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Review

A role for epigenetics in hearing: Establishment and maintenance of auditory specific gene expression patterns

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Abstract

Epigenetics is a large and diverse field encompassing a number of different mechanisms essential to development, DNA stability and gene expression. DNA methylation and histone modifications work individually and in conjunction with each other leading to phenotypic changes. An overwhelming amount of evidence exists demonstrating the essential nature of epigenetics to human biology and pathology. This field has spawned a vast array of knowledge, techniques and pharmaceuticals designed to investigate and manipulate epigenetic phenomena. Despite its centricity to molecular biology, little work has been conducted examining how epigenetics affects hearing. In this review, we discuss both the basic tenets of epigenetics and highlight the most recent advances in this field. We discuss its importance to human development, genomic stability, gene expression, epigenetic modifying agents as well as briefly introduce the expansive field of cancer epigenetics. We then examine the evidence of a role for epigenetics in hearing related processes and hearing loss. The article concludes with a discussion of areas of epigenetic research that could be applied to hearing research.

Keywords: Presbycusis; Hair cells; Organ of Corti; DNA methylation; Histone modifications; Deafness

1. Introduction

The term epigenetics encompasses a variety of biological process and represents a vast and well developed field. It is perhaps best described as a change in phenotype that is not caused by a change in DNA sequence. The two most well understood mechanisms of epigenetic alterations that lead to these phenotypic changes are DNA methylation and histone modifications. While the two will initially be discussed separately, it must be remembered that epigenetic regulation is often a dynamic and coordinated process involving both as DNA resides in close association with histone proteins and the two together with the nuclear scaffold represent chromatin.

Although a number of well written and informative review articles on epigenetics already exist in the literature, there is a noticeable absence of epigenetics work in the field of hearing research. Indeed, epigenetics is an essential player in the developmental process, and a well established biological process in the pathogenesis of cancer. Despite its importance to a number of research fields, epigenetics has yet to play a major role in explaining development, function and pathology of hearing. There are myriad

Abbreviations: CpG, the DNA sequence "CG" where DNA methylation occurs; SINES, short interspersed transposable elements; LINES, long interspersed transposable elements; DNMT, DNA methyltransferase; siRNA, small interfering RNA; miRNA, Micro RNA; H, histone; HAT, histone acetyltransferases; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor; PRMTs, protein arginine methyltransferases; SAM, *S*-adenosyl-L-methionine; LSD1, lysine specific demethylase; JmjC, Jumonji C – a demethylase enzyme; PAD4, peptidylarginine deiminase 4; PcG, polycomb group protein; trxG, trithorax group protein; MeCP, methyl-CpG-binding proteins; VS, vestibular schwannoma; SC, Schwann cell; NF2, neurofibromatosis type 2; 5-aza-dC, decitabine – a methyltransferases inhibitor; 5-azaC, Vidaza – a methyltransferases inhibitor; FSHD1, facioscapulohumeral muscular dystrophy; ICF, syndrome immunodeficiency–centromeric instability–facial anomalies syndrome

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benefits to discovering epigenetic mechanisms to diseases of hearing. Epigenetic mediated gene silencing is a naturally occurring process, which, in many instances, is non pathologic. As such, organisms retain a host of mechanisms to reverse these epigenetic modifications. A number of pharmaceuticals have also been developed to target these antagonistic processes. These compounds stand as an untapped resource for understanding hearing related illness. An epigenetically targeted pharmacologic intervention also avoids some of the known difficulties and complications associated with other experimental treatments for hearing loss such as gene therapy and stem cell transplantation. This review article aims to make a rapid tour of epigenetics, taking time to explore its role in development and hearing related malignancies, touch upon some of the epigenetic modifying agents that could be utilized in hearing research, explore the epigenetic basis for known causes of hearing loss and finish with possible areas of future intersections between epigenetics and hearing research. Epigenetics offers a relatively unexplored area of hearing research and presents vast opportunities to those endeavoring to better understand the normal and pathologic processes affecting hearing.

