

Chapter 11

Environmental Epigenetics and Epigenetic Transgenerational Inheritance

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Abstract The developing role of environmental epigenetics in biology and medicine is discussed in relationship to its impact on transgenerational inheritance. The ability of environmental factors, such as nutrition and toxicants, to promote transgenerational adult-onset disease through alterations in the germline epigenome is reviewed. Observations suggest epigenetic transgenerational inheritance has a significant impact on evolutionary biology, disease etiology, and toxicology.

Keywords Epigenetics • Developmental origin of disease • Environment • Germline • Inheritance • Toxicants • Transgenerational

Abbreviations

BPA Bisphenol A

11.1 Introduction

Although the influence of environmental factors on biology has been appreciated and investigated for hundreds of years, the basic molecular mechanisms by which the environment regulates biology have for the most part been lacking.

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The majority of environmental factors from nutrition, temperature, and toxicants cannot alter DNA sequence. Nevertheless, they are known to have long-lasting effects on phenotype and disease for most organisms. Early observations by Lamarck and others suggested phenotypic changes resulted from environmental exposures (Jirtle and Skinner 2007). Potential mechanisms for these interactions were initially proposed in the 1940s by Conrad Waddington, the person who started the field of epigenetics (Waddington 1940, 1956). The specific molecular mechanisms involved, however, were not elucidated until more recently (Chen and Riggs 2005; Holliday and Pugh 1975).

Epigenetics is defined as molecular factors and processes around DNA that regulate genome activity independent of DNA sequence and that are mitotically stable (Skinner et al. 2010). These factors include DNA methylation, histone modifications, chromatin structure, and some noncoding RNAs (Jirtle and Skinner 2007; Skinner et al. 2010). Epigenetics is a critical element in the regulation of genome activity, and it enables the environment to interact with genetic factors in the regulation of biology. Thus, in contrast to genetic factors and classic Mendelian genetics that are generally resistant to environmental influences, epigenetic factors provide an efficient means by which the environment can influence genomic activity and have long-lasting effects on physiology, phenotype, and biology (Skinner 2011).

Epidemiology studies for decades have suggested significant environmental impacts on biology that could not be explained by genetics alone. Examples are as follows:

1. Regional differences in specific disease types and frequencies worldwide. If individuals are moved early in life to a different region, they will often acquire the disease types and frequencies associated with that region.
2. The majority of diseases have a rather small component that can be attributed to genetic abnormalities or mutations. This suggests a potential alternate mechanism for disease etiology other than genetics.
3. Nearly all diseases have shown a dramatic increase in frequency over the past several decades; this observation cannot be explained by genetic mechanisms.
4. Hundreds of environmental compounds or toxicants are associated with the onset of disease, but many do not have the ability to alter DNA sequence or promote mutations.
5. With regard to evolutionary biology, the same organism does not evolve at the same rate in different parts of the world, indicating environmental impacts on the process.

These are just a few of the biological observations that cannot be easily explained through classical genetic mechanisms. Epigenetics provides a molecular mechanism that can help explain all these phenomena, providing a general mechanism of how the environment can influence biology. This scientific field of research is called environmental epigenetics (Jirtle and Skinner 2007).

The majority of environmental exposures will act on somatic cells to influence biology. This includes nutrition, temperature, stress, and toxicological agents.

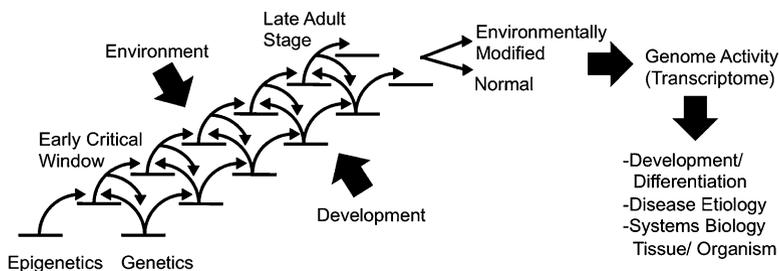


Fig. 11.1 Epigenetic and genetic cascade of events in development (Skinner 2011)

At critical windows of exposure for a given somatic cell type or tissue, these environmental exposures can shift the normal differentiation through modifications of the epigenome. The altered epigenome then interacts with genome and results in an abnormal state of cellular or tissue differentiation (Fig. 11.1). The primary reason this phenomena occurs is because of the mitotic stability of epigenetic modifications and the presence of a critical window of susceptibility during early development. Thus, the ability to replicate the cellular epigenome during mitosis results in cells that are influenced by environmental exposures early in development to form an altered epigenome that persists throughout the life of the individual.

