

A REVIEW ON EPIGENETIC REGULATION IN BACTERIAL PATHOGENESIS AND RESISTANCE**Ahmed Majeed Abdzaid**Department of Pathological Analysis, College of Science,
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Abstract: The study of bacterial epigenetics has become important, because it helps in understanding the mechanisms used by bacteria to regulate gene expression while keeping their DNA sequence. This regulation has been known to play an important role in bacterial pathogenesis and resistance mechanisms, which assist the bacteria to easily adapt to environmental changes and withstand hard conditions, including antibiotic exposures. In this review, we clarify the essential mechanism of epigenetic regulation of the bacteria that includes DNA methylation, histone-like protein modifications, and non-coding RNAs. We focus on their importance to bacterial virulence and resistance, focusing on understanding how to use new therapeutic strategies against antibiotic resistance and invasive diseases.

Keywords: epigenetic regulation, DNA methylation, resistance gene, non-coding

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Bacterial pathogens are very important for human health, so it is necessary to understand how to control bacterial infections through antibiotics and vaccines development.

However, the antibiotic-resistant bacteria emerging and spreading rapidly that pose a real risk to global health and ultimately necessitating for discovering the adaptation and survival mechanisms of the bacteria. Genetic mutations, horizontal gene transfer and epigenetic regulation play a major role in bacterial pathogenesis and antibiotic resistance.

Epigenetics is the heritable changes in gene expression which do not make any alterations in the DNA sequence itself. These changes can affect the behavior of the bacteria, making the bacteria readily adapted to hard environments, which include resistant to the immune system of the host and resistant antimicrobial agents. Epigenetics differs from genetic mutations, that are permanent and can be transmitted other generations, epigenetic modifications are mostly reversible, that permitting

bacteria to easily modify gene expression in response to changes in the environmental conditions (Casadesús and Low, 2006).

Bacterial virulence and resistance are affected by controlling gene expression by some mechanisms which are the tools used by the bacteria and consider the primary mechanisms of epigenetic regulation in the bacteria such as DNA methylation, histone-like protein modifications, and the action of non-coding RNAs. For example, the expression of genes involved in pathogenicity and antibiotic resistance can be modulated by DNA methylation, while the restructuring of the bacterial chromosome to control the access to genetic information can be done by histone-like proteins (Navarre et al., 2007). Similarly, post-transcriptional gene expression can be controlled by non-coding RNAs, adding extra level of regulatory control (Novick and Geisinger, 2008).

Understanding the epigenetic mechanisms of the bacterial pathogens help to understand the survival strategies and the therapeutic of the antibiotic's resistant bacteria. This review aims to clarify the key mechanisms of bacterial epigenetic regulation and discovering their roles in pathogenesis and antibiotic resistance and highlighting the therapeutic suggestions of targeting these epigenetic processes.

Epigenetic Mechanisms in Bacteria

In bacteria, the epigenetic regulation comprises different mechanisms which include DNA methylation, modifications of histone-like proteins in addition to the action of non-coding RNAs. These processes facilitate the bacteria to rapid adaptation to changing in environments by control gene expression.

DNA Methylation

DNA methylation in bacteria primarily occurs at adenine or cytosine residues and mediated by specific DNA methyltransferases. This change effects many cellular processes, such as DNA replication, repair mechanisms or gene expression. For instance, in *Escherichia coli*, the Dam methylase adds methyl groups to adenine residues in GATC sequences, playing a crucial role in DNA mismatch repair and the time of the DNA replication initiation (Marinus and Casadesus, 2009). In addition, the processes of phase variation which is reversible process allowing bacteria to alternate between different phenotypic states, which is often involves differential methylation patterns. This mechanism is considered an essential mechanism for evading host immune responses and allowing adaptation to new environments (Hernday et al., 2002).

Phase variation driven by DNA methylation in pathogenic bacteria such as *Salmonella*, permit it to alter surface structures and evade immune system. Control the expression of virulence genes done by methylation, that ensuring they are under specific conditions that favor infection will be activated (Gerlach et al., 2007).

Histone-like Proteins

Bacteria lack true histones but instead they contain histone-like proteins for example HU, H-NS, and Fis, these proteins effect DNA topology and gene expression. H-NS, for example, preferentially binds

to AT-rich DNA regions and will silence foreign DNA that include atherogenicity islands in *Salmonella* (Navarre et al., 2006). Managing the expression of virulence genes and adapting to host environments is done by this regulation which is crucial for it.

Histone-like proteins has important role in the structural organization of bacterial chromosomes and gene expression. The nucleoid-associated proteins (NAPs) either can repress or activate genes, and this depends on the context. For instance, horizontally acquired genes that contain virulence factors and antibiotic resistance genes is silent by H-NS (Lucchini et al., 2006). This process of silencing is necessary to prevent the unwanted expression of these genes, that is very important to bacterial fitness in the absence of selective pressures.

Non-coding RNAs

In bacteria, the non-coding RNAs (ncRNAs) play important roles in regulation gene post-transcriptionally. Small RNAs (sRNAs) which can be binding to messenger RNAs (mRNAs), through stabilizing them or either by facilitating their degradation. In *Staphylococcus aureus*, the regulation of virulence factor expression through base-pairing with target mRNAs is done by RNAIII which is well-known sRNA (Novick and Geisinger, 2008).

