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Epigenetics, microbiota, and intraocular inflammation: New paradigms of immune regulation in the eye

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ABSTRACT

Sight threatening immune responses that damage the eye characterize intraocular inflammatory diseases. These diseases including uveitis and age-related macular degeneration are worryingly common and quality of life shattering. Genetic studies in past decades significantly advanced our understanding of the etiology of these devastating diseases. Unfortunately, patient genetics alone failed to adequately explain disease origin, susceptibility, and progression. Non-genetic factors such as the epigenetic regulation of ocular diseases and the environmental factors triggering intraocular inflammation offer new insight into intraocular inflammatory disorders. Importantly, mounting evidence is signaling that dysbiosis of human microbiota leads to rapid epigenomic reprograming of host cells and results in the onset of many diseases. In this review, we discuss how epigenetic mechanisms and microbiota may cooperate to initiate and perpetuate ocular inflammation. Lastly, we propose that the discovery of intraocular microbiota presents a significant shift in thought affecting current approaches to the diagnosis, treatment, and prevention of intraocular inflammatory diseases such as uveitis and age-related macular degeneration. The geographical and genetic background difference in both disease presentation and genetic association of intraocular inflammatory diseases may be due to the variation of intraocular microbiota.

1. Epigenetics

1.1. What is epigenetics?

In the course of biological study, many researchers found numerous biological phenomena could not be explained by genetic principles alone. Conrad Waddington (1905–1975) proposed the word “epigenetics” phenomena in 1942 (Waddington, 1942). The prefix “*epi*” of Greek origin means “over, outside of, or around”. Therefore, the epigenetics refers to the study of phenomena “in addition to” genetics (Waddington, 1968). Examples of epigenetics include DNA methylation, post-translational protein modification of histones around which DNA is wrapped, and large scale differences in genome structure. Epigenetic functions are of fundamental importance during literally all biological processes (Goldberg et al., 2007), and an explosion of research efforts in past decades explored these important non-genetic functions.

The concept of epigenetics has evolved gradually from a general definition to a category of molecular mechanisms controlling the “in addition to genetic” phenomena. It was first defined broadly as “the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being” (Waddington, 1942). Later, Holliday defined epigenetics as “the study of the mechanisms of temporal and spatial control of gene activity during the development of complex organisms” (Holliday, 1990), Russo et al. defined epigenetics as “the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence” (Russo and Riggs, 1996). Bird defined epigenetics as “the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states” (Bird, 2007). Broadly, epigenetics bridges gaps between genotype and phenotype and provides a conceptual explanation for why the same genotype can result in various stable and heritable phenotypes (Wu and Morris, 2001). In particular, epigenetics constitutes the molecular events controlling gene expression and activity without changes of DNA sequence. These molecular events include covalent and noncovalent modifications of DNA and histones that shape/reshape the chromatin structure according to environmental cues (Allis and Reinberg, 2006). Therefore, the study of chemical reactions shaping chromatin accessibility, regulating output of genetic information in terms of expression, and the signals from the environment that coordinate these chemical reactions represents the fundamental aspects of epigenetic research.

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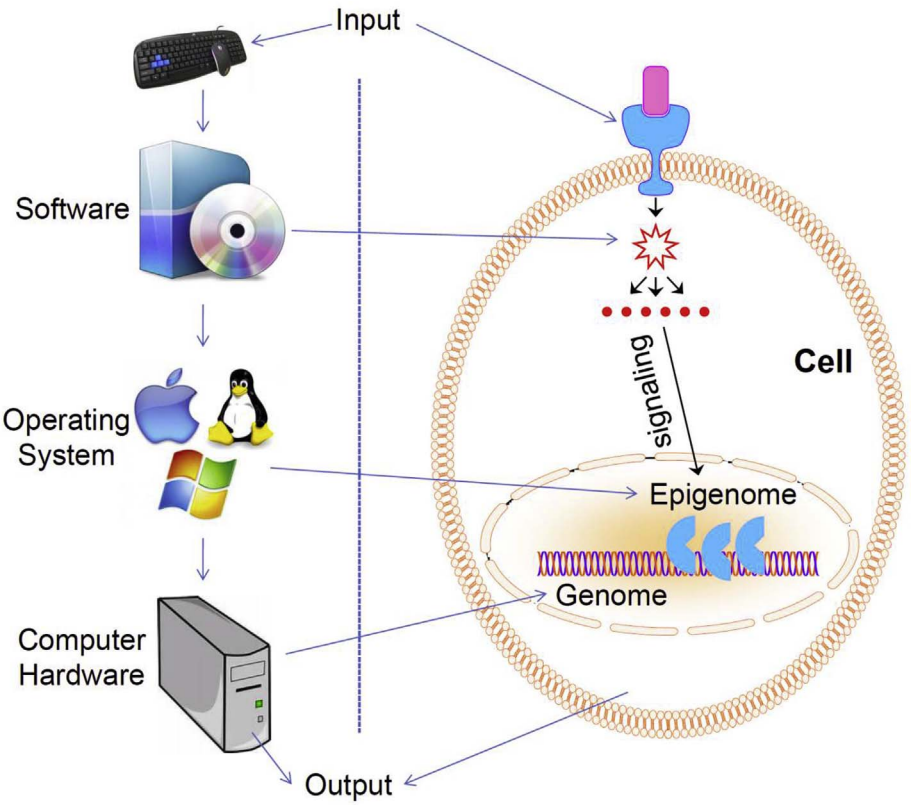

