Health Science Inquiry

ASK AN

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Getting ready for the future: modifying our epigenome to prevent the effects of developing in an adverse environment.

Our environment is rapidly changing. Since the industrial revolution, life forms have been exposed to increasing amounts and variety of products of human activity. Fortunately, life forms have evolved adaptive mechanisms that have allowed us to cope with different stimuli in our fast-changing world. However, such adaptive mechanisms operate only within limits. Figuring out those limits, and the effects of an adverse environment, is gaining relevance in present days as we are becoming aware of complex gene-environment interactions and that environmental stimuli can significantly impact on human health [1]. It is not uncommon now to read or hear that pollutants, certain kinds of food, etc., can negatively affect our health, which suggests that the thresholds for proper function of our adaptive mechanisms are being surpassed [1]. Emerging genomic editing technologies hold promise to help us in preventing the long-term effects of exposure to an adverse environment.

Adaptation to an adverse environment depends on the capacity of the cell to activate or repress specific genes that function to alleviate stress in specific organs. For example, continued consumption of a high fat diet can cause chronic inflammation, which stresses the heart and reduces its capacity to pump blood [2]. The heart then activates genes promoting enlargement of heart muscle cells, or cardiomyocytes, to preserve contractile function at least temporarily [3]. However, if the stimuli persist, the heart could decompensate and fail. In this example, activation and maintenance of the proper expression of genes promoting cardiomyocyte hypertrophy could be considered key for adaptation of the heart to environmental stimuli. Following the example, if the stimuli were no longer present, mechanisms repressing hypertrophy-promoting genes would be equally important for proper heart function [3]. Mechanisms activating, maintaining and silencing gene expression depend on the accessibility of DNA to regulatory proteins. How accessible a gene is to its regulators, and thus its activity, depends in large part on chemical modifications on DNA, and post-translational modifications on histones and other chromatin components that scaffold DNA inside the nucleus. For example, DNA methylation is associated generally with gene repression. Methylations on the lysine 4 and 36 of histone H3 are associated with relaxed and active chromatin, whereas methylations on lysine 9 and/or 27 favor chromatin compaction and gene repression. Distribution of the broad variety of DNA and histone marks in different combinations at specific loci, and across the genome, is known as the epigenome. The activity of DNA and histone methyltransferases and demethylases is altered by environmental stimuli, resulting in changes in the epigenome translating into global changes in gene expression.

Thus, DNA and chromatin modifiers regulate the epigenome and are key for coordinating the adaptive response of cells and organisms to environmental change.

Epigenetic features composed of multiple chromatin marks can be maintained through multiple cell divisions. Chromatin marks have an important function in stabilizing gene expression patterns in the long-term so that cells and tissues can keep performing tissue-specific functions throughout the life of the organism. Thus, altering the epigenome can cause long-term alterations in gene expression. This has important implications in health. Our own research indicates that altering the epigenome during early embryonic development causes abnormal long-term activation of specific genes that promote heart disease in the adult life [4]. In line with this evidence, numerous studies have demonstrated that exposure to environmental factors that alter the epigenome during fetal development, for example obesity during pregnancy, can program adult disease. This overwhelming evidence is making us realize that complex environment - gene interactions are shaping the future of our health. We are only starting to understand how different environmental factors alter the epigenome, and large efforts are underway to uncover the modifications altered on the specific genes mediating disease development [1]. This knowledge could then be leveraged towards the direction of epigenetic marks to such genes to restore their normal activity using genome-editing tools.

The CRISPR/Cas9 system has recently emerged as a versatile and effective tool for genome editing. The CRISPR (clustered regularly interspaced short palindromic repeats) /Cas9 (CRISPR-associated protein 9) system can be used in genome editing in several ways. It is used for gene inactivation by inducing mutations in unique loci. In this application Cas9 is guided by an RNA fragment containing a short sequence complementary to the target site to induce a cleavage on double stranded DNA. The cells DNA repair system, which is prone to errors, repairs the DNA often introducing insertions or deletions, which then disrupt the target locus [5]. In a second application, an additionally provided DNA template homologous to the target site donates a designed nucleotide combination to induce specific DNA modifications. This application of the CRISPR/Cas9 system has been useful in generating mutant models to investigate the function of genes and intergenic regulatory elements. This application has also allowed for repair of disease-inducing mutations in cellular and animal models, and even in human embryos [6]. In a third application, CRISPR/Cas9 can also be used to recruit epigenetic modifiers. In this application, the endonuclease of Cas9 is inactivated to generate what is known as a dead Cas9, or dCas9. dCas9 is then fused to, for example, histone, or DNA de-methylases, so that instead of inducing a DNA double strand cut, dCas9 recruits epigenetic regulators, which facilitate control of the transcriptional state of the target gene [5] (**Figure 1**). Following the example discussed before, it is exciting to speculate that targeting epigenetic regulators to genes involved in programming disease, for example, those controlling inflammation and cardiac hypertrophy, could be useful for long-term gene control. This approach could potentially translate into ways to prevent the negative effects of developing in an adverse environment, and improve health in future generations.

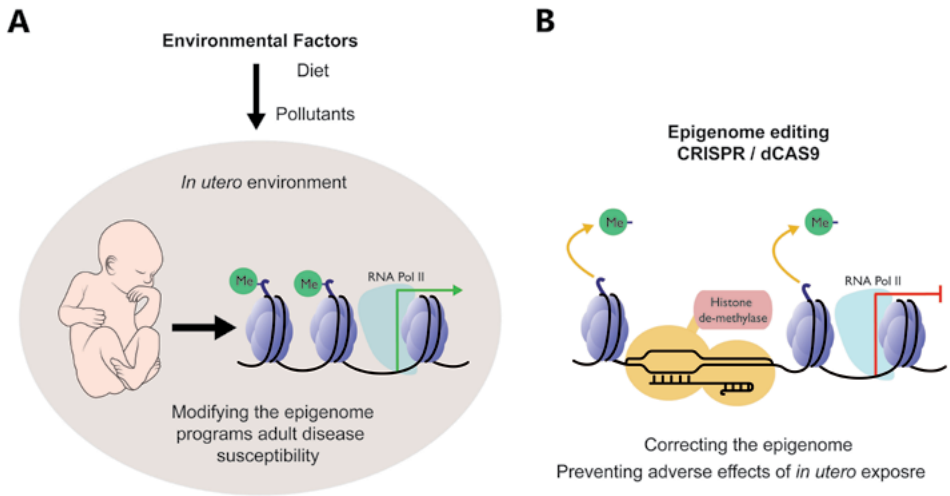

Figure 1: **Modifying our epigenome to prevent the negative effects of developing in an adverse environment.** A) Development in an adverse environment can alter the epigenome, for example by deposition of histone methyl marks (green circles) that promote abnormal activation (green arrow) of disease-promoting genes. B) CRISPR/dCas9 (orange) could be used to target histone de-methylases (pink) to remove (orange arrows) activating histone marks (green circles), correcting the epigenome to restore a normal inactive state on disease-promoting genes (red arrow). *Artwork by Melanie Delgado-Brand.*

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