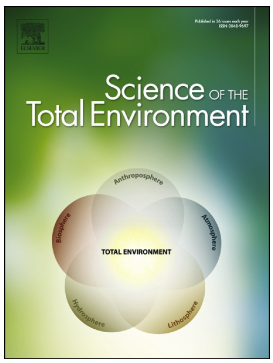

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Heredity determined by the environment: Lamarckian ideas in modern molecular biology

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ABSTRACT

Inheritance of acquired characteristics (IAC) is a well-documented phenomenon occurring both in eukaryotes and prokaryotes. However, it is not included in current biological theories, and the risks of IAC induction are not assessed by genetic toxicology. Furthermore, different kinds of IAC (transgenerational and intergenerational inheritance, genotrophic changes, dauermodifications, vernalization, and some others) are traditionally considered in isolation, thus impeding the development of a comprehensive view on IAC as a whole. Herein, we discuss all currently known kinds of IAC as well as their mechanisms, if unraveled. We demonstrate that IAC is a special case of genotype×environment interactions requiring certain genotypes and, as a rule, prolonged exposure to the inducing influence. Most mechanisms of IAC are epigenetic; these include but not limited to DNA methylation, histone modifications, competition of transcription factors, induction of non-coding RNAs, inhibition of plastid translation, and curing of amyloid and non-amyloid prions. In some cases, changes in DNA sequences or host-microbe interactions are involved as well. The only principal difference between IAC and other environmentally inducible hereditary changes such as the effects of radiation is the origin of the changes: in case of IAC they are definite (determined by the environment), while the others are indefinite (arise from environmentally provoked molecular stochasticity). At least some kinds of IAC are adaptive and could be regarded as the elements of natural selection, though non-canonical in their origin and molecular nature. This is a probable way towards synthesis of the Lamarckian and Darwinian evolutionary conceptions. Applied issues of IAC are also discussed.

Key words: acquired characteristics, epigenetic inheritance, dauermodifications, genotrophic changes, transgenerational inheritance, intergenerational inheritance.

1. Introduction

The impact of the environment on all biological processes is very high; in particular, it significantly affects hereditary factors. According to classical genetics and evolutionary biology, such influence is realized via random mutations and recombinations, and therefore should always be indefinite (Lewis, 1980; Darlington, 1983; Mayr, 1988). However, some hereditary effects of the environment are definite, thus supporting the Lamarckian idea of inheritance of acquired characteristics (IAC).

First, various dauermodifications, environmentally determined phenotypic changes with limited heritability, were discovered (Jollos, 1913; Woltereck, 1919; Sonneborn, 1950). Although such changes have been known since the early 20th century, they were often regarded as 'untrue' inheritance. The fact is that most dauermodifications, under cessation of the inducing influence, persisted just for several generations, whereas 'true' inheritance should be potentially unlimited. Moreover, all dauermodifications, including quite stable ones (see Section 3), were almost non-transmissible via sexual reproduction. Now it becomes clear that inheritance, being either canonical or non-canonical, cannot be classified into 'true' and 'untrue' (Jablonka and Lamb, 2005; Tikhodeyev, 2015); so, dauermodifications deserve much more attention.

Second, several kinds of genotrophs, sexually heritable varieties induced by modified nutrition, were obtained (Durrant, 1962) including those that displayed stability in dozens of generations (Bogdanova, 2003; Chen et al. 2005). Similar effects can be produced by some other compounds which are neither mutagenic nor recombinogenic from the canonical point of view (see Section 4).

Third, numerous cases of so-called 'transgenerational inheritance' are known. In particular, they cover transmission of an environmentally determined characteristic from a parental organism (F0) over, at a minimum, one generation unexposed to the stimulus (Skinner, 2008; Tollefsbol, 2019). In addition, some acquired characteristics are transmissible just to the next generation; such cases illustrate 'intergenerational inheritance' (Skinner, 2008). Both terms

are traditionally used only in relation to sexual reproduction; here is again a rudiment of the idea that inheritance via asexual reproduction is ‘less true’ comparing to that via sexual one.

All of the three aforementioned phenomena are well-documented and, in some cases, the underlying mechanisms have been uncovered (see below). However, these phenomena are generally considered in isolation, thus strongly impeding the development of a comprehensive view on IAC as a whole.

Recognition of the IAC conception is additionally complicated due to the following problem. During Stalin’s regime in USSR, the Lamarckian views have been revived by Trofim Lysenko, an odious fighter against genetics and science-based breeding (see Section 2.4). Lysenko abandoned all the laws of genetics including the role of DNA as a hereditary material; he claimed that any matter within a cell can undergo heritable changes. Initially, this idea was totally groundless but, after discovery of epigenetic inheritance, it began to seem not so astonishing. Moreover, hereditary effects could potentially be produced by almost any mechanisms involved in gene expression and/or gene-product functioning (Jablonka and Lamb, 2005; Tikhodeyev, 2018). In this regard, epigenetic inheritance is sometimes interpreted as a direct molecular support of the Lysenko’s doctrine (Zhivotovsky, 2014). Thus, the principal question arises: whether the ideas of Lysenko should also be revived?