The sRNAs are used in a large variety of regulation functions that include influencing bacterial stress responses, metabolism, and pathogenicity. For example, in *Vibrio cholerae*, controls the quorum sensing response is done by the sRNA which is known as Quorum regulatory RNA (QRR), which is necessary to biofilm formation and virulence that can be obtained through regulating genes necessary for this (Svenningsen et al., 2008) and this is essential for virulence factors expression through the infection.

Epigenetics and Bacterial Pathogenesis

The ability of the bacteria to regulate virulence genes through epigenetic mechanisms is associated with bacterial pathogenicity. By these regulatory processes, the virulence factors expression is done only at infection or survival conditions.

Phase Variation and Pathogenesis

In bacteria switching the expression of surface structures reversibly is done by phase variation, for example pili and flagella that helping in escaping from immune system. *Neisseria gonorrhoeae* can evade host immune system detection by phase variation of pili which is mediated by slipped-strand mispairing, (Srikhanta et al., 2005). In *Helicobacter pylori*, the expression of outer membrane proteins, which is contributing to persistent infection and chronic gastritis is affected by the phase variation (Salaün et al., 2003).

Additionally, to immune evasion, the colonization and persistence of bacteria in various positions within the host is aiding by the phase variation. This providing survival ability to bacteria through switch between different phenotypes and allowing the bacteria to adaptation for alteration in environmental conditions and host defenses (van der Woude and Bäumlner, 2004).

Virulence Gene Regulation

Listeria monocytogenes control virulence gene expression through the PrfA regulator. PrfA activity is depending on temperature changes in its mRNA secondary structure, which is an epigenetic mechanism that ensuring ensures the virulence genes are expressed only by human body temperature and not in the environment temperature (Johansson et al., 2002).

Yersinia pestis which is causing plague is another example of the regulation of virulence gene. The *Yersinia pestis* RovA protein regulates virulence gene expression in response to temperature, so it is playing role as as a thermosensor and enhancing the pathogen's ability to infect warm-blooded hosts (Herbst et al., 2009).

Epigenetics and Antibiotic Resistance

Epigenetic mechanisms posing significant challenges to public health through play an important roles in the development and spreading of antibiotic resistance.

Methylation and Resistance Genes

Influencing the antibiotic resistance genes expression is done by DNA methylation. In *Mycobacterium tuberculosis*, the multidrug resistance mechanisms are done by the promoter region methylation of the efflux pump gene *whiB7* which is leading to upregulation of this region, so epigenetic regulation is very important for allowing the bacteria to rapid adapt to antibiotic treatment (Reeves et al., 2013).

In *Escherichia coli*, multidrug resistance feature is due to the regulation of the expression of resistance genes by methylation-sensitive promoters, for example, regulating the *acrAB-tolC* efflux pump system by DNA methylation and associated transcriptional factors (Hirakawa et al., 2008).

Histone-like Proteins in Resistance

Silencing the antibiotic resistance genes that acquired by horizontal gene transfer is done by histone-like proteins such as H-NS. Mutations as well as environmental signals can relieve this repression and finally allowing the expression of resistance genes and this balancing bacterial ability to resistance antibiotics and survival under antibiotic stress because of this dynamic regulation (Lucchini et al., 2006).

Complex regulatory networks which resulted from interacting NAPs and antibiotic resistance genes can be leading to facilitate rapid adaptation to antibiotics. For example, in *E. coli* expression of the *marA* that controls genes of multiple antibiotic resistance and efflux pumps can be influenced by FIS which is the global regulator (Schneider et al., 2013).

Therapeutic Implications and Future Directions

New avenues for therapeutic interventions can be done by the understanding of the epigenetic mechanisms in bacterial pathogenesis and resistance. epigenetic regulators such as DNA methyltransferases, histone-like proteins, and sRNAs targeting can offers a new approach to control bacterial infections as well as antibiotic resistance..

Epigenetic Inhibitors

A new class of antibiotics can be developed through developing inhibitors that target bacterial DNA methyltransferases or histone-like proteins. The role of these inhibitors is to prevent the virulence factors or resistance genes expression, that making the bacteria more susceptible to some antibiotics. For example, DNA replication and repair can destroy in *E. coli* inhibitors Dam methylase and this lead to bacterial death (Heus et al., 2017).

RNA-based Therapeutics

Another therapeutic strategy is offered by harnessing the regulatory potential of sRNAs. Using synthetic sRNAs or antisense oligonucleotides could be influenced the expression of essential virulence genes or antibiotics resistance. This approach has appeared to be affected in other studies in the same area, for example in *Pseudomonas aeruginosa* virulence genes silencing is done by sRNAs which cause to reduced pathogenicity (Petrova and Sauer, 2010).

Phage Therapy and CRISPR-Cas Systems

Utilizing bacteriophages to target specific bacteria which is known as phage therapy, can be improved by using CRISPR-Cas systems to destroy epigenetic regulators. Targeting and disrupting bacterial genes used in virulence or resistance can be done by engineered phages carrying CRISPR-Cas components that could provide a very important therapeutic tool (Citorik et al., 2014).

Conclusion

In bacteria, epigenetic regulation is important for their adaptation, and their pathogenicity, and antibiotic resistance. Understanding these mechanisms submit new approach for developing new therapeutics and controls to antibiotic resistance. As research progresses, the complex mechanisms of bacterial epigenetics will solve complexities in the future and opportunities for intervention

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