This provides the mechanism for the early life basis of adult-onset disease and phenotype. Environmental exposures throughout life affect various somatic cell types at their specific critical windows of development to promote a later-life disease or phenotypes associated with that somatic cell type. For example, a fetal exposure to abnormal nutrition promotes metabolic disease later in life due to the critical developmental windows of the associated organs. In contrast, a pubertal exposure affects developing organs such as the mammary gland and prostate gland since their somatic cells are developing during puberty. After the individual has become an adult and the developmental process is complete, the individual develops a resistance to environmental exposures and shifts in phenotype. Thus, environmental exposures of somatic cells during development will provide the majority of altered phenotypes and disease states that are observed in humans. These somatic cell effects generally are restricted to isolated cell types and will not be able to be transmitted to the next generation (Skinner 2010; Skinner et al. 2010).

However, it is possible to also transmit environmental exposure information to the next generation through epigenetic modifications in the germlines (i.e., sperm and egg). An environmental exposure that affects the germline has a relatively narrow critical window of development, while the germ cell programs its epigenome and development. If the germline epigenome is modified, impacts on the generation derived from that germline can occur; however, this is still not considered transgenerational since the germline was directly exposed. Nevertheless, if the epigenetic modification becomes permanently programmed, a potential transgenerational phenotype can be inherited. Thus, the majority of environmental exposures affect somatic cells that cannot produce transgenerational effects.

Direct germline exposures can influence the individual developed from that germ cell, but the effects primarily end with that individual. In rare instances, environmental exposures that permanently modify the germline epigenome and promote a transgenerational phenotype can profoundly affect the incidence of human diseases.

11.2 Epigenetic Transgenerational Inheritance

The transmission and inheritance of epigenetic information transgenerationally can have significant impacts on biology. The definition of epigenetic transgenerational inheritance is as follows: *Epigenetic transgenerational inheritance involves the germline transmission of epigenetic information between generations in the absence of direct environmental exposures.* An environmental exposure of the germline that produces a phenotype in the next generation that germline develops is not a transgenerational phenomenon (Fig. 11.2).

The concept and clarifications of an environmental exposure involving a multi-generational exposure or a transgenerational phenomenon have been previously described (Skinner 2008, 2010). Exposure of a gestating female (F0 generation) also exposes the fetus (F1 generation) and the germline that will generate the F2 generation (Fig. 11.2). Therefore, exposure of a gestating female involves a multiple-generation exposure influencing the F0, F1, and F2 generations. The F3 generation is the first generation that is not directly exposed and is considered to potentially result from epigenetic transgenerational inheritance. The exposure of an adult male involves the exposure of the adult individual (F0 generation) and the germline that will generate the F1 generation (Fig. 11.2). Therefore, it is not until the F2 generation that epigenetic transgenerational inheritance can be considered. Since direct environmental exposure simply involves classic pharmacological or toxicological effects of the exposure, only a phenotype that appears in an unexposed generation is considered to potentially result from epigenetic transgenerational inheritance.

The epigenetic transgenerational inheritance requires the involvement of the germline. The critical windows of environmental exposure for the germline primarily involve the development of primordial germ cells and cell fate determination in the sperm or egg during embryonic gonadal sex determination. When the primordial germ cells migrate down the genital ridge during embryonic development in mammals, DNA demethylation of the primordial germ cell genome occurs such that upon colonization of the gonad prior to gonadal sex determination, the primordial germ cell is in a nearly unmethylated, pluripotent state. At the onset of gonadal sex determination, the primordial germ cell initiates DNA remethylation to develop a male- or female-specific DNA methylation pattern and commitment to a sperm or egg cell lineage (Fig. 11.3) (Allegrucci et al. 2005; Durcova-Hills et al. 2006). Due to this DNA demethylation and remethylation prior to and during gonadal sex determination, the germline is sensitive to disruption in epigenetic programming from environmental agents. This results in epigenetic alterations having the