In the present review, all currently known kinds of IAC are discussed. For each case of IAC, we analyze the mode of its inheritance, the inducing environmental influence, and the underlying mechanism, if disclosed. This analysis allows us to suggest that there are no specific mechanisms of IAC: the examined phenomenon could be produced by almost any mechanism involved in DNA-mediated or epigenetic inheritance. We demonstrate that the IAC conception, being adequately updated, does not contradict the basics of current biology. On the contrary, the Lysenko’s doctrine should be rejected since any epigenetic hereditary factor, regardless of its molecular nature and the mode of inheritance, is a bimodular system with significant role of DNA.

2. Origin, rejections and revivals of the IAC conception

2.1. What are acquired characteristics?

It is basically mentioned that acquired characteristics (ACs) are any functional or structural changes gained by an organism during its ontogeny under specific environmental influences. However, this definition requires clarification: it embraces not only ACs but also some other kinds of environmentally induced changes.

First, Lamarck explicitly points out that ACs are not the direct effects of the environment but gradual responses of living organisms to longitudinal environmental influences (Shatalkin, 2009). Therefore, various types of diseases or injuries are not ACs; only organism reactions to such events could be taken into account.

Second, Lamarckian ACs are, *per se*, equal to Darwinian definite variations, uniform changes gained under specific environmental influences by all or almost all individuals treated (Darwin, 1869). The origin of definite variations is fundamentally different from that of indefinite ones: the formers are determined by the environment, while the latters are due to environmentally provoked internal fluctuations (for a review, see Tikhodeyev and Shcherbakova, 2019). In this regard, various phenocopies in *Drosophila* induced by heat shock during the critical stages of ontogeny (Mitchell and Petersen, 1982) do not belong to ACs since they are strikingly diverse in their manifestation. The same is relevant to induction of abnormal gametophytes in mosses by subjecting the haploid spores to X-rays or ethyl methane sulfonate (Engel, 1968). An efficient epimutagen 5-azacytidin does not also produce ACs due to high diversity of the resulting variants (Jones, 1985; Maletskaya et al., 2002; Akimoto et al., 2007). Notably, some molecular genetic approaches such as gene knockout technology (Tymms and Kola, 2001), when used in haploids under strictly specific conditions, induce uniform phenotypic changes via destruction of a certain targeted gene. However, this effect is not observed in all

treated cells (the efficiency of such technologies is comparably low); so, the obtained gene knockouts are not ACs.

Thus, ACs are definite changes gained by organisms during their ontogeny as the reactions to specific environmental influences.

2.2. The IAC conception: a brief overview

The idea that ACs are heritable is rather old. For many centuries, it was strongly believed that hereditary features of an organism could be modified by long-lasting environmental influences (López-Beltrán, 2007). The first scientific theory explaining this belief has been articulated in the early 19th century by Jean-Baptiste Lamarck in his book 'Zoological Philosophy' (Lamarck, 1809). Strictly speaking, Lamarck never uses the words 'heredity' or 'inheritance' in his theory: that time, the former had not yet been coined, and the latter was used only in terms of jurisprudence (López-Beltrán, 2004; Shatalkin, 2009). Nevertheless, Lamarck's Second Law which claims that '*All the acquisitions or losses wrought by nature on individuals, through the influence of the environment…, are preserved by reproduction in the new individuals…*' (Lamarck, 1914, p. 113; translated by H. Elliot) is exactly about heredity, in current terms.

Although the main Lamarck's interests relate to zoology, he illustrates this idea using both animal and plant species; so, IAC is implicitly introduced as a general biological phenomenon. However, Lamarck does not mention that any AC should be heritable. If an environmental influence is comparably short-term, it may affect an organism but the induced changes are reversible, as a rule. Only if the influence is continuous, especially covering many generations, can it cause heritable changes (Lamarck, 1809).

This idea became the first scientifically based conception of biological evolution; it has been thoroughly reviewed many times (Zirkle, 1935; Gissis and Jablonka, 2011; Burkhardt,

2013; Weiss, 2015), and therefore will not be further described herein. We'll just stress that Lamarck considers any indefinite variations as occasional and non-heritable.

