ (2006) Pathogenesis of Helicobacter pylori infection. Clin Microbiol Rev 19:449–490
Lai HC, Lin YW, Chang CC, Wang HC, Chu TW, Yu MH et al (2007) Hypermethylation of two consecutive tumor suppressor genes, BLU and RASSF1A, located at 3p21.3 in cervical neoplasias. Gynecol Oncol 104:629–635
Lan R, Reeves PR (1996) Gene transfer is a major factor in bacterial evolution. Mol Biol Evol 13:47–55
Ledford H (2015) Epigenetics: the genome unwrapped. Nature 528:S12–S13
Li B, Carey M, Workman JL (2007) The role of chromatin during transcription. Cell 128:707–719
Liang TJ (2009) Hepatitis B: the virus and disease. Hepatology 49:S13–S21
Luger K, Mader AW, Richmond RK, Sargent DF, Richmond TJ (1997) Crystal structure of the nucleosome core particle at 2.8 A resolution. Nature 389:251–260
Maas NL, Miller KM, Defazio LG, Toczyski DP (2006) Cell cycle and checkpoint regulation of histone H3 K56 acetylation by Hst3 and Hst4. Mol Cell 23:109–119
Maejima Y, Sadoshima J (2014) SUMOylation: a novel protein quality control modifier in the heart. Circ Res 115:686–689
Malhotra M, Sood S, Mukherjee A, Muralidhar S, Bala M (2013) Genital Chlamydia trachomatis: an update. Indian J Med Res 138:303–316
Mandal P, Azad GK, Tomar RS (2012) Identification of a novel histone H3 specific protease activity in nuclei of chicken liver. Biochem Biophys Res Commun 421:261–267
Mandal P, Verma N, Chauhan S, Tomar RS (2013) Unexpected histone H3 tail-clipping activity of glutamate dehydrogenase. J Biol Chem 288:18743–18757
Mandal P, Verma N, Azad GK, Singh V, Golla U, Tomar RS (2014) Epigenetics: role of histone proteases in cellular functions and diseases. Springer, New York
Medicine IO (2015) Emerging viral diseases: the one health connection: workshop summary. The National Academies Press, Washington, DC
Mesri EA, Cesarman E, Boshoff C (2010) Kaposi's sarcoma and its associated herpesvirus. Nat Rev Cancer 10:707–719
Messner S, Hottiger MO (2011) Histone ADP-ribosylation in DNA repair, replication and transcription. Trends Cell Biol 21:534–542
Metzger E, Wissmann M, Yin N, Muller JM, Schneider R, Peters AH et al (2005) LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription. Nature 437:436–439
Milne JC, Denu JM (2008) The Sirtuin family: therapeutic targets to treat diseases of aging. Curr Opin Chem Biol 12:11–17

