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Transgenerational epigenetic inheritance: Focus on soma to germline information transfer

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ABSTRACT

In trangenerational epigenetic inheritance, phenotypic information not encoded in DNA sequence is transmitted across generations. In germline-dependent mode, memory of environmental exposure in parental generation is transmitted through gametes, leading to appearance of phenotypes in the unexposed future generations. The memory is considered to be encoded in epigenetic factors like DNA methylation, histone modifications and regulatory RNAs. Environmental exposure may cause epigenetic modifications in the germline either directly or indirectly through primarily affecting the soma. The latter possibility is most intriguing because it contradicts the established dogma that hereditary information flows only from germline to soma, not in reverse. As such, identification of the factor(s) mediating soma to germline information transfer in transgenerational epigenetic inheritance would be pathbreaking. Regulatory RNAs and hormone have previously been implicated or proposed to play a role in soma to germline communication in epigenetic inheritance. This review examines the recent examples of gametogenic transgenerational inheritance in plants and animals in order to assess if evidence of regulatory RNAs and hormones as mediators of information transfer is supported. Overall, direct evidence for both mobile regulatory RNAs and hormones is found to exist in plants. In animals, although involvement of mobile RNAs seems imminent, direct evidence of RNA-mediated soma to germline information transfer in transgenerational epigenetic inheritance is yet to be obtained. Direct evidence is also lacking for hormones in animals. However, detailed examination of recently reported examples of transgenerational inheritance reveals circumstantial evidence supporting a role of hormones in information transmission.

1. Introduction

Transgenerational epigenetic inheritance (TEI) refers to transmission across generations of phenotypic information not encoded in DNA sequence. Enough confusion about what it signifies and what it does not however persists in the literature. Clarifications provided by several authors have been valuable in counteracting problems associated with the semantics and definitions of TEI (Chong et al., 2007; Ho and Burggren, 2010; Kovalchuk, 2012; Youngson and Whitelaw, 2008). The controversies surrounding TEI essentially stem from use of the term transgenerational and the phrase epigenetic inheritance. A brief explanation will help avoid the confusion. In its broadest sense, epigenetic inheritance implies non-genetic transfer of phenotypic information across generations. Non-genetic is an excluding term here, signifying factors other than DNA sequence variations. These may include (Fig. 1) chromatin associated factors such as DNA methylation and several kinds of histone modifications as well as trans-acting and non-nuclear factors like RNA (Daxinger and Whitelaw, 2012; Ho and Burggren, 2010; Ilnytskyy and Kovalchuk, 2011; Jablonka, and Raz, 2009; Schübeler, 2012; Singh and Li, 2012). Although not known to be inherited across generations through gametes, self-assembling structures like prions, and self-sustaining feedback loops such as those involved in bistable behavior of *Escherichia coli* lac operon are other epigenetic factors that are transmitted through mitosis (Ho and Burggren, 2010; Jablonka and Raz, 2009; Jablonka, 2012a). The pre-requisite to infer a phenomenon as epigenetic inheritance is therefore exclusion of the possibility of the involvement of DNA sequence variation. Knowledge of the exact epigenetic mechanism involved may not be however absolutely essential (Ho and Burggren, 2010).

The prefix transgenerational signifies that environmental effects caused in the exposed generation also appear in the unexposed future generation(s). An oft-repeated example will clarify what exposed and unexposed generations mean (Feil and Fraga, 2012;

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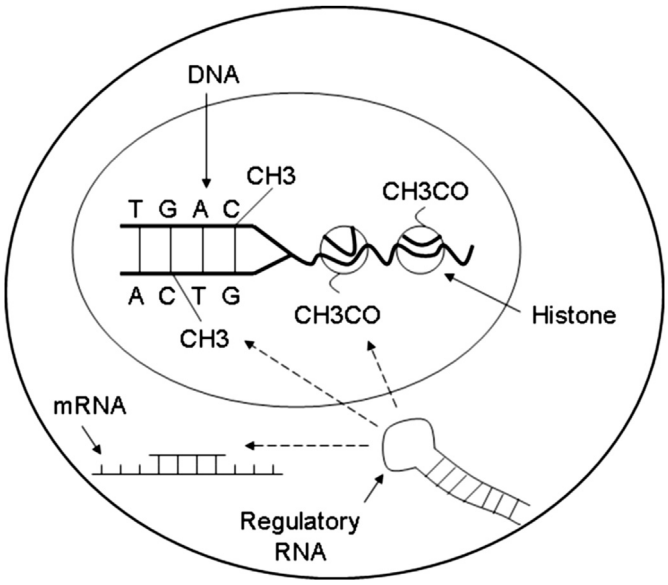

Fig. 1. Epigenetic factors potentially underlying transgenerational inheritance. DNA methylation, histone modifications and non-coding RNAs are mainly considered to mediate transmission of environmental effects across generations. DNA methylation at the cytosine of CpG dinucleotides and post-translational histone modifications including methylation and acetylation are associated with change in chromatin structure and activation and suppression of gene expression. Several types of regulatory RNAs mediate transcriptional and/or post-transcriptional control of gene expression through mRNA silencing, translational repression and upregulation, histone modifications and/or DNA methylation.