2.3. Rejection of the IAC conception by Darwinism and classical genetics

Charles Darwin in his theory of natural selection does not insist that definite variations (i.e. ACs) are unhelpful for heredity, but gives clear preference to indefinite ones (Darwin, 1869). Unlike Lamarck, he suggests that evolution takes place via randomly occurring hereditary changes which are not determined by the environment; so, the role of the environment is limited to survival of the fittest. This viewpoint has further been accepted by most biologists especially after August Weismann published his germ-plasm theory (Weismann, 1892).

Weismann distinguishes two entities in an animal organism: germ-plasm, and soma. The former produces gametes, while the latter provides all other functions. Weismann claims that any AC affects soma exclusively, while only germ-plasm can transmit its hereditary material to the descendants; thus, no ACs should be heritable. This idea has been 'proven' in a long-term experiment on white mice: Weismann cut off their tails and crossed the tail-less individuals with each other in many sequential generations, but the length of the tails in the progeny remained the same (Weismann, 1889).

In the early 20th century, the Weismann's ideas appeared to be in good agreement with the mutation theory proposed by Hugo de Vries (1901, 1903). According to this theory, hereditary changes occur through mutations, random saltatory alterations having no similarity with environmentally determined Lamarckian ACs. In its turn, the mutation theory fitted well the laws of Mendelian inheritance which operated with discrete hereditary factors not depending on the environment in their origin (Bateson, 1902; Morgan, 1926; Johannsen, 1926). As a result, the Lamarckian conception has been refuted for several decades.

2.4. Revival of the IAC conception by Lysenko

Despite the strongly negative attitude given by Darwinism and classical genetics, the idea of IAC remained quite attractive; it was much easier to believe in definite hereditary effects of the environment than to recognize the existence of some indefinite variations subjected to invisible natural selection. Moreover, the Lamarckian conception has been revitalized by notorious Trofim Lysenko and his doctrine (Lysenkoism) during Stalin's regime in USSR.

Herein, neither methodological mistakes of Lysenko, nor his role in prosecution of Soviet genetics will be recounted: both have been comprehensively reviewed in numerous publications (Medvedev, 1969; Gaissinovitch, 1980; Roll-Hansen, 2005; Graham, 2016; Kolchinsky, 2017; deJong-Lambert and Krementsov, 2017). We will focus just on the origins of Lysenkoism.

Since the mid-1920s, Lysenko studied the impact of various environmental stimuli such as temperature and nutrition on agricultural plants. In particular, he has demonstrated that the exposure of wheat seedlings to prolonged chill (this approach was later called 'vernalization') resulted in significant acceleration of flowering, and this change appeared to be heritable in several sexual generations. Although the finding has been made using very few plants, and the initial material was not homozygous thus allowing segregation for unknown recessive alleles in the obtained progeny (for details, see Graham, 2016), Lysenko presented this fact as a proof of IAC, denying all the laws of classical genetics.

This 'discovery' is full of cruel ironies and ambiguities. First, in many plant species, vernalization is a true biological phenomenon (Chouard, 1960; Henderson et al., 2003) which effect is indeed heritable but only in asexual reproduction, as a rule (see Section III). Thus, Lysenko was not too far from the truth; however, his conclusions appeared to be dramatically wrong and caused extremely negative consequences.

Second, the effect of chilling on flowering time had been described long before Lysenko (Evelyn, 1662; Schwarz, 1837; Klippart, 1857; Gassner, 1918) but became widely recognized only after his highly announced statements that vernalization could provide quick and amazing

benefits for agriculture. If the biological effects of vernalization were better studied by their actual discoverers, the Lysenko's findings would not have attracted such attention.

Third, the Lysenko's pledges to improve agriculture initially seemed to be quite reasonable. At the Sixth International Congress of Genetics, outstanding Russian geneticist Nikolay Vavilov, one of the subsequent victims of Lysenkoism, assessed the Lysenko's ideas as very perspective (Vavilov, 1932). Even in 1948, when Vavilov had already died in prison, and genetics in USSR had been ruined, Vernalization and Photoperiodism Symposium was hold in USA, involving dozens of world-known plant biologists who considered the Lysenko's approach as revolutionary (Murneek and Whyte, 1948). Thus, the real harm of the Lysenko's ideology became obvious only after 1948.

Fourth, using his 'data' on hereditary vernalization, Lysenko drastically dismissed Mendelian genetics, and this opposition did not look groundless. The fact is that the basics of classical genetics are called 'the chromosome theory of inheritance' (Morgan et al., 1922; Morgan, 1926; Rhoades and McClintock, 1935). Meanwhile, numerous examples of cytoplasmic inheritance have been known since the early 20th century (Conklin, 1908; Correns, 1928) clearly demonstrating that non-chromosomal heredity exists as well. Thus, the absence of theoretical backgrounds covering all known types of inheritance allowed Lysenko to deny the hereditary role of chromosomes, and later, the hereditary role of DNA. Implicit transition to the DNA theory of inheritance in the mid-1950s (Portin, 2014) also did not solve the problem due to further discovery of epigenetic inheritance.