Moosavi A, Motevalizadeh Ardekani A (2016) Role of epigenetics in biology and human diseases. Iran Biomed J 20:246–258
Murray K (1964) The occurrence of epsilon-N-methyl lysine in histones. Biochemistry 3:10–15
Nelson CJ, Santos-Rosa H, Kouzarides T (2006) Proline isomerization of histone H3 regulates lysine methylation and gene expression. Cell 126:905–916
Niwa T, Toyoda T, Tsukamoto T, Mori A, Tatematsu M, Ushijima T (2013) Prevention of Helicobacter pylori-induced gastric cancers in gerbils by a DNA demethylating agent. Cancer Prev Res (Philadelphia, Pa.) 6:263–270
Noma K, Allis CD, Grewal SI (2001) Transitions in distinct histone H3 methylation patterns at the heterochromatin domain boundaries. Science 293:1150–1155
Ochman H, Lawrence JG, Groisman EA (2000) Lateral gene transfer and the nature of bacterial innovation. Nature 405:299–304
Paddock CD, Childs JE (2003) Ehrlichia chaffeensis: a prototypical emerging pathogen. Clin Microbiol Rev 16:37–64
Paschos K, Allday MJ (2010) Epigenetic reprogramming of host genes in viral and microbial pathogenesis. Trends Microbiol 18:439–447
Pennini ME, Perrinet S, Dautry-Varsat A, Subtil A (2010) Histone methylation by NUE, a novel nuclear effector of the intracellular pathogen Chlamydia trachomatis. PLoS Pathog 6:e1000995
Persat A, Nadell CD, Kim MK, Ingremeau F, Siryaporn A, Drescher K et al (2015) The mechanical world of bacteria. Cell 161:988–997
Pollina EA, Brunet A (2011) Epigenetic regulation of aging stem cells. Oncogene 30:3105–3126
Porwollik S, Boyd EF, Choy C, Cheng P, Florea L, Proctor E et al (2004) Characterization of Salmonella enterica subspecies I genovars by use of microarrays. J Bacteriol 186:5883–5898
Qin S, Parthun MR (2006) Recruitment of the type B histone acetyltransferase Hat1p to chromatin is linked to DNA double-strand breaks. Mol Cell Biol 26:3649–3658
Rea S, Eisenhaber F, O'Carroll D, Strahl BD, Sun ZW, Schmid M et al (2000) Regulation of chromatin structure by site-specific histone H3 methyltransferases. Nature 406:593–599
Redon C, Pilch DR, Rogakou EP, Orr AH, Lowndes NF, Bonner WM (2003) Yeast histone 2A serine 129 is essential for the efficient repair of checkpoint-blind DNA damage. EMBO Rep 4:678–684
Riggs MG, Whittaker RG, Neumann JR, Ingram VM (1977) n-Butyrate causes histone modification in HeLa and Friend erythroleukaemia cells. Nature 268:462–464
Rogakou EP, Pilch DR, Orr AH, Ivanova VS, Bonner WM (1998) DNA double-stranded breaks induce histone H2AX phosphorylation on serine 139. J Biol Chem 273:5858–5868
Rossetto D, Avvakumov N, Cote J (2012) Histone phosphorylation: a chromatin modification involved in diverse nuclear events. Epigenetics 7:1098–1108
Rouphael NG, Stephens DS (2012) Neisseria meningitidis: biology, microbiology, and epidemiology. Methods Mol Biol (Clifton N.J.) 799:1–20
Salguero FJ, Sanchez-Martin MA, Diaz-San Segundo F, De Avila A, Sevilla N (2005) Foot-and-mouth disease virus (FMDV) causes an acute disease that can be lethal for adult laboratory mice. Virology 332:384–396
Santos-Rosa H, Schneider R, Bannister AJ, Sherriff J, Bernstein BE, Emre NC et al (2002) Active genes are tri-methylated at K4 of histone H3. Nature 419:407–411
Schulze JM, Jackson J, Nakanishi S, Gardner JM, Hentrich T, Haug J et al (2009) Linking cell cycle to histone modifications: SBF and H2B monoubiquitination machinery and cell-cycle regulation of H3K79 dimethylation. Mol Cell 35:626–641
Shanbhag NM, Rafalska-Metcalf IU, Balane-Bolivar C, Janicki SM, Greenberg RA (2010) ATM-dependent chromatin changes silence transcription in cis to DNA double-strand breaks. Cell 141:970–981
Shi Y, Lan F, Matson C, Mulligan P, Whetstine JR, Cole PA et al (2004) Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. Cell 119:941–953
Shi X, Hong T, Walter KL, Ewalt M, Michishita E, Hung T et al (2006) ING2 PHD domain links histone H3 lysine 4 methylation to active gene repression. Nature 442:96–99

Smale ST, Tarakhovsky A, Natoli G (2014) Chromatin contributions to the regulation of innate immunity. Annu Rev Immunol 32:489–511

Smith I (2003) Mycobacterium tuberculosis pathogenesis and molecular determinants of virulence. Clin Microbiol Rev 16:463–496

Steward MM, Lee JS, O'Donovan A, Wyatt M, Bernstein BE, Shilatifard A (2006) Molecular regulation of H3K4 trimethylation by ASH2L, a shared subunit of MLL complexes. Nat Struct Mol Biol 13:852–854