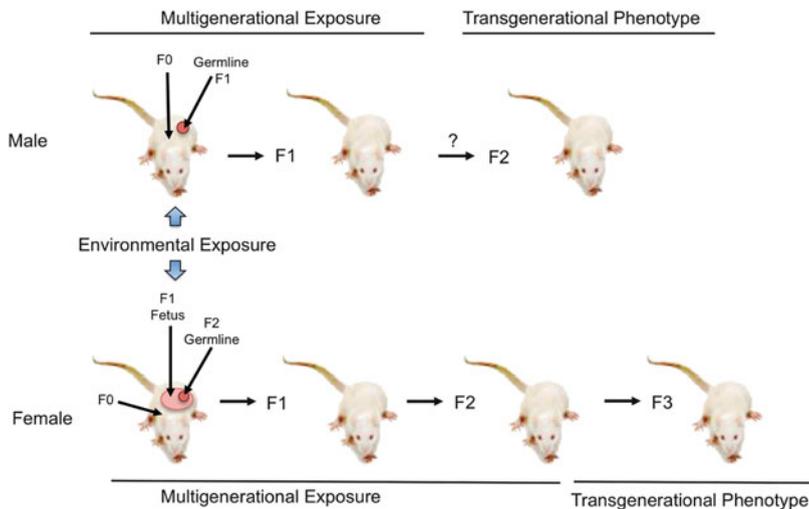


Fig. 11.2 Transgenerational epigenetic inheritance in males and females in response to environmental agents. In a gestating mother, there is multiple-generation exposure of the F0 female, the F1 embryo, and the F2 generation germline to environmental factors. The transgenerational transmission of disease phenotypes through the male germline (labeled red) is indicated. Both male and female offspring develop disease, but the transgenerational phenotype is transmitted only paternally after exposure to vinclozolin (Skinner 2010)

capacity to become permanently programmed in an abnormal manner in the germ cells (Anway et al. 2005; Guerrero-Bosagna et al. 2010). These imprinted-like sites act like imprinted genes that have a parent-of-origin allele-specific DNA methylation program that is transgenerationally inherited (Guerrero-Bosagna et al. 2010).

The other developmental stage where the germ cell epigenome undergoes demethylation is after fertilization. The early developing embryo then initiates remethylation around the blastula stage of development prior to implantation. Genomically imprinted genes escape this demethylation while the rest of the genome, for the most part, is demethylated and reset to erase the prior generation’s effects on the germ cell epigenome (Fig. 11.3) (Morgan et al. 2005). Therefore, the programming of the germline epigenome during gonadal sex determination is the most critical window of exposure to permanently alter the epigenome for transmission transgenerationally (Jirtle and Skinner 2007; Morgan et al. 2005; Skinner et al. 2010). Although epigenetic alterations during gametogenesis in the adult gonads are possible, these changes do not appear to become permanently programmed. They can promote multigenerational effects in the next generation the exposed germline generates, but these epigenetic sites seem to be corrected at subsequent

