Transgenerational-Epigenetic Inheritance and Immune System

Subjects: Developmental Biology | Biochemistry & Molecular Biology | Immunology

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Definition

Epigenetic modifications cause heritable changes in gene expression which are not due to alterations in underlying DNA sequence. Inside the eukaryotic nucleus, there is condense packing of DNA around histone proteins to constitute chromatin structure. Epigenetic modifications are caused by factors that alter chromatin structure. Some epigenetic factors are enzymes that regulate DNA methylation and histone modifications, non-coding RNA, and prions. An offspring inherits parental epigenetic modifications but most of them are deleted and reset during early developmental stages. Some epigenetic modifications are retained and persist across multiple generations. If any epigenetic modification is the result of a stimulus or immune response in one generation, such that the modification continues to be inherited in subsequent generations which are not subjected to the stimulus; and the inheritance continues beyond the 3rd generation in the female germline and 2nd generation in male, then the phenomenon is called transgenerational epigenetic inheritance (TGEI). This entry is focused on a review which discusses some examples of TGEI that are reported in association with immune system development and disorders.

1. Introduction

Embryonic development is tightly orchestrated by various epigenetic mechanisms caused by multiple factors, like gene-environment interaction, and modifications of chromatin, histones, DNA, RNA, and proteins. Disruption of epigenetic regulation leads to diseases like cancers, neurodegeneration, and developmental disorders. Hence, it is important to understand how epigenetic information is processed, stored, and transmitted during the lifecycle of an organism in the context of development and disease. This submission is based on a review in MDPI which focuses on studies that address various aspects of TEI in the context of immune system development, function, and pathologies. Findings from diverse studies have the potential to inform future research on the subject. The results can possibly impact a wide range of applications including therapies against various diseases, addressing issues like substance abuse and mental health, and benefitting agriculture, the environment, and ecology.

2. Transgenerational Epigenetic Inheritance

Epigenetic alterations can be induced randomly and from a myriad of environmental factors including toxins, nutrition, and stress. If the epigenetic change is induced in a gestating female (F0 generation), both the fetus in utero (F1 generation) and the germline of the fetus (F2 generation) are considered to be directly exposed, therefore, making the F3 generation the first instance of transgenerational inheritance [1][2]. In contrast, if the epigenetic change is induced in a male, then only he (F0) and his germline (F1) are considered to be directly exposed, making the F2 generation the first instance of transgenerational inheritance [1][2][3][4][5][6].

2.1. Transgenerational Epigenetic Inheritance in Development

There are two main developmental periods: during the early embryonic stage post-fertilization and during the specification of germ cell at gonadal sex determination during which epigenetic reprogramming occurs [7][8][9][10]. Certain instances of TGEI of DNA methylation during development have been reported [11][12].

2.2. Transgenerational Epigenetic Inheritance in Disease

Studies also indicate transgenerational epigenetic inheritance stemming from human disease outbreaks like the Swedish and Dutch famines, where increased mortality risk from diabetes is observed in men whose grandfathers were exposed to famine, and in women whose grandmothers were exposed [13][14]. Epigenetic information carriers (unlike DNA) are highly dynamic and are often modulated by environmental conditions [15], suggesting that the environment experienced by parents may influence the phenotype of offspring via alterations to the gametic "epigenome" [16]. Studies of cell-state and transgenerational epigenetic inheritance have identified chromatin structure, DNA modifications, small RNAs, and prions as the main molecular carriers of epigenetic information [15].

2.3. Transgenerational Epigenetic Inheritance and Histone Modifications

Histone modifications are also implicated in transgenerational epigenetic inheritance [17][18]. During spermatogenesis, histones and their modifications are known to be inherited [19][20][21][22][23][24]. Studies on the female germline have also reported that it role in TGEI [25][26]. Overall, studies strongly indicate that when germlines are exposed to epigenome-altering environmental stimuli, the epigenomes of ESCs are perturbed, which impacts the epigenetic and transcriptomic landscapes of downstream somatic cell populations [6][27][28].

2.4. Transgenerational Epigenetic Inheritance and non-coding RNA (ncRNA)

Various epigenetic mechanisms are caused by ncRNA which also regulate immune system development. Some examples are ncRNA-mediated histone and DNA modifications, and development of cells of the immune system.