According to Lysenko, neither a specific matter, nor a specific part of a cell/organism provides heredity. These ideas, taken together with the strong belief in hereditary effects of the environment, brought Lysenko to a revival of the Lamarckian conception. As a result, the Lysenko's doctrine was usually regarded as neo-Lamarckism (Gaissinovitch, 1980; Graham, 2016; Kolchinsky, 2017).

2.5. Re-rejection of the IAC conception due to crush of the Lysenko's doctrine

The Lysenko's expectations to improve agriculture appeared to be a fiction, and in 1965 he fell into disfavor (Medvedev, 1969; Roll-Hansen, 2005; Graham, 2016). Both scientific and social consequences of his ideology were so dramatic that the name of Lysenko became a synonym of pseudoscience, and the IAC conception has been refuted again, even harder than previously.

Only in the 1990s, under the increasing interest to hereditary changes at the chromatin level, slightly positive references to the Lamarckian ideas began to appear (*Landman, 1991;* Jablonka and Lamb, 1995), but they were generally met without enthusiasm (Sang, 1995). Moreover, attempts were made to justify fundamental unreality of IAC. This task was impeded by the discovery of such phenomena as mitotic inheritance of chromatin structure in mammals, and stable genotrophic changes in plants; so, the opponents of the Lamarckian views had to distinguish IAC from the mentioned events. In particular, neurogeneticist Leonid Korochkin claimed that only those changes that (i) occur in organisms with clearly distinguishable soma and germ-plasm, (ii) affect soma, and (iii) are transmissible to the progeny via gametes might be attributed as IAC (Korochkin, 2006). He believed that these requirements were unrealizable and thus enough to borrow the Lamarckian ideas forever.

To explain such attempts the opinion of Michael Golubovsky is helpful: *"…unwittingly, many basic principles of classical genetics that were rejected by Lysenko achieved, in opposition to him, the status of an almost undisputed truth. When a serious scholar found something that apparently confirmed the Lysenko's views, he was afraid to make his discovery public, because he was afraid of being ostracized by the academic community*" (Golubovsky, 2001, p. 8.). Here is a spectacular example of how ideological frameworks, even made in good faith, eventually lead to strongly negative results.

2.6. Current attitude to the IAC conception

Although most ACs are not heritable, conventional criticism of the IAC conception was not enough cogent. The Weismann's experiment on mice had nothing to do with ACs: injuries do not belong to what Lamarck mentions as a continuous disuse of an organ (Shatalkin, 2009). The attempts to consider only the narrowest meaning of ACs (Korochkin, 2006) were deliberately purposed to cut off all the examples of non-canonical inheritance which could be interpreted in the Lamarckian sense. Meanwhile, in his 'Second Law' (see above), Lamarck does not imply any limitations in the organism structure or mode of reproduction. Thus, the phenomenon of IAC comprises any proven cases where definite changes gained by organisms during their ontogeny as the reactions to specific environmental influences are transmitted to the descendants.

The idea that the Lamarckian conception should be somehow synthesized with the Darwinian one has been voiced many times (Chernoff, 2001; Shatalkin, 2009; Gissis and Jablonka, 2011; Smythies et al., 2014; Penny, 2015; Schmidt and Kornfeld, 2016). Below, different variants of IAC and the underlying mechanisms are considered to map out the probable basics of such synthesis. Our task is not to scrutinize all known details, but to analyze the general regularities of the examined phenomena.

3. Dauermodifications

This term has been derived by German protozoologist Victor Jollos (1913) from two German words: 'Dauer' and 'Modifikationen'. The former means duration or durability, while the latter requires some comments. In the mid-19th century, Swiss botanist Carl Nägeli suggested using the word 'Modifikationen' to designate environmental effects on living things (Nägeli, 1865); only definite ones were implicitly mentioned. This suggestion has been accepted by many biologists, especially German and Russian ones (see Klebs, 1907; Filipchenko, 1929); so, the wording 'modificational variation' is still very common in Russian genetic literature as an equivalent of English 'environmental variation'.

According to canonical genetics and evolutionary biology, all changes determined by the environment should be non-heritable (Lewis, 1980; Darlington, 1983; Mayr, 1988). However, dauermodifications violate this rule. No wonder they were often viewed with outright skepticism.