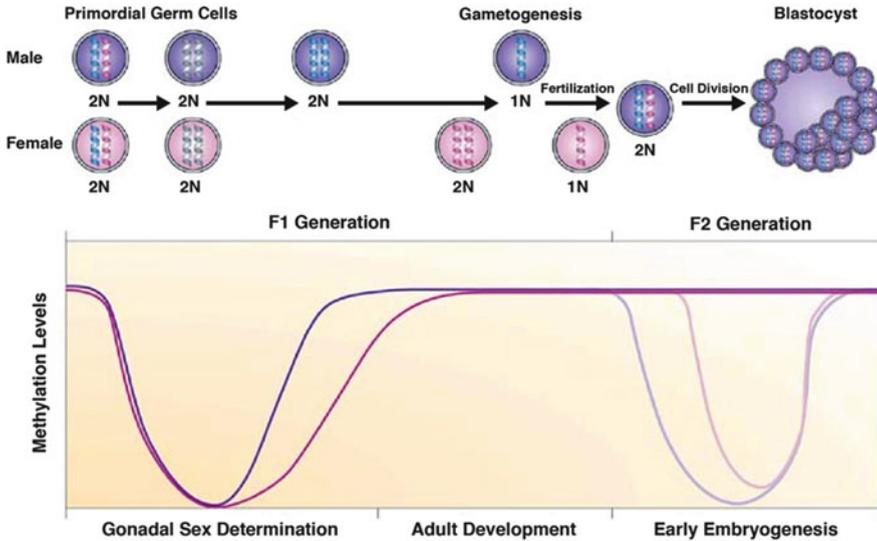


Fig. 11.3 Alterations in methylation status during development. During embryonic development and gonadal sex determination, primordial germ cells undergo genome-wide demethylation, which erases previous parental-specific methylation marks that regulate imprinted gene expression. In the male germline (colored purple), paternal methylation marks in imprinted genes are laid down in developing gonocytes that will develop into spermatogonia. The female germline (colored pink) establishes maternal methylation marks in imprinted genes at a later stage of development. After fertilization, the paternal genome is actively demethylated (indicated by the lighter purple line in the graph), whereas the maternal genome undergoes passive demethylation (indicated by the lighter pink line in the graph). Genome-wide remethylation occurs on both parental genomes before implantation; however, imprinted genes maintain their methylation marks throughout this reprogramming. This allows for the inheritance of parental-specific monoallelic expression in somatic tissues throughout adulthood (Jirtle and Skinner 2007)

generations (Skinner 2010). More extensive research in this area is required to determine if unique epigenetic modifications allow for the formation of direct or indirect transgenerational phenotypes.

The environmental exposures that alter the epigenome of the germline to promote epigenetic transgenerational inheritance do not follow classic genetics or Mendelian processes. Therefore, epigenetic inheritance provides an alternate mechanism of heritability not previously appreciated. An important aspect of this process is that it is responsive to environmental factors and exposures. Therefore, epigenetic transgenerational inheritance provides a mechanism by which the environment can alter biology and fills a void in classic genetics. Non-Mendelian and familial inheritance of different disease states and phenotypes can now include epigenetic modifications as potential mechanisms for transgenerational inheritance.

11.3 Environmental Induction of Epigenetic Transgenerational Inheritance

One of the initial demonstrations of environmental toxicants producing epigenetic transgenerational inheritance involved the actions of the endocrine disruptors, vinclozolin and methoxychlor (Anway et al. 2005). Vinclozolin is one of the most commonly used fungicides in agriculture and is an antiandrogenic endocrine disruptor (Wong et al. 1995). Methoxychlor is a commonly used pesticide and has a combination of estrogenic, antiestrogenic, and antiandrogenic endocrine disruptor activities (Tiemann 2008). These compounds promote transgenerational adult-onset disease and spermatogenic defects in the F1 to F4 generations (Anway et al. 2005). Vinclozolin also promotes a series of adult-onset diseases, including infertility, prostate disease, kidney disease, and mammary gland tumors in aging rats in the F1 to F3 generations (Anway et al. 2006; Nilsson et al. 2008). Recently, the transgenerational epigenetic modifications in the sperm of the male F3 generation animals were mapped (Guerrero-Bosagna et al. 2010). Significant effects on the DNA methylation of different promoters were identified genome-wide. The actions of these epigenetic transgenerational effects are mediated through the male germline (Anway et al. 2005) and affect the transcriptomes of all developing tissues examined (Anway et al. 2008). In addition to an epigenetic transgenerational effect on the differential DNA methylation marks in sperm (Guerrero-Bosagna et al. 2010), all tissues derived from that sperm have transgenerational effects on tissue-specific transcriptomes.

Thus, endocrine disruptor-induced epigenetic transgenerational inheritance involves actions that alter gonadal sex determination programming by modifying DNA methylation in the developing male germline which permanently programs the sperm so that the altered epigenome can be transmitted to subsequent generations. This ultimately leads to all tissues that developed from the male germline to develop altered transcriptomes and increased susceptibility to develop adult-onset disease (Fig. 11.4) (Skinner et al. 2010). Therefore, environmental exposures can promote transgenerational inheritance of adult-onset disease or phenotypes through this elucidated epigenetic mechanism.

