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Epigenetics

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Abstract :
Epigenetics has recently evolved from a collection of diverse phenomena to a defined and far-reaching field of study. During the past year, more than 2,500 articles, numerous scientific meetings and a new journal were devoted to the subject of epigenetics. The following article is a brief overview about the mechanisms of epigenetics , examples , its involvement in the pathogenesis of diseases and the relation of epigenetics with the development of drugs .

INTRODUCTION :

Epigenetics has several meanings with independent roots. To Conrad Waddington, it was the study of epigenesis: that is, how genotypes give rise to phenotypes during development[1]. By contrast, Arthur Riggs and colleagues defined epigenetics as "the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence.[1,2]

The cells in a multicellular organism have nominally dependent DNA sequences, yet maintain different terminal phenotypes. This nongenetic cellular memory, which records developmental and environmental cues is the basis of epigenetics.

The lack of identi ed genetic determinants that fully explain the heritability of complex traits, and the inability to pinpoint causative genetic effects in some complex diseases, suggest possible epigenetic explanations for this missing information. This growing interest, along with the desire to understand the "deprogramming" of differentiated cells into pluri potent/ toti potent states, has led to "epigenetic" becoming shorthand for many regulatory systems involving DNA methylation, histone modifi cation, nucleosome location, or noncoding RNA. So what is epigenetics? An epigenetic system should be heritable, self-perpetuating, and reversible [3.]Whether histone modifi cations (and many noncoding RNAs) are epigenetic is debated; it is likely that relatively few of these modifi cations or RNAs will be self-perpetuating and inherited. Looking beyond DNA-associated molecules, prions (infectious proteins) are clearly epigenetic, perpetuating themselves through altered folding states. These states can act as sensors of environmental stress and, through the phenotypic changes they promote, potentially drive evolution [4.]

Over the years, numerous biological phenomena , some considered bizarre and inexplicable, have been lumped into the category of epigenetics. These include seemingly unrelated processes, such as paramutation in maize (an interaction between two alleles in which one allele causes heritable changes in the other allele); position effect variegation in the fruit fly *Drosophila* [5](in which the local chromatin environment of a gene determines its expression); and imprinting of specific paternal or maternal loci in mammals.

EPIGENETIC MECHANISMS AT WORK :

Much of today's epigenetic research is converging on the study of covalent and non covalent modifications of DNA and histone proteins and the mechanisms by which such modifications influence overall chromatin structure. Chromatin, the complex of DNA and its intimately associated proteins, provides an attractive candidate for shaping the features of a cell's epigenetic landscape[6] . Diverse epigenetic phenomena have recently led researchers to conserved molecular mechanisms involving chromatin modification, a theme reinforced throughout this special issue. The macromolecular entities described below all significantly contribute to the physiologically relevant organization of most eukaryotic genomes. These entities, and possibly others yet unknown, should be considered collectively when exploring epigenetic mechanisms.

1) DNA METHYLATION :

DNA methylation plays a role in many cellular processes including silencing of repetitive and centromeric sequences from fungi to mammals; X chromosome inactivation in female mammals; and mammalian imprinting, all of which can be stably maintained[7]. It is perhaps the best characterized chemical modification of chromatin. In mammals, nearly all DNA methylation occurs on cytosine residues of CpG dinucleotides[8].

2)CHROMATIN VARIATION : COVALENT AND NON COVALENT MECHANISMS :

