Unconventional forms of inheritance

Editorial

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Unconventional forms of inheritance

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The discourse on hard (mendelian) versus more unconventional "soft" forms of inheritance has been blazing for long. In the early 19th century Jean-Baptiste Lamarck set a ground stone for an environmentally directed evolution which he believed was mediated by movements of bodily fluids and could be passed on [1,2]. His, and the assumption of others of his time, that "use" and "disuse" determined the acquisition and loss of characteristics and that once acquired these characteristic were heritable was then complemented by Charles Darwin`s and Alfred Russel Wallace`s proposition on natural selection as an additional driver of evolution[3]. Darwin still considered most of Lamarck`s ideas as valid and even proposed the mechanism of pangenesis to reconcile responsiveness to the environment with the forces of natural selection[4]. Yet August Weismann in the early 20th century rejected most interaction between the soma and the germline and hereby the theory of "use" and "disuse" by postulating the Weissman barrier[5,6]. This barrier assigned any hereditary function solely to the germ cells, which are protected from influences of the environment. Despite great effort of many prominent scientists to proove Lamarckian ideas on the inheritance of acquired traits, among them Trofim Lysenko[7] in the field of agriculture and Paul Kammarer[8] in the field of zoology, they were defeated by the accumulating evidence by Hugo de Vries[9], Eric von Tshermakin and Carl Correns[10] in support of Gregor Mendel´s work on peas from the late 19th century. The Modern Evolutionary Synthesis finally prevailed postulating the newly coined "genetics" as the sole substrate for natural selection[11]. Ernst Mayr retrospectively stated: "According to the more-or-less unified theory of Fisher and his colleagues, evolution was defined as a change in gene frequencies in a population, a change brought about through the gradual natural selection of small random mutations."[12]. He further hypothesized that "it was perhaps the greatest achievement of the young science of genetics to show that soft inheritance does not exist."[13]. Soft inheritance delineates the "belief in a gradual change of the genetic material itself, either by use and disuse, or by some internal progressive tendencies, or through the direct effect of the environment."[14] Yet evidence of non mendelian inheritance was lingering all along [15–19].
Meanwhile, Waddington was arguing for an "epigenotype" as key to explain how a multitude of phenotypes can arise from a single genotype during the development and how canalization can account for the stabilization of acquired traits across generations.

Mechanistic explanations were waiting around the corner of the discovery of the structure of DNA by Watson and Crick in 1953. In 1956 Alexander Brink introduced a non-mendelian type of inheritance he termed "paramutation". Paramutation explained the inheritance of unique patterns of corn kernel pigmentation in maize, in that it suggested an interaction between two alleles of the red1 locus that caused phenotypes stable over many generations [20,21]. 9 years later, Barbara McClintock published her findings on Transposable elements, genes that can "jump" around the genome and thereby cause surprising and heritable patterns in maize leaf color[22]. Importantly she later on also observed that transposition was susceptible to environmental factors[23]. Another phenomenon at odds with mendelian rules was the parental specific behavior of chromosomes that for instance contributes to sex determination in some Arthropod species[24]. In this particular case the "imprinting" was due to a paternal specific chromosome elimination, but the term would eventually evolve to strictly refer to "parental-specific gene expression in diploid cells"[25]. The discovery of several chemical modifications on the DNA and histones, the proteins that DNA is wound around, by Charles David Allies and Thomas Jenewein[26] then paved the way to detailed mechanistic studies of how phenotypic alterations can be passed on from one generation to the next epigenetically[27].

While currently studies on phenomena and underlying mechanisms of inter and transgenerational inheritance are accumulating, criticism about the validity of findings, interpretations and implications are as vivid as ever. The controversy of the topic might be due to the paradigm shifting implications of such additional non-social forms of inheritance. Especially given the great resonance that publications of transgenerational effects receive, a cautious evaluation of their relevance for non-laboratory settings is prompted. Criticism especially on the studies in human cohorts evolves around (1) small sample size, (2) “fishing expeditions” - no clear a-priory hypothesis in combination with extensive uncorrected multiple testing, (3) a lack of mechanism to explain the observed phenomena (Wiring the brain) and (4) confounding genetically induced secondary epimodifications with primary epimodifications [28,29]. Recent studies seriously address these matters and succeed to replicate findings on the effects of paternal grandfathers food access on all-cause and cancer mortality in grandsons using for instance much larger sample size[30] . This study clearly defines an a priori hypothesis based on the previous publications and can hence not be charged of “fishing”. Also studies in model organisms have evolved to scrutinize some possible confounders, such as mating behavior by using artificial insemination [31] and to evaluate a range of potential information carriers such as DNA methylation and sperm RNA in the same model [32]. Yet plenty of room for improvement remains, including a revision of the definition of “statistical unit” in the experimental design[31].