A number of other studies from different laboratories have now also identified environmentally induced epigenetic transgenerational inheritance of adult-onset disease phenotypes (Table 11.1) (Skinner et al. 2010). These studies involve the actions of environmental endocrine disruptors and toxicants, such as bisphenol A (BPA) to promote testis abnormalities (F3 generation) (Salian et al. 2009), dioxin to promote uterus abnormalities (F3 generation) (Bruner-Tran and Osteen 2011), and vinclozolin to promote imprinted gene DNA methylation abnormalities (F3 generation) (Guerrero-Bosagna et al. 2010; Stouder and Paoloni-Giacobino 2010). Likewise, pharmaceutical agents, such as thyroxine and morphine, can promote behavioral abnormalities in the F1 to F3 generations (Vyssotski 2011). In addition to environmental toxicant exposures, abnormal nutrition also promotes epigenetic transgenerational inheritance of disease states (Bertram et al. 2008; Kaati et al. 2007;

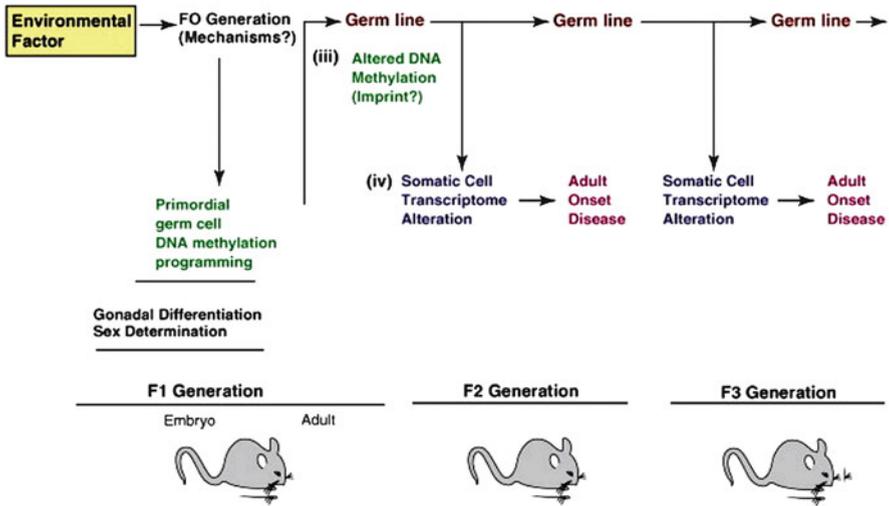


Fig. 11.4 Role of the germline in epigenetic transgenerational inheritance. An environmental factor acts on the F0 generation gestating female to influence the developing F1 generation fetus and alter gonadal development to reprogram the primordial germ cell DNA methylation. This altered DNA methylation in the germline becomes permanently programmed similar to an imprinted-like gene and is transferred through the germline to subsequent generations. The embryo generated from this germline starts with an altered epigenome that causes developing somatic cells and tissues to have an altered transcriptome. This altered somatic cell transcriptome can then promote adult-onset disease associated with the transgenerational phenotype (Skinner et al. 2010)

Table 11.1 Epigenetic transgenerational inheritance

Environmental epigenetic transgenerational inheritance	Reference
Vinclozolin induced epigenetic transgenerational adult-onset disease in rats (F1–F4)	Anway et al. (2005)
BPA-induced transgenerational testicular abnormality (F1–F3)	Salian et al. (2009)
Dioxin induced transgenerational uterine abnormality (F1–F4)	Bruner-Tran and Osteen (2011)
Morphine induced	Vyssotski (2011)
Stress induced behavior alterations (F0–F2)	Mathews and Phillips (2010, 2011)
Nutrition induced transgenerational obesity in mice (F1–F3)	Waterland et al. (2008), Bertram et al. (2008), Pentinat et al. (2010), Kaati et al. (2007)
Transgenerational response in longevity to nutrition (F0–F2)	Waterland et al. (2008), Bertram et al. (2008), Pentinat et al. (2010), Kaati et al. (2007)
Tumor susceptibility in <i>Drosophila</i> (F1–F3)	Xing et al. (2007)
Stem cell culture-induced adult-onset disease (F0–F4)	Lee et al. (2009)