Fig. 1. The cell as a computer: An analogy for genetics and epigenetics. Imagine the cell as a computer. The genome represents the unchanging but fundamental hardware, and the epigenome represents the operating system. The epigenome makes use of the underlying hardware (genome). to execute software programs (regulatory programs) that will interact with the outside work (the signaling cascade), create outputs (secreted proteins), and even reprogram the operating system (epigenetic reprogramming).

Genetics and epigenetics in higher organisms can be simply understood using a analogy with a modern computer. Thinking of a single cell as a computer system, the genome represents the “hardware” while the epigenome can be viewed as the “operating system” of our computer. The signaling cascades transferring information between outside and inside of cells can be viewed as “software” (Fig. 1). Nowadays it becomes much easier to change the hardware of a computer. Similarly CRISPR-cas9 systems are making genome editing fast and efficient. However, the interdependent nature of software and hardware make it necessary to build a good operating system and run diverse software in order to take full advantage of the hardware. We will continue to discuss in this review the interdependency of genetic and epigenetic factors as they relate to eye health.

1.2. Why epigenetics?

In general, all physiology and pathology of living organisms are controlled by either genetic or epigenetic mechanisms. Originally genetic mutations were thought to be the sole source of phenotypic variations; however, the many examples of heritable phenotypes resulting from identical DNA sequence forced researchers to look to epigenetics for an adequate theory (Dupont et al., 2009). For example, most cells in complex organisms share an identical genome but feature diverse morphology and function. A naïve $CD4^+$ T cell is activated upon antigen stimulation, differentiates into Th1, Th2, or Th17 cells, and acquires helper T cell functions, without genotypic modifications (O'Shea and Paul, 2010; Wei et al., 2009). A fully committed somatic cell can be converted back to an induced pluripotent stem cell (iPSC) (Takahashi and Yamanaka, 2006) or transdifferentiated into another cell type by introducing certain key factors or by stimulation of small molecules without changing the cell's genome (Xie et al., 2017). Therefore, it is crucial to appreciate that cellular phenotype and function are not solely decided by genetic information. Instead, they can be regulated by signals generated in the gene's environment through epigenetic mechanisms.

Inherited genetic materials were once blamed for causing most of human diseases before the human genome was sequenced. However, recent studies have revealed that dysfunction in epigenetic regulation underlies the mechanisms of many common and complex human diseases such as cancer (Ashford et al., 2015; Feinberg, 2007; Tomasetti et al., 2017). In the past two decades, twin studies have been used to dissect the causal contribution from heritable versus environmental factors in the pathogenesis of complex phenotypical traits and diseases including those in the eye (Montezuma et al., 2007; Sanfilippo et al., 2010; Tan et al., 2015). We summarized the heritability of eye diseases identified by large twin studies in Table 1. The heritability of various eye diseases such as myopia and hyperopia, measured by the concordant rate between identical twin pairs, is as high as 90% (Hammond et al., 2001b). In contrast, the heritability of other ocular diseases such as AMD is relatively low (37%) (Hammond et al., 2002). Other than a few cases, no reports have been made on the concordant rate of uveitis between identical twin pairs. Other factors such as lifestyle, stress, nutrition/diet, and behaviors such as smoking can all change the risk of disease onset (Sobrin and Seddon, 2014). These reports argue that non-genetic factors, often referred to as environmental factors, play a crucial role in the pathogenesis of most eye diseases.

1.3. What to study in epigenetics?

Environmental factors including protein and chemical molecules rarely function by modifying DNA sequences. In most cases, they directly or indirectly interact with and adjust the epigenome to alter gene expression. Therefore, the search for environmental mechanisms of disease focus on the epigenetic changes of chromatin structure, DNA methylation status, histone modifications, or non-coding RNAs that modulate gene expression regulation resulting from environmental cues (Fig. 2) (Bernstein et al., 2007).

DNA methylation at the 5’ cytosine is a predominant form of DNA methylation found in eukaryotes and generally contributes to gene silencing (Suzuki and Bird, 2008). Its prevalence in eukaryotic genomes