Initially, dauermodifications (in English, they are sometimes called 'endured modifications'; see Rubin, 1990) have been described in ciliates. In these unicellular organisms, prolonged exposure (adaptation) to moderate doses of heat, cold, or some toxic compounds induces resistance to sub-lethal doses of the same stimulus (Jollos, 1913; 1921; Orlova, 1941). All cells of the treated culture become resistant, and the gained characteristic is heritable for dozens or even hundreds of mitotic generations after removal of the inducing factor, with eventual fading to the initial state. Since the fading is strongly provoked by fertilization, the molecular basics of dauermodifications in ciliates are likely macronucleus-specific (Jollos, 1921; Orlova, 1941) but their exact nature remains unclear.

Dauermodifications have also been obtained in *Daphnia* (Woltereck, 1919). Under prolonged maternal starvation, parthenogenetic descendants with definite morphological alteration were produced; this AC persisted in several normally fed asexual generations, and then vanished. The underlying mechanisms are still uncovered.

Another phenomenon closely related to dauermodifications is vernalization in plants, e.g. *Arabidopsis*. Exposure of seeds to prolonged chill induces repression of the *FLC* gene – one of the key regulators of flowering time – due to tri-methylation of H3K27 (H3K27me3) at the corresponding genomic region (Swiezewski et al., 2009; Heo and Sung, 2011). The gained epigenetic mark is reproducible in mitoses by POLYCOMB REPRESSIVE COMPLEX 2, with stable inheritance in vegetative generations even after regeneration from calli (Nakamura and Hennig, 2017). Fertilization leads to resetting of *FLC* expression; thus, the vernalized state is heritable only asexually, as a rule (Crevillen et al., 2014).

In theory, any environmentally determined epigenetic marks, if transmissible through mitoses but not sexual process, might promote dauermodifications. DNA methylation patterns are the most likely candidates because the mode of their transmission is similar to that of H3K27me3 (for a review, see Lebedeva et al., 2017). If the mitotic retention of an epigenetic mark is efficient, the resulting AC could display unlimited inheritance in asexual generations (like in vernalized plants); otherwise the AC should fade and eventually vanish. Apparently, this is the only difference between stable and unstable dauermodifications.

Under specific circumstances, both H3K27me3 and DNA methylation patterns can display meiotic heritability as well (Kakutani et al., 1999; Akimoto et al., 2007; Crevillen et al., 2014). So, it looks likely that some dauermodifications could be potentially transformed into meiotically heritable traits. This suggestion has already been proved for vernalization (Crevillen et al., 2014).

4. Genotrophic changes and related phenomena

The term ‘genotroph’ has been coined by Alan Durrant to designate sexually heritable morphological varieties induced in plants by modified nutrition (Durrant, 1962). Such varieties were initially obtained in flax using specific combinations of mineral fertilizers; under standard growing conditions, some of these genotrophs gradually reversed to the parental line, while others displayed unfading inheritance through self-pollination (Durrant, 1971; Cullis, 1979). Two stable ones, L (large) and S (small), have been involved in genetic analysis. The changes were shown to be very complex in their nature: they affected the total DNA content, copy number of the rRNA genes, microRNAs spectra, isozyme mobility, and some other molecular characteristics (Cullis, 1973; Tyson et al., 1978; Cullis and Charlton, 1981; Chen et al. 2005; Melnikova et al. 2016). But what exact changes relate to the modified phenotypes is unclear.

Using the same combinations of fertilizers, stable genotrophs have also been obtained in *Nicotiana rustica* (Hill, 1965), but their molecular nature is unknown. Notably, in both species,

only some lines can produce genotrophs, and prolonged exposure to the inducing agent is required (Durrant, 1962; Hill and Perkins, 1969; Bickel et al., 2012). Thus, genotroph induction is the result of genotype×environment interaction.

Some other components of nutrition are also effective in genotroph induction. In particular, these include high concentrations of niacin acid in wheat (Bogdanova, 2003), and 5mM guanidine-HCl in yeast (Cox et al., 1988). Each of these cases is of significant interest.

Wheat line Kazakhstanskya-126 treated with high concentrations of niacin acid gained a set of morphological and physiological changes stable in more than 65 generations of selfing (Bogdanova, 2003). At the molecular level, the obtained genotrophs differ from the parental line in DNA structure of three enzyme-encoding loci (Vinichenko et al., 2010), but whether these changes are principal for the gained phenotype is unknown.

In lower fungi, numerous amyloid hereditary prions have been described (Liebman and Chernoff, 2012; Tikhodeyev et al., 2017). Their propagation requires HSP104 chaperone activity which is repressed by 5mM guanidine-HCl (Wergzin et al., 2001). Thus, exposure to guanidine-HCl induces curing of such prions, and the obtained [*prion*¯] state is stably heritable both mitotically and meiotically (Cox et al., 1988; Tikhodeyev et al., 2017). Notably, curing of non-amyloid hereditary prion *C* in *Podospora anserina* can be achieved by heat, high concentrations of sucrose and some antibiotics (Silar et al., 1999).