2.4. Transgenerational Epigenetic Inheritance and prions

Prions are misfolded proteins that are undergo TGEI and regulate stress response for survival. Prions are implicated in immune response under certain conditions. Certain epigenetic effects like histone modifications and gene expression are also mediated through prions.

3. Disease Context

Some disorders associated with the immune system how the presence of certain epigenetic modifications that underwent TGEI. Certain immune disorders, neurodegenerative and neurodevelopmental disorders show TGEI. Aging is another interesting field of research where TGEI is implicated. With the advent of advanced high-throughput technology coupled to next generation sequencing like ChIP-seq, ATAC-seq, RNA-seq, Hi-C, CUT&TAG, etc., the study of epigenetics if becoming more convenient, as described in the review.

4. Conclusions

Building on current studies and technological advances, further exploration of the molecular mechanisms behind transgenerational inheritance of specific epigenetic factors and their pathological outcomes will be beneficial from discovery and therapeutic perspectives. Identification of new targets at various levels of epigenetic modifications like DNA methylation, histone modifications, ncRNA, and prions will provide new insights into how these factors can regulate transgenerational inheritance and impact diseases including immune disorders.

A practical application of knowledge on epigenetics and the immune system is seen in several clinical trials, which can show new directions as to how epigenetic modulation can be used to treat immune disorders. For example, a clinical trial is investigating epigenetics regarding stem cells and trained innate immunity in patients with atherosclerosis, which is an immune disease (clinicaltrials.gov/ct2/show/NCT03172507 (accessed on 1 April 2021)). Lupus is an autoimmune disease where DNA methylation is employed in one of its clinical trials (clinicaltrials.gov/ct2/show/NCT04648059 (accessed on 1 April 2021)). DNA methylation sequencing and RNA-seq are some of the tools used in a clinical trial against immune-mediated eye diseases (clinicaltrials.gov/ct2/show/NCT00647439 (accessed

on 1 April 2021)) and asthma (clinicaltrials.gov/ct2/show/NCT01382836 (accessed on 1 April 2021)). Histone deacetylase inhibitors (HDACi) are used in clinical trials involving graft versus host disease (clinicaltrials.gov/ct2/show/NCT01111526 (accessed on 1 April 2021)), and immune checkpoint blockade in cancers (clinicaltrials.gov/ct2/show/NCT03233724 (accessed on 1 April 2021)). Some clinical trials on autoimmune diseases like rheumatoid arthritis and lupus focus on pregnancy-induced epigenetic changes regarding microRNAs (clinicaltrials.gov/ct2/show/NCT02350491 (accessed on 1 April 2021)).

Based on the above clinical trials, studies can be designed to specifically address immune profiles and epigenetic landscapes in diseases that are transgenerationally inherited. During the ongoing COVID-19 pandemic, epigenetic profiles of patients are under focus due to chromatin landscape changes of ACE2 and other histone modifications [29][30][31][32][33]. Although it is too early to comment on the transmission of the COVID-19 infection or its impact on epigenetic and immune profiles across generations, studies indicate a possibility [34].

The transgenerational inheritance of immune response is important beyond biomedical research as it has been linked to immune priming, which is a memory-like event occurring due to any sub-lethal exposure that prepares the immune system to combat a future lethal exposure [35]. In this direction, findings on farm animals [36], birds [37], plants [38][39], microbes [40], and invertebrates like Artemia [41][42] and Lepidoptera [43] link transgenerational epigenetic inheritance to immunity. Hence, the process impacts agriculture, the environment, and ecology. One study showed that when Artemia is exposed to pathogenic bacteria, then three subsequent generations of progenies show altered expression of major immune-related genes, with stochastic patterns of H4 acetylation and H3K4me3 [41]. It is only a matter of time before we will discover similar well-defined mechanisms in vertebrates.

Overall, the significance of transgenerational epigenetic inheritance is already established [4][44][45][46] with a major outcome being adaptability to stress; hence, why its intricate relationship with immune system development and activation must be focused upon.

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Keywords

transgenerational;epigenetic;development;immune system;chromatin;histone;non-coding RNA;prion;NGS;clinical trials