Stewart GS, Panier S, Townsend K, Al-Hakim AK, Kolas NK, Miller ES et al (2009) The RIDDLE syndrome protein mediates a ubiquitin-dependent signaling cascade at sites of DNA damage. Cell 136:420–434

Stucki M, Clapperton JA, Mohammad D, Yaffe MB, Smerdon SJ, Jackson SP (2005) MDC1 directly binds phosphorylated histone H2AX to regulate cellular responses to DNA double-strand breaks. Cell 123:1213–1226

Swanson EC, Schleiss MR (2013) Congenital cytomegalovirus infection: new prospects for prevention and therapy. Pediatr Clin N Am 60:335–349

Taylor LH, Latham SM, Woolhouse ME (2001) Risk factors for human disease emergence. Philos Trans R Soc Lond Ser B Biol Sci 356:983–989

Tsukada Y, Fang J, Erdjument-Bromage H, Warren ME, Borchers CH, Tempst P et al (2006) Histone demethylation by a family of JmjC domain-containing proteins. Nature 439:811–816

Utley RT, Lacoste N, Jobin-Robitaille O, Allard S, Cote J (2005) Regulation of NuA4 histone acetyltransferase activity in transcription and DNA repair by phosphorylation of histone H4. Mol Cell Biol 25:8179–8190

Vaquero A, Scher MB, Lee DH, Sutton A, Cheng HL, Alt FW et al (2006) SirT2 is a histone deacetylase with preference for histone H4 Lys 16 during mitosis. Genes Dev 20:1256–1261

Vilchez RA, Butel JS (2004) Emergent human pathogen simian virus 40 and its role in cancer. Clin Microbiol Rev 17:495–508, table of contents

Vishwakarma S, Iyer LR, Muley M, Singh PK, Shastry A, Saxena A et al (2013) Tubastatin, a selective histone deacetylase 6 inhibitor shows anti-inflammatory and anti-rheumatic effects. Int Immunopharmacol 16:72–78

Vitousek PM, Mooney HA, Lubchenco J, Melillo JM (1997) Human domination of Earth's ecosystems. Science 277:494–499

Wang H, Wang L, Erdjument-Bromage H, Vidal M, Tempst P, Jones RS et al (2004) Role of histone H2A ubiquitination in Polycomb silencing. Nature 431:873–878

West MH, Bonner WM (1980) Histone 2B can be modified by the attachment of ubiquitin. Nucleic Acids Res 8:4671–4680

Whetstine JR, Nottke A, Lan F, Huarte M, Smolikov S, Chen Z et al (2006) Reversal of histone lysine trimethylation by the JMJD2 family of histone demethylases. Cell 125:467–481

Wu X, Qi J, Bradner JE, Xiao G, Chen LF (2013) Bromodomain and extraterminal (BET) protein inhibition suppresses human T cell leukemia virus 1 (HTLV-1) tax protein-mediated tumorigenesis by inhibiting nuclear factor kappaB (NF-kappaB) signaling. J Biol Chem 288:36094–36105

Yaseen I, Kaur P, Nandicoori VK, Khosla S (2015) Mycobacteria modulate host epigenetic machinery by Rv1988 methylation of a non-tail arginine of histone H3. Nat Commun 6:8922

Zhao D, Fukuyama S, Sakai-Tagawa Y, Takashita E, Shoemaker JE, Kawaoka Y (2015) C646, a novel p300/CREB-binding protein-specific inhibitor of histone acetyltransferase, attenuates influenza A virus infection. Antimicrob Agents Chemother 60:1902–1906

Zhou P, Wu E, Alam HB, Li Y (2014) Histone cleavage as a mechanism for epigenetic regulation: current insights and perspectives. Curr Mol Med 14:1164–1172

Zhu B, Nethery KA, Kuriakose JA, Wakeel A, Zhang X, Mcbride JW (2009) Nuclear translocated Ehrlichia chaffeensis ankyrin protein interacts with a specific adenine-rich motif of host promoter and intronic Alu elements. Infect Immun 77:4243–4255