Research Highlights

Highlights from the latest articles in transgenerational epigenomics

The role of epigenetic inheritance in stress regulation

Evaluation of: Crews D, Gillette R, Scarpino SV, Manikkam M, Savenkova MI, Skinner MK. Epigenetic transgenerational inheritance of altered stress responses. *Proc. Natl Acad. Sci. USA* 109(23), 9143–9148 (2012).

Chronic stress can disturb the homeostasis of the body by stimulating the nervous and endocrine systems and can greatly influence behavioral phenotypes of exposed individuals, causing vulnerability to anxiety, drug abuse and cognitive impairment [1–3]. Epigenetic remodeling of chromatin in the brain may contribute to stress-induced pathology [4,5]. Previous studies have demonstrated that fungicide vinclozolin exposure during pregnancy could affect the fertility of F3 generation male mice and alter the DNA methylation level of sperm [6]. Crews *et al.* found that a single exposure to vinclozolin alters the physiology, behavior, metabolic activity and transcriptome in discrete brain nuclei in descendant males, and changes their response to chronic restraint stress [7]. The F3 males of vinclozolin lineage exposed to chronic stress showed higher level of anxiety and more interactions with the familiar individual and displayed changed metabolic activity in the hippocampus and amygdala, brain areas involved in emotion-related memories. cDNA microarray analysis of these lineages revealed alterations of specific signaling pathways related to neurodegeneration. These findings are potentially ground-breaking. The work of Crews *et al.* suggests that ancestral exposure to an environmental chemical, such

as fungicide, may change their descendants' response to a stress experienced during their own life. The environmental toxicant-induced transgenerational epigenetic modification in the specific brain areas may be one of the factors that contribute to the increased risk of mental diseases.

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Environmental toxicants induce ovarian disease across generations

Evaluation of: Nilsson E, Larsen G, Manikkam M, Guerrero-Bosagna C, Savenkova MI, Skinner MK. Environmentally induced epigenetic transgenerational inheritance of ovarian disease. *PLoS ONE* 7(5), e36129 (2012).

Primary ovarian insufficiency (POI) and polycystic ovarian syndrome (PCOS) are common female endocrine disorders that could markedly influence fertility and cause other accompanying symptoms such as diabetes [1–3]. Exposure to environmental toxicants such as pesticide can affect fetal and postnatal development and result in diseases, which might pass to the next generation [4]. Nilsson *et al.* gave toxicants (vinclozolin, pesticide, plastics, dioxin or jet fuel) to the gestating rats from E8 to E14, and observed a significant decrease in the number of primordial follicles from

not only F1 but also F3 generation [5]. Interestingly, the numbers of both small and large cysts were increased in the F3 generation compared with the F1 generation. These ovarian abnormalities observed in rat are consistent with the biology of POI and PCOS in humans. Furthermore, microarray analysis of F3 generation granulosa cells of vinclozolin lineage revealed significant differential expression of 523 genes and DNA methylation in the promoter regions of 43 genes in these rats, suggesting that environmental exposure-induced epigenetic changes can be passed to future generations. The findings of Nilsson *et al.* demonstrate that ancestral toxicant exposures may lead to transgenerational inheritance of ovarian diseases, and further investigations may shine light on the identification of the epigenetic molecular markers for diagnosis of ovarian diseases and pathogeny, as well as the treatment strategies of POI and PCOS.

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The role for maternal piRNA in transgenerational inheritance

Evaluation of: Grentzinger T, Armenise C, Brun C *et al.* piRNA-mediated transgenerational inheritance of an acquired trait. *Genome Res.* doi:10.1101/gr.136614.111 (2012) (Epub ahead of print).

Transposable elements (TEs) are DNA sequences capable of changing their position in the genome and may thus create phenotypic mutations. piRNAs, a class of small ncRNAs that interact specifically with piwi proteins, are generated in animal cells to recognize and silence the complementary TE targets and maintain genome integrity [1]. In *Drosophila*, antisense

primary piRNAs are produced from defective TE-rich transcripts located in pericentromeric heterochromatin, and the large amounts of antisense secondary piRNAs, which target functional TE transcripts, are generated through a feed-forward amplification loop called the ping-pong cycle. In the ping-pong cycle, the primary piRNAs guide the cleavage of the sense transcripts of the functional euchromatic TEs to produce sense secondary piRNAs, and the sense secondary piRNAs in turn recognize the heterochromatic defective TE transcripts to generate antisense secondary piRNAs [2,3].

I-element is a germinal-specific long interspersed element-like TE that regulates the fertility of *Drosophila*. In the inducer (I)–reactive (R) hybrid dysgenesis

system, the R strain of *Drosophila* has defective I-element and generates low level of I-element piRNAs, while the I strain possesses functional I-element and produces abundant I-element piRNAs [4]. Grentzinger *et al.* split R female strains into short generation (from young parents; R^L) and long generation (from old parents; R^H) stock, and crossed R^L and R^H females with I males [5]. They found that the daughters from R^H mothers were more fertile and had almost threefold increase in I-element piRNAs in their ovaries compared with those from R^L mothers. Furthermore, the ovarian I-element piRNAs of daughters of R^H, but not R^L *Drosophila*, showed a classic ping-pong signature, and this feature was correlated with I-element repression. However,

the level of primary I-element piRNA in R^H and R^L ovaries did not change. Analysis of sequences of the small RNAs in the ovaries and eggs from R^H suggested that aging over several generations may result in active I-element secondary biogenesis in the progeny. The work of Grentzinger *et al.* revealed that the ability of TE inhibition can be inherited transgenerationally via a piRNA mechanism, providing an insight into how phenotype is passed from generation to generation. However, the role of aging in secondary I-element piRNA biogenesis in R strain is still unknown.

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