Modified nutrition is conventionally thought to be neither mutagenic nor recombinogenic; so, genotroph induction is astonishing for canonical genetics. However, some other ‘non-mutagenic’ and ‘non-recombinogenic’ compounds can also produce definite sexually heritable changes. Streptomycin is a spectacular example. It inhibits plastid translation in various plants; under prolonged exposure to this antibiotic, all plastid ribosomes undergo degradation, and none plastid-encoded proteins can further be synthesized (Zubko and Day, 1998). Even after streptomycin removal, plastid ribosomes cannot be restored because a significant portion of their proteins is encoded by the plastid genome. The photosynthetic apparatus also degrades, thus

producing irreversible *albino* phenotype; this trait is unlimitedly heritable in vegetative generations and shows stable inheritance through ova in crosses with wild-type plants (Zubko and Day, 1998; 2002).

5. Environmentally determined transgenerational inheritance

5.1. The notion of transgenerational inheritance

The wording 'transgenerational inheritance' (Trans-I) has been widely used in genetics since the 1980s. It means that an epigenetic change determined by the environment or mutation is enough stable to persist over, at a minimum, one generation not exposed to the inducing factor. Namely, in case F0 is a female, the change should be transmissible at least to F3 (transmission to F2 might be promoted by specific effects on F1 gametogenesis due to the embryo development within the exposed maternal organism); in case F0 is a male, the change should be transmissible at least to F2 (Skinner, 2008; **Tollefsbol,** 2019).

In the aforementioned scenarios, the word **'**transgenerational' covers only the changes occurring in multicellular organisms and transmissible via gametes. However, this notion poorly fits the basic biological meaning of generations. First, in protists, fungi, plants, and even animals, various kinds of generations exist. Some of them are due to asexual reproduction like vegetative propagation in pseudo-annual plants (Hiirsalmi, 1969), reproduction by spores in mosses, ferns, and most algae (Miles and Longton, 1990), diploid parthenogenesis in *Daphnia* and some lizards (Cole, 1975), or callus induction and plant regeneration (Nakamura and Hennig, 2017). Second, in protists and fungi, alternation of haploid and diploid generations often occurs without gametes (Heitman, 2015). Third, such alternation is characteristic even of some unicellular organisms (Herskowitz, 1988). Finally, the results of subsequent cell divisions in microbes are also described as different generations (Fenchel and Finlay, 1991).

Thus, the traditional notion of Trans-I is nothing more than slang. To get a clear biological term, this notion should be expanded to all cases where an epigenetic change is

transmissible over at least one unexposed generation regardless of the mode of reproduction and organism complexity (Figure 1). Herein, we will use the expanded notion with appropriate clarifications like ‘mitotic Trans-I’, ‘mitotic-and-meiotic Trans-I’, ‘Trans-I in animals’, ‘Trans-I in bacteria’, etc.

Please, insert Figure 1 somewhere here.

5.2. Examples of environmentally determined transgenerational inheritance

Several kinds of such Trans-I have already been considered in previous sections. In particular, any stable genotrophic change is a mitotic-and-meiotic Trans-I induced by modified nutrition, while any abovementioned dauermodification is a mitotic Trans-I. Below, we will briefly discuss some spectacular examples of environmentally determined Trans-I in animals.

Under starvation, the nematode *Caenorhabditis elegans* can reversibly arrest its postembryonic development at the first larval stage (Baugh, 2013). This effect is programmed by drastic alterations in expression of protein-encoding genes, in part, due to upregulation of specific metabolism-controlling microRNAs (Zhang et al., 2011). Some of these microRNAs remain upregulated in normally fed F1, F2, and F3 thus promoting Trans-I of the gained metabolic changes (Rechavi et al., 2014).

In *Drosophila*, low-protein early-life diet causes shortened longevity (Xia and de Belle, 2016). The underlying mechanism involves histone modification: the level of H3K27me3 is significantly increased due to higher amount of E(z), a specific H3K27 methyltransferase (Xia et al., 2016). Even under normal feeding, the established hypermethylated state and the corresponding phenotype are transmitted to F3, with E(z) function required for this transmission. Notably, high-protein early-life diet also promotes Trans-I of shortened longevity (Xia and de Belle, 2016), but the mechanisms are yet uncovered.

Benzo[a]pyrene affects embryogenesis in zebrafish; it provokes a set of developmental disorders including deprivations in bone integrity, physiological deficits, and neurobehavioral impairments (Seemann et al., 2017; Knecht et al., 2017). After removal of the agent, such deprivations can retain in the offspring up to F3. The obtained effects are apparently due to benzo[a]pyrene-induced decrease in the level of global DNA methylation (Knecht et al., 2017).