Recently has genetic and biochemical evidence converged to clearly connect covalent histone modifications with long standing epigenetic phenomena .Genetic screens for *su*ppressors of position effect *var*iegation [*Su(var)*] in *Drosophila*, for example, revealed over 100 genes that encode vital constituents of heterochromatin. Many of these genes are conserved from flies to humans, including heterochromatin protein 1 (HP1) and the histone H3K9 methyl transferase [9] .*Drosophila* genetics also provides another link between epi genetics and histone modifications ,in the form of two evolutionarily conserved families of proteins that regulate homeotic genes antagonistically during development: the Polycomb Group (PcG) and the Trithorax Group(TrxG)[10].Charge-altering modifications such as acetylation and phosphorylation can directly alter the physical properties of the chromatin fiber, leading to changes in higher-order structures. Noncovalent mechanisms such as chromatin remodeling and the incorporation of specialized histone variants provide the

cell with additional tools for introducing variation into the chromatin template[11]. Co valent modification, nucleosomere modeling, and histone variants work together to introduce meaningful variation into the chromatin fiber, and their collective contribution to epigenetics is only now being rigorously explored[12].

3)NON CODING RNA :

Recently it has become evident that noncoding RNA's play a role in various epigenetic phenomena . Clear examples of RNA involvement range from dosage compensation mechanisms in *Drosophila* and mammals mediated by the *rox* and *XIST* RNAs, respectively, to the silencing of both genes and repetitive DNA sequences by posttranscriptional Cell (PTGS) and transcriptional (TGS) RNA interference (RNAi)-related pathways, respectively, in almost all eukaryotes[13].

EXAMPLES OF EPIGENETICS

Identical twins are known to have different body features, personalities and preferences, as well as differences in the onset of disease and the severity of symptoms, despite possessing identical genes[14]. Moreover, these differences are small when twins are young and increase with age. Also, in the case of cloned animals, the exact same fur pattern is not passed down from the original animal to the clone, even though their genomes are identical15. Moreover, epigenetics is associated with many diseases. Epi genetics is pliable and the condition of genetic expression changes in response to external stimulation, such as environment and lifestyle as well as aging, which may alter healthy genetic expression. This is called "epigenetic breakdown" and is deeply related to various diseases, including cancer[16].

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ROLE OF EPIGENETICS IN DISEASES

Since the 1990s there have been many reports about the abnormality of the methylation of DNA in genes related to multiple cancers in various cancerous cells, bringing attention to the relationship between epigenetics and the onset of cancer. In particular, gastric cancer is believed to be deeply related to epigenetics[18]. One of the factors that increase the risk of gastric cancer is *Helicobacter pylori*, the infection of which was recently discovered as inducing epigenetic mutations.

Regarding neuro developmental disorder, there are about nine disorders that are known to have congenital abnormality in genes related to epigenetics, such as DNA methylation, chromatin remodeling (conformational changes of chromatin), histone modification and X chromosome inactivation. A report in 2005 investigated the effect of exposure to poor nutrition in the pregnant mother and normal feed to the offspring after birth on genes related to fat metabolism in the liver at postnatal day 50 in animals (adult)[19]. The result showed that DNA methylation was decreased and expressions of multiple genes were increased 3 to 10 fold, indicating that the effects of changes in the fetal environment are still observed in adults.

DRUG DEVELOPMENT AND EPIGENETICS

The development of drugs for cancer treatment targeting epigenetics is underway. In particular, inhibitors of DNA methyl transferase (DNMT) and Histone Deacetylase (HDAC) are reported to be effective[20].

CONCLUSION

What determines the outcome of organisms, including humans, is a question that has been debated since ancient times. Is it nature (genes) or nurture (environment), or both? It is a little bit of both. However, there has been no scientific evidence to support this belief. As opposed to the genome, which does not change over a lifetime, epigenetics is constantly changing, right from the moment of fertilization. This means that epigenetics adds the two variables of the external influence of environment and the passage of time to the genetic information of an organism, called the genome. From the perspective of epigenetics, humans keep changing in response to external influences, and though the base is already determined at birth, the details are uncertain and possess much potential. Epigenetics is known to change with the process of aging. Therefore, in the future, epigenetics research may contribute to the development of treatment for diseases and disorders specifically related to the elderly. Epigenetics is a research area that has the full potential for future achievements and is the subject of much international attention.

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