Guerrero-Bosagna and Skinner, 2012; Jablonka and Raz, 2009; Jirtle and Skinner, 2007; Skinner, 2008; Skinner et al., 2010; Skinner, 2011; Whitelaw and Whitelaw, 2008; Zamudio et al., 2008). When a female mammal (F0) is exposed to a stimulus during pregnancy, both F1 generation embryo and F2 generation germline are also exposed. Given this, demonstration of a phenotype in F3, the first unexposed generation, is minimally required to unequivocally establish TEI (Fig. 2A). In case of exposure to an adult male or non-gestating female mammal (F0), the F1 generation germline is also exposed. Here, demonstration of a phenotype at least in F2, the first unexposed generation, will be required to unambiguously establish TEI (Fig. 2B). In this germline-dependent inheritance, the

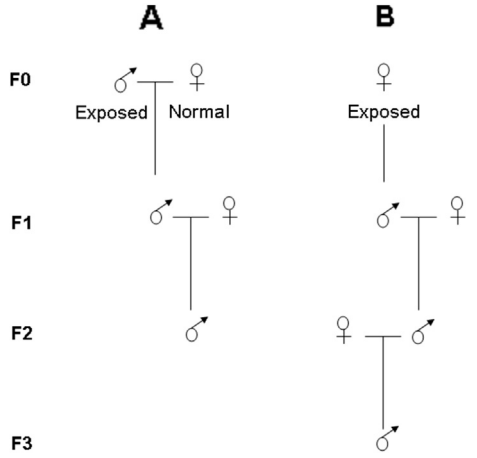

Fig. 2. Mating schemes for demonstrating germline-dependent transgenerational epigenetic inheritance. Following (**A**) male and (**B**) female environmental exposure in mammals, for example, demonstration of phenotype in F2 and F3, in that order, is required to establish gametogenic transmission.

epigenetic change is integrated in the germline and can be expressed in future generation(s) that are not exposed to the causative factor (Crews, 2008; Crews et al., 2012). Theoretically, the environmental exposure can cause epigenetic modification in the germline directly or indirectly through effects on the soma (Jablonka, 2012a; Jablonka and Raz, 2009). Of these two main possibilities, the former (Fig. 3A) is easier to comprehend because it is in keeping with the basic tenet of hereditary information transfer. In contrast, for the latter (Fig. 3B) possibility to happen, a seemingly improbable information transfer from soma to the germline will be required. The "central dogma" of hereditary information transfer states that it occurs unidirectionally from the germline to soma, not in reverse. It is therefore counterintuitive that environmental factors can cause heritable epigenetic modifications in the germline through their primary effects on soma. Notwithstanding, experimental evidence for gametogenic TEI of acquired somatic characters, where a soma to germline information transfer is implicit, has been obtained in recent years. This is surprising. Of note, context-dependent inheritance (Fig. 3C) represents another mode of inheritance where epigenetic modification caused due to an altered maternal–fetal environment expresses in future generation only when the causative factor persists (Crews, 2008; Crews et al., 2012). Though non-genetic in nature, context-dependent inheritance does not involve information transfer via gametes (Whitelaw and Whitelaw, 2008), and is therefore not considered by many as true TEI (Crews, 2008; Crews et al., 2012). A broader definition however covers both context- and germline-dependent transmission under TEI (Jablonka and Raz, 2009; Jablonka, 2012b). Also, epigenetic mechanisms underlying context-dependent and gametogenic inheritance may converge on similar cellular correlates like altered DNA methylation and RNA-based processes (Jablonka, 2012b). Excellent reviews have been published recently on TEI, with focus on germline-dependent inheritance in animals (Daxinger and Whitelaw, 2012; Guerrero-Bosagna and Skinner, 2012), context-dependent inheritance in animals (Bohacek et al., 2012; Matthews and Phillips, 2012), epigenetic inheritance in plants (Becker and Weigel, 2012; Boyko and Kovalchuk, 2011), and epigenetic inheritance in plants and animals both (Jablonka, 2012a,b). The present review will narrowly concentrate on experimental evidence of inheritance of acquired somatic characters involving soma to germline hereditary information transfer (Fig. 3B). This form of germline-based TEI is most fascinating because it contradicts the Weismann barrier, the established doctrine that genetic information flows from soma to the germline, not in reverse (Sabour and Schöler, 2012). Discovery of these factors as modern avatars of Darwin's "gemmules" will also revive some interest in the largely discredited Darwinian pangenesis and Lamarckian inheritance (Koonin and Wolf, 2009; Liu, 2007, 2008; Liu and Li, 2012). Factors such as RNAs and hormones, including neurohormones and neuropeptides, have previously been considered to potentially mediate soma to germline communication in epigenetic inheritance (Jablonka and Raz, 2009; Jablonka, 2012a; Irmak et al., 2005; Li and Huang, 2008; Liu, 2007; Liu and Li, 2012; Sharma and Singh, 2009). In this review, it will be examined if recent evidence supports a role of RNAs and hormones in information transfer.

2. Mobile RNAs as potential mediators

In last decade, small non-coding RNAs (sncRNAs) such as small interfering RNAs (siRNAs), microRNAs (miRNAs) and piwi-interacting RNAs (piRNAs) have emerged as master regulators of gene expression in eukaryotes (Borges et al., 2011; Bourc'his and Voinnet, 2010; Chen, 2012; Djuranovic et al., 2011; Finke et al., 2012; Lochmatter and Mullis, 2011; McCue et al., 2012; Okamura,