In rats, exposure of gestating F0 females between E8 and E15 to vinclozolin, an antiandrogenic endocrine disruptor, promotes significant decrease of sperm number and motility in F1, F2, F3, and even F4 males (Anway et al., 2005). This Trans-I is orchestrated by a cascade of vinclozolin-induced epigenetic changes which affect DNA methylation at numerous genomic regions and are transmissible through spermatozoa (Skinner et al., 2019). Similar effects are caused by another endocrine disruptor, methoxychlor; in addition to impaired spermatogenesis, it increases the risks of obesity as well as kidney and ovary diseases, and this increase traces up to F3 (Manikkam et al., 2014).

5.3. Mechanisms of environmentally determined transgenerational inheritance

As usual, Trans-I is underlain by DNA methylation, histone modifications, or non-coding RNAs (Tollefsbol, 2019), but other mechanisms have also been described. Inhibition of plastid translation in various plants by streptomycin (see above) is a spectacular example: the induced ribosome-free plastids undergo consecutive divisions stably replicating this state and allowing its transmission via ova over an unlimited number of the unexposed generations. Interestingly, inhibition of plastid translation by high temperature does not produce Trans-I (Zubko and Day, 2002). This means that the same mechanism, depending on numerous circumstances, can either promote Trans-I or not (for more examples, see below).

Among non-trivial mechanisms of environmentally determined Trans-I, antibiotic-induced elimination of gut bacteria in *Drosophila* is noteworthy. Exposure of larvae to G418 provokes a set of phenotypic effects, which are transmissible up to F6 (Stern et al., 2012;

Fridmann-Sirkis et al., 2014). Such mechanism of inheritance, though rather exotic, is in good agreement with the Hologenome theory of evolution (Rosenberg and Zilber-Rosenberg, 2013) which claims that any multicellular organism is a biological community comprising the host and its microbial symbionts (Margulis and Fester, 1991), and that all the genomes of this community are collectively subjected to natural selection.

6. Environmentally determined intergenerational inheritance

Trans-I is traditionally opposed to intergenerational inheritance (Inter-I), where some substances (specific molecules or their chemical modifications) induced by a certain exposure are thought to be physically transmissible to the offspring but not reproducible in further generations (Skinner, 2008). Here, inheritance is again classified into 'true' and 'untrue': the former is believed to be promoted by induced substances reproducible in the offspring, while the latter is apparently due to those which are either removed or progressively diluted during ontogeny.

However, if the induced substances are highly stable and synthesized in significant amounts, their physical transmission might be enough to cause Trans-I, especially in unicellular organisms. On the contrary, if such substances are reproducible but display poor stability, they might provide merely Inter-I. Thus, the difference between Trans-I and Inter-I is not principal.

The mechanisms of environmentally determined Inter-I are poorly studied so far. DNA methylation and/or histone modifications seem to be the most likely candidates. This suggestion is based on the fact that the abovementioned mechanisms underlie Inter-I of some diseases conditioned by mutations affecting chromatin organization in mammals; Inter-I of cancer susceptibility promoted by knockout of the *Kdm6a* gene in male mice is a spectacular example (Lesch et al., 2019). However, cognitive improvement induced in mice by physical exercises – this AC is transmissible to F1 via spermatozoa – does not depend on the above mechanisms

(McGreevy et al., 2019). Thus, the mechanisms of environmentally determined Inter-I are apparently various but their spectrum remains to be uncovered.

7. Other kinds of IAC

A very interesting and still unclassified kind of IAC has been described in *Escherichia coli*. It is produced by a bistable digenic network constructed from the lambda phage genome: one gene consists of the P_L promoter linked to the coding region of *lacI*, while another is represented by the P_{trc} promoter linked to the coding region of *cI* (Tchuraev et al., 2000). Both *lacI* and *cI* code for transcription repressor proteins which targets are the P_{trc} and P_L promoters, respectively (Figure 2). As a result, the engineered genes display negative cross-regulation through their products; so, the system can be expressed in two alternative regimes depending on what gene product prevails, and the chosen regime is retained in further cell divisions (Tchuraev et al., 2000). Moreover, since the used cI_{857} allele encodes the temperature-sensitive protein, under exposure to 42°C, all the cells previously expressing *cI* are reprogrammed towards *lacI* expression, and the gained characteristic is stably transmitted over many hundreds of the untreated cell generations (Tchuraev, 2006). Here is, *per se*, an example of Trans-I in bacteria. The key distinctions of this IAC from all abovementioned ones are (i) the mechanism based on competing transcription factors, and (ii) specificity to prokaryotes, where neither meiosis nor mitosis exists.

Please, insert Figure 2 somewhere here.

