Molecular and Cellular Endocrinology xxx (2018) 1–13

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Epigenomic drugs and the germline: Collateral damage in the home of heritability?

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ARTICLE INFO

Article history:
Received 18 January 2018
Received in revised form
16 February 2018
Accepted 16 February 2018
Available online xxx

Keywords:
Germline
Epigenetic
Epigenomic drug
Fetal
Sperm
Oocyte

ABSTRACT

The testis and ovary provide specialised environments that nurture germ cells and facilitate their maturation, culminating in the production of mature gametes that can found the following generation. The sperm and egg not only transmit genetic information, but also epigenetic modifications that affect the development and physiology of offspring. Importantly, the epigenetic information contained in mature sperm and oocytes can be influenced by a range of environmental factors, such as diet, chemicals and drugs. An increasing range of studies are revealing how gene-environment interactions are mediated through the germline. Outside the germline, altered epigenetic state is common in a range of diseases, including many cancers. As epigenetic modifications are reversible, pharmaceuticals that directly target epigenetic modifying proteins have been developed and are delivering substantial benefits to patients, particularly in oncology. While providing the most effective patient treatment is clearly the primary concern, some patients will want to conceive children after treatment. However, the impacts of epigenomic drugs on the male and female gametes are poorly understood and whether these drugs will have lasting effects on patients' germline epigenome and subsequent offspring remains largely undetermined. Currently, evidence based clinical guidelines for use of epigenomic drugs in patients of reproductive age are limited in this context. Developing a deeper understanding of the epigenetic mechanisms regulating the germline epigenome and its impact on inherited traits and disease susceptibility is required to determine how specific epigenomic drugs might affect the germline and inheritance. Understanding these potential effects will facilitate the development of informed clinical guidelines appropriate for the use of epigenomic drugs in patients of reproductive age, ultimately improving the safety of these therapies in the clinic.

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https://doi.org/10.1016/j.mce.2018.02.008
0303-7207/

1. Introduction

The testis and ovary provide specialised environments in which the male and female germlines develop, and sperm and oocytes are produced. Perhaps the most important role for sperm and oocytes is the transmission of genetic and epigenetic information from parent to offspring. Although genetic inheritance is well understood, the extent to which epigenetic information contained in the germline regulates outcomes in offspring remains relatively poorly understood. However, studies over recent decades have significantly contributed to the understanding of the germline epigenome and its effects on offspring. As epigenetic modifications can be influenced by environmental factors, such as diet, drugs and chemicals, the epigenome is considered to provide an interface between genome function and the environmental conditions to which a particular cell or organism is exposed. Consistent with this, exposure of the developing germline or maturing sperm and eggs to environmental factors that induce epigenetic change in the gametes can alter offspring development, and result in inherited phenotypes. Understanding the germline epigenome and how it is influenced by the environment is therefore central to understanding disease inheritance.

Epigenetic modifications primarily include DNA methylation and post-translational changes to histones, but also integrate other mechanisms involved in writing or interpreting this information, including non-coding RNAs. Methylation of DNA or post-translational modifications to histones (e.g. methylation, acetylation, phosphorylation, etc.) provide a heritable chromatin roadmap, or cellular memory, that enables cells to interpret the DNA and maintain transcriptional patterns that are essential for specialised cell identity and function (Bonasio et al., 2010; Cedar and Bergman, 2009; Hemberger et al., 2009). Epigenetic modifications are established, read, maintained and removed by an extensive range of enzymes and proteins that modify specific chromatin sites across the genome. The collective epigenetic profile of each cell type is known as the epigenome for that cell type. Both, the diversity and stability of epigenetic mechanisms provide the capacity for a single genome to establish the impressive range of specialised cell types that constitute multicellular organisms. Conversely, altered epigenetic states underlie dysregulated cell function and disrupt cellular identity as demonstrated in many cancers (Jones et al., 2016). Understanding epigenetic mechanisms therefore goes hand-in-hand with understanding development and disease.