Pentinat et al. 2010; Waterland et al. 2008). This includes caloric restriction promoting metabolic disease phenotypes (F3 generation) (Waterland et al. 2008) and high-fat diets promoting adult-onset metabolic disease and obesity (Pentinat et al. 2010). Furthermore, factors such as stress (Matthews and Phillips 2010, 2012), temperature (Xing et al. 2007), and cell culture (Lee et al. 2009) influence transgenerational phenotypes (Table 11.1). A number of endocrine (Walker and Gore 2011) and genetic (Nadeau 2009) influences also effect epigenetic transgenerational inheritance. All these environmental exposures used the critical window of germline programming during gonadal sex determination. Moreover, several epidemiology studies provide evidence for epigenetic inheritance of disease phenotypes in humans (Pembrey et al. 2006). It is anticipated that any environmental exposure that significantly alters normal fetal gonadal development will promote epigenetic transgenerational inheritance. The biological impacts of this phenomenon are significant and are a previously unappreciated regulatory factor in biology.

11.4 Conclusions and Biological Impacts

The ability of environmental exposures to influence generational effects significantly alters our understanding of the basic regulation of biology. Consequently, a number of different areas now need to be considered with regard to how the environment can have long-lasting effects, not only on the individual exposed but on subsequent progeny for generations to come. Environmental epigenetics provides a molecular mechanism by which environmental factors promote immediate and long-term effects on the individual exposed (Skinner et al. 2010). If the normal germline program is permanently altered, epigenetic transgenerational inheritance of disease or phenotypes can also be promoted. Due to the continued effect on subsequent programming and generations, several basic biological phenomena need to be reevaluated.

Basic developmental biology processes are currently thought to utilize primarily classic genetic mechanisms. Environmental epigenetics at critical windows of development can promote a different path for a developmental system and provide a mechanism of plasticity by which the environment can directly impact development (Fig. 11.1). This could help explain biological variation in the phenotypes of specific organisms and even tissues within an organism. Since an organism does not develop in a vacuum, but instead needs to respond to its environment, environmental epigenetics and transgenerational inheritance of epigenetic changes have a profound impact on developmental biology.

A large number of environmental compounds are known to be associated with the onset of disease, but how these compounds cause disease is often unknown. Molecular toxicology has been focused on the initial signal transduction processes without consideration of later-life effects. Environmental epigenetics enables molecular toxicologists to explain how the initial signaling events can promote both short- and long-term effects on disease susceptibility without causing DNA

mutations. Again, if the germline is modified, epigenetic transgenerational inheritance of these disease states and phenotypes will also need to be considered. The degree by which toxicological effects are transgenerational needs to be established within the population. Clearly, the impacts not only on the individual exposed but on subsequent generations raise the potential biohazards of environmental toxicants.

The current paradigm for the causal factor in disease etiology involves genetic mutations and chromosomal abnormalities. Nevertheless, only a small percentage of nearly all disease states are associated with known genetic mutations. Epigenetics provides a molecular mechanism that is anticipated to have a significant role in disease etiology and can respond to environmental factors to directly influence the onset of disease. As discussed, the prenatal and early postnatal exposures are likely more critical in disease etiology than the adult exposures that are more resistant to epigenetic change due to the mature differentiated state of the cells. The mitotic stability of the early life epigenetic alterations allows these transient environmental exposures to influence adult-onset disease. Epigenetic phenomena also can occur at high frequency and are reproducible compared to the extremely low frequency and nonreproducible nature of genetic mutations. Environmental epigenetics will likely play a critical role in disease etiology and cooperate with genetic processes and susceptibilities to influence disease.

The ability to permanently alter the epigenome of the germline to promote transgenerational disease or phenotypes also has significance with regard to evolutionary biology. Environmental epigenetics can play a significant role in the induction of phenotypic variation that facilitates adaptation events and natural selection. If these epigenetic alterations are transgenerational and the phenotypes appear in subsequent generations, the natural selection process is also facilitated and the inheritance of such phenotypes explained. Epigenetic transgenerational inheritance of environmentally induced phenotypic variation can explain rapid evolutionary processes and how the environment can influence evolution. This provides a solution for the time period issue that is problematic when only random genetic mutations are considered as the primary evolutionary events. Therefore, environmental epigenetics and epigenetic transgenerational inheritance are anticipated to impact most areas of biology and medicine. This should not be seen as a challenge to classic genetics and genomics, but instead seen as a complementary molecular mechanism to regulate genomic activity and provide a mechanism by which environmental factors can influence biology and disease formation.

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