2. DNA methylation

DNA methylation offers less complexity than the histone modifications that affect gene expression. Through DNA methylation, a single methyl group is added to cytosine on position 5 at CpG dineucleotides (Bird, 2002). This phenomenon is evident in a wide variety of plant and animal species and serves a number of useful roles in non pathologic genetic processes (Morel et al., 2000; Vaucheret and Fagard, 2001). Upon methylation of the DNA, transcription is repressed either through the recruitment of methyl-CpG-binding proteins (MeCP) (Cross et al., 1997) or by preventing the transcriptional machinery, namely the transcription factors, from binding to the DNA (Tate and Bird, 1993). The methyl-CpG-binding proteins will be discussed in further detail in a later section.

The methylation of cytosine also increases the risk of mutational events occurring. When cytosine is unmethylated, deamination results in a cytosine to uracil change; uracil is recognized and removed from DNA by uracil DNA glycosylase. However, deamination of a methylated cytosine causes a cytosine to thymidine mutation. While mutations of cytosine to uracil are normally recognized and repaired by the body, the cytosine to thymidine mutations are not as easily recognized and repaired (Hermann et al., 2004). This allows them to go undetected and could explain why CpGs are mutational hotspots (Dean et al., 2005).

CpG location provides evidence of the role of DNA methylation in regulating gene expression. Genome wide analysis shows that the observed frequency of CpG sites occurs with a lower frequency then would be expected (Wilson et al., 2007). Moreover, where they do exist they tend to be clustered into groups called CpG islands. While most CpG contained in islands are unmethylated (Bird, 2002), those located outside of islands are usually methylated (Baylin et al., 2000). This association corresponds with the finding that most CpG islands are located at the 5′ ends of genes. Indeed, about 50% of all human genes have a CpG island at their 5′ end. Placement of the CpG islands within the 5′ regulatory regions of genes provides a powerful tool for gene regulation. Some gene promoters are highly methylated during development while others undergo increasing methylation with age (Issa et al., 2001). While CpG location within promoters is well known and widely studied, their position within introns and exons has also been documented to control gene expression (Januchowski et al., 2004; Uchida et al., 2004; Wutz et al., 1997).

2.1. DNA methyltransferases

DNA methylation occurs through the action of a family of proteins called the DNA methyltransferases (DNMT). These proteins are responsible for the two forms of DNA methylation: *de novo* methylation and maintenance of an established methylation pattern. DNMT1, is primarily responsible for maintenance methylation. The protein's importance is demonstrated by the lethality of the DNMT1 knock out mouse (Li et al., 1992). Its maintenance function is evidenced by is preference for hemimethylated DNA in contrast to unmethylated DNA. This allows DNMT1 to read methylated DNA strands during DNA replication and place a methyl group on the corresponding daughter stand (Bacolla et al., 1999,2001; Pradhan et al., 1999). It has additional roles in interacting with other members of the chromatin remodeling machinery such as histone methyltransferases and MeCP proteins. This involvement in the interplay between histone modifications and DNA methylation enables cooperative repressive effects of DNA methylation and some histone modifications (Bird, 2002; Hermann et al., 2004). DNMT2's function remains to be fully described. Its weak DNA methylation capability appears to be non essential given the viability of knock out animals (Okano et al., 1998), but recently it has been shown to have an RNA methylating capacity (Goll et al., 2006). The third member of the DNMT family, DNMT3, actually consists of a number of different proteins involved in *de novo* DNA methylation (Okano et al., 1999). These proteins, essential for life, establish methylation patterns in CpG rich areas as well as isolated CpG sites. They play an essential role in development and are responsible for the DNA methylation patterns necessary for genomic imprinting and gene inactivation. DNMT3a is distributive in that it is targeted to a specific CpG location for DNA methylation, thereby resulting in *de novo* methylation (Hata et al., 2002). The DNMT3a protein is found as two different isoforms with DNMT3a expression found in adults while DNMT3a2 is expressed mostly in embryos (Chen et al., 2002). When expressed in adults, the enzyme is usually associated with condensed, transcriptionally inactive