Because epigenetic modifications are reversible and dysregulated in diseases such as cancer, a range of epigenomic drugs that specifically target the enzymes and proteins that regulate epigenetic modifications has been developed. Some of these epigenomic drugs are already providing effective disease therapies that significantly improve patient outcomes (Jones et al., 2016). However, while these drugs are clearly offering important therapeutic approaches, some patients will want to conceive children after treatment. As epigenomic drugs act systemically and the germline conveys epigenetic information to offspring, it is important to understand how these drugs might alter the epigenome in the sperm or oocytes of patients during treatment, how long these effects persist and whether they might affect outcomes in offspring. Nonetheless, we have only a rudimentary understanding of the epigenetic information contained in sperm and oocytes, the enzymes that function to regulate this information and the impacts that germline epigenetic information has on offspring. Investigating whether epigenomic drugs induce germline epigenetic changes is timely as the range of these drugs being introduced to clinical trials has increased over recent years and is expected to increase further in the future.

Although epigenomic drugs directly target specific epigenetic mechanisms, most studies of epigenetic inheritance have focussed on dietary or other environmental influences on the epigenome. These studies have been summarized in a range of recent reviews which discuss the effects of broader environmental impacts in the parent on the germline epigenome and outcomes in offspring (Daxinger and Whitelaw, 2012; Grossniklaus et al., 2013; Miska and Ferguson-Smith, 2016; Prokopuk et al., 2015). These reports provide a significant red flag for clinical management of epigenomic drugs, which may be more likely to directly impact on the germline epigenome than broader environmental exposures, such as nutritional state or diet, environmental chemicals or habitual drugs such as alcohol.

This discussion is not intended to discourage, or be critical of, the use of epigenomic drugs, which are providing new therapeutic options for patients and an effective pathway back to health. Obviously in cases where epigenomic drugs provide the best treatment option, they will be used in therapies. However, it is prudent to consider the potential impacts of epigenomic drugs on the germline and inheritance. Developing an appropriate understanding of epigenomic drugs and the systems they affect will ultimately provide the best clinical care to patients for their immediate care and, where possible, for the health and wellbeing of future generations.

2. Germline development

To understand the impacts of environmental influences on germline epigenetic modifications and the outcomes that they mediate, it is essential that a detailed understanding of normal germline epigenetics is developed. Although substantial insights have been derived from model invertebrates, less is understood of germline epigenetic programming in mammalian species outside mice and humans (Miska and Ferguson-Smith, 2016). Since this review is concerned with epigenomic drugs and their potential impacts on germ cells, this discussion will focus on studies in humans and mice, the latter which provides the most accessible epigenetic model in mammals.

The role of germ cells in transmitting genetic and epigenetic information to offspring places them in a critical position in biology. Not only do germ cells transmit epigenetic information, but they must also regulate the germline epigenome to ensure the transmission of epigenetic modifications that will best support offspring health and development. This is enabled by a series of epigenetic reprogramming events that allow the removal of epigenetic information present in germline precursor cells which was inherited from the previous generation. Once removed, new, parent specific (i.e. paternal or maternal) epigenetic modifications are written into the germline, before being conveyed by sperm and oocytes to offspring at fertilisation (Hogg and Western, 2015; Saitou et al., 2012; Stringer et al., 2013; Tang et al., 2016; von Meyenn and Reik, 2015). As this process is integrated throughout the developmental life of germ cells in the fetus, in neonates and in adults, it is essential to discuss the epigenome in the context of the developmental cycle of germ cells, from their specification in the embryo to the combination of mature gametes at fertilisation and subsequent epigenetic regulation during preimplantation development.

In mice, the earliest germ cells are induced from surrounding epiblast cells that relocate to the extra-embryonic mesoderm in pre-gastrulation stage embryos (Fig. 1) (Lawson et al., 1999; McLaren, 2001; Ohinata et al., 2005; Payer et al., 2006; Saitou et al., 2002). Commitment to the germline initiates a series of molecular changes including epigenetic repression of pathways leading to somatic cell differentiation and the re-establishment of genetic networks that maintain pluripotency (Irie et al., 2015; Kurimoto et al., 2008; Nakaki and Saitou, 2014; Nakamura et al.,

Please cite this article in press as: Western, P.S., Epigenomic drugs and the germline: Collateral damage in the home of heritability?, Molecular and Cellular Endocrinology (2018), https://doi.org/10.1016/j.mce.2018.02.008