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Models and tools used to study epigenetics

The social honey bee in biomedical research: realities and expectations

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The social honey bee, *Apis mellifera*, is an organism of great value for behavioural, ecological and evolutionary studies. It is also an important agricultural insect and a source of allergies. In recent years its usefulness for research communities has been significantly expanded as a result of progress in genomics and epigenomics. While the bee is not to be misjudged as a model for a specific human disease, it complements other invertebrate models in areas of DNA methylation, metaboloepigenetics and is a source of medically and epigenetically active compounds. This article outlines the anticipated benefits flowing from the epigenome-inspired projects in honey bees and draws attention to the most promising avenues that are likely to strengthen the value of this organism in biomedical research.

Introduction

Animal-based research has been the primary driving force for both corporate and academic communities attempting to find cures for various diseases and trying to develop novel drugs. In addition to rodents and other mammals [1,2], the genetic power of comparatively simple organisms like yeast, nematodes and flies [3–6] has been used as a 'trade-off' for studying the most intricate molecular events, which when disturbed may lead to disease phenotypes. The rationale for using animal models as surrogates for human conditions is based on the idea that a high level of molecular conservation between humans and animals can be harnessed to develop new cures or drugs [7]. However, genomics has not yet yielded the promised revolutionary cures for complex diseases on a widespread scale. Although the value of massive inflow of genomic information has already been acknowledged, it also is becoming clear that translating DNA sequences into a meaningful biology is a much more challenging task than previously anticipated. One reason for the apparent difficulties is that animals currently used in biomedical research are quite different from humans [8,9]. In spite of a high level of similarities at the gene/protein level, the organismal biology and behavioural complexity is organism-specific and converting functional genomics data into clinical situations is rarely straightforward. An evolutionarily selected strategy used by a given species to solve a particular biological problem may be quite different from that employed by another organism. Particularly in metazoan species, organismal outcomes strictly depend on epigenetic context and the so-called proximal and distal regulatory networks in which any protein is transiently engaged [10,11]. Modelling such epigenetic processes is exceptionally difficult because of the degenerate nature of network-level interactions whereby structurally different elements in diverse organisms can be selected to perform similar functions [12]. It is becoming increasingly obvious that most challenging issues in biomedical research can only be resolved by a combined power of many models, each one providing a unique contribution to complement the others.

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Table 1. The honey bee in relation to other models

Model organism	Gene number	Genetic tools	Regulation via DNA methylation	Level of genomic methylation	Diet-driven phenotypic plasticity	Behavioural complexity
Mouse	22,000	Yes	Yes	Very high	No	High
C. elegans	20,000	Yes	No	None	No	Low
Drosophila	18,000	Yes	No	None	No	Moderate
Honey bee	~15,000	No	Yes	Low	Yes	High

Here we review the potential of (epi)genome-inspired projects in honey bees and highlight the most realistic lines of research that can enhance the value of this species in biomedical sciences.

The emergence of honey bee epigenomics

The familiar social honey bee, *Apis mellifera* is a semi-domesticated insect that has been part of human evolution for thousands of years. In addition to its critical role in agriculture, bees have been exploited as a source of nutritional and health commodities like honey, beeswax, propolis and royal jelly. In modern times, the potential of bee products as therapeutic compounds is being extensively explored [13,14]. Although some claims regarding the benefits of royal jelly or propolis for humans are not yet proven, the antimicrobial potency of honey is well documented including its efficacy against antibiotic resistant 'super-bugs' [14]. The bee has also made an impact on research. Ever since the discovery of the honey bee symbolic communication language by the Nobel laureate Karl von Frisch in the first half of the 20th century, an impressive amount of experimental work has been carried out on virtually every aspect of honey bee biology with the main emphasis on behaviour, both social and individual, and ecology [15,16]. Unfortunately, the bee cannot be maintained in a lab, and similarly to many interesting invertebrates, studies in this species are not assisted by sophisticated genetics tools developed in the mouse, the fly *Drosophila melanogaster*, yeast and the nematode *Caenorhabditis elegans*. Given these shortcomings, what are the perceived benefits of using the honey bee as a 'disease model' in biomedical research?

To put the idea of the honey bee disease model in a proper context it is important to recognise several key developments that have been reshaping biological sciences in the last 10–12 years. The advent of cheap DNA sequencing has led to a deluge of genomic information and raised hopes that new cures for many human diseases including better drugs will be developed with greater speed and efficacy [7,17,18]. Wonder drugs based on DNA were supposed to change our lives and personalised medicine was going to replace a traditional visit to a doctor. The Western honey bee is just one example of a rapid rise to prominence resulting from technical innovations that generate unprecedented research opportunities even for the most exotic and inaccessible organisms. The honey bee joined the modern era of genomics in 2006 when *Nature* published a special issue reporting the draft sequence of its genome [19]. The preliminary analyses of the first genome of a social insect revealed several surprises suggesting that in some areas this insect is more similar to humans than to other invertebrate species. Nearly 700 genes missing in classic model organisms, such as *Drosophila* or *C. elegans*, have been found in the honey bee including genes encoding large proteins implicated in complex diseases, for example, Huntingtin and Hydin (Hydrocephalus-inducing protein). Importantly, for the first time, DNA methyltransferases (DNMTs), or the 'DNA methylation toolkit' with characteristics similar to the mammalian methylation system has been found in an insect (Table 1). Following these initial analyses a number of studies have shown that honey bees can be successfully used to investigate the functional significance of DNA methylation and other epigenomic modifications in the context of organismal function [20–25].

Modelling epigenetic diseases networks using honey bee biology

Many diseases referred to as 'complex' are now considered to be of 'epigenetic' origin [26–28]. Cancer, mental disorders, neurodevelopmental syndromes, certain type of metabolic diseases and many others cannot easily be explained as simple Mendelian traits. Defining these types of diseases is exceptionally challenging. They often progress in severity, their symptoms and responses to treatment vary between individuals and are difficult to treat with drugs. Phenotypic indicators of devastating mental disorders like schizophrenia or bipolar depression are not only variable between individuals, but recent data suggest that such diseases may have distinct molecular origins. For example, a comprehensive analysis of published data on samples from schizophrenics generated with a wide range of technologies and drug perturbation approaches has shown largely non-overlapping gene sets [11]. This and similar studies suggest that researchers have to invent novel conceptual approaches to understand underlying molecular mechanisms of non-Mendelian disorders. The emerging evidence suggesting that aetiology of major mental disorders and other complex diseases involves a multifaceted interplay of genomes and environments is