In this special issue we aim at providing a broad overview of unconventional intra-, inter- and transgenerational phenomena with a special focus on potential novel mediating mechanisms (Fig.1).
Carlos Guerrero-Beossagna kicks off by introducing a fundamental question in evolutionary biology: how heritable variability is obtained. He discusses ideas about the involvement of classical epigenetic players such as DNA methylation, and its potential interplay and/or consequences on mutations rate. Bertozzi and Ferguson-Smith further consider the potential implications of metastable epiallels in genome evolution, their prevalence and responsiveness to the environment in mammals. Peter Sarkies describes environmentally inducible alterations more broadly, also in the context of plants and from an evolutionary angle. Adelheid Lempradl takes a closer look on histones post-translational modifications, DNA methylation and their reprogramming while also reviewing the potential of non-coding RNA in epigenetic inheritance of several animal model organisms. Rassoulzadegan and Bohacek focus on advances in the field of sperm non-coding RNA in mammals and introduce potential unexplored sperm-RNA niches. We further consider novel and forefront players in the repertoire of mechanisms leading to unconventional inheritance. The review form Morgan and Watkins introduces seminal fluid as a determinant of offspring health in response to paternal low protein diet. Johannes Manjrekar acquaints us with prions and their potential to self-propagate not only within a cell but also across cells and potentially even across generations. van den Ameele et al. delineate mitochondrial heteroplasmy and mutation induced dysfunction and familiarize us with the potential contribution of mitosis-dissociated mitochondrial inheritance to mediate unexpected effects that deviate from mendelian rules. Dana Landschaft sheds light on potential implications of gap junctions in the transmission of signals from the soma to the germline.
Anne Gabory reminds us on the persistent consequences of developmental programming and shows how this is often intertwined with intergenerational effects generally. She discusses the central role of energy metabolism, cell structure and classical receptor signaling and how tales learned from developmental programming could inform mechanisms underlying cases of non-mendelian inheritance. For the specific case of maternal immune challenge, Pollak and Weber-Stadlbauer explore inter and transgenerational effects of developmental programming and their interesting interaction with behavioral outcomes.
Rounding up our special issue on the biological mechanisms and phenomena from a natural science point of view the article from Ruth Müller puts the findings into a social sciences perspective. She calls for every biologist to familiarize her/him self with this history in order to prevent reductionism and the danger of concluding an “inheritance of determinism” two prime problems for the social dimension. According to her only a conscious experimental design in dialog with history enables a sensible capture

of non-genetically inheritance research.

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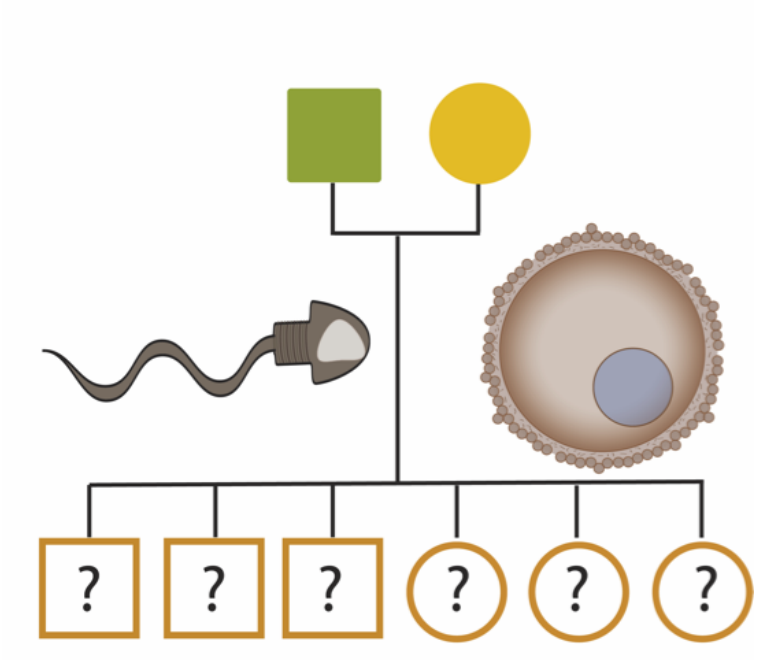

Figure 1: Not all patterns of inheritance follow mendelian rules. Discoveries of explanatory mechanisms are on the rise.

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