Although canonical mutagens and recombinogens are environmental factors that efficiently induce hereditary changes, they do not relate to IAC because the promoted effects are indefinite (see Section 2.1.). However, ethidium bromide, a specific mutagen causing huge deletions in the mitochondrial genome, under prolonged exposure, produces complete loss of

mitochondrial DNA in yeast (Goldring et al., 1970). All the treated cells eventually become respiratory deficient, and can unlimitedly inherit this AC both mitotically and meiotically. Thus, some cases of IAC are underlain by definite changes in DNA sequences.

8. General view on IAC

8.1. Modes of IAC

Phenomenology of IAC is highly diverse, and this manifests in two aspects. The first one is the way in which an AC is transmitted to the offspring. Some mechanisms (for example, specific histone modifications in eukaryotes) involved in retention of an AC through asexual reproduction can be downregulated or switched off in sexual reproduction (see Allis et al., 2007; Lebedeva et al., 2017), but the opposite scenario is presently unknown. As a result, sexual heritability of an AC guarantees that the change is asexually heritable, but not *vice versa*. Therefore, we distinguish two ways of AC transmission: asexual-only and universal (asexual-and-sexual). Both are applicable for eukaryotes and prokaryotes as well. In particular, DNA methylation patterns in bacteria are transmissible not only in cell divisions, i.e. asexually, but also via conjugation which is, *per se*, a variant of sexual reproduction (Shin et al., 2016); here we deal with the universal way of transmission. Meanwhile, the gained expression of TF2 in the engineered bistable system in *E. coli* (see Section 7) apparently should be inherited asexually-only since transcription factors are scarcely transmitted through bacterial conjugation. This kind of IAC can be regarded as a dauermodification in bacteria.

The second aspect is the steadiness of an AC in generations. In some cases like stable genotrophs in flax and wheat, curing of prions by guanidine-HCl in yeast, or streptomycin-induced *albino* phenocopies in plants, an AC displays unfading heritability. However, in most dauermodifications and some genotrophs, an AC gradually fades in generations and eventually vanishes. Most spectacular fading is characteristic of Trans-I in animals, and especially of Inter-I

where an AC is transmissible just to the next generation. Basing on these facts, we distinguish unfading and fading IAC.

Two abovementioned aspects can be combined, thus producing four possible modes of IAC (Table 1). As a result, several non-canonical hereditary phenomena (dauermodifications, genotrophic changes, vernalization, hereditary prion curing, Trans-I and Inter-I) that were used to be considered in isolation become now the elements of the same general scheme. In our opinion, integration of these phenomena is very helpful since the edges between them are ambiguous, as a rule.

Please, insert Table 1 somewhere here.

8.2. Mechanisms of IAC

IAC can be orchestrated by a wide diversity of mechanisms (Table 1). These include but not limited to DNA methylation/demethylation, histone modifications, competition between transcription factors, induction of non-coding RNAs, inhibition of plastid translation, curing of amyloid or non-amyloid prions, changes in DNA sequences and host-microbe interactions. Most of the listed mechanisms are epigenetic.

Notably, different modes of IAC can be promoted by the same mechanism. For example, increased trimethylation of H3K27 serves as the basis of unfading asexual-only IAC in plants (Heo and Sung, 2011) as well as of fading universal IAC in *Drosophila* (Xia et al., 2016). In its turn, different mechanisms can underlie the same mode of IAC. In particular, unfading universal inheritance of a recessive cytoplasmic AC in yeast is based on either curing of amyloid prions (Wergzin et al., 2001) or elimination of mitochondrial DNA (Goldring et al., 1970). Thus, the knowledge of the mode of inheritance does not guarantee clear prediction of the underlying mechanisms and *vice versa*; this scenario is characteristic not only of IAC and seems to be one of

the fundamental biological taboos like well-known fundamental taboos is physics (for a review, see Sverdlov, 2009; Tikhodeyev, 2018).

9. Theoretical insights of IAC: rethinking Lamarck but rejecting Lysenko

The tremendous diversity of the mechanisms of IAC brings us back to the Lysenko's idea that the role of DNA in heredity is not crucial. At the beginning of the epigenetic era, especially when various mechanisms of protein-based inheritance had been discovered (Chernoff, 2007; Tuite, 2015, Tikhodeyev et al., 2017), such a view seemed to be quite acceptable. However, it has recently been shown that any epigenetic hereditary factor represents a bimodular system which features are cooperatively conditioned by DNA and epigenetic determinants (Table 2). In this system, a DNA determinant (DD) is a certain DNA region, while an epigenetic determinant (ED) is a specific epigenetic mark associated with DD or its molecular product, either RNA or protein (Tikhodeyev, 2018).

Please, insert Table 2 somewhere here.

If any of these two determinants undergoes non-lethal alteration, a novel hereditary factor occurs (Figure 3). It can either display its own manifestation or retain the effects of the initial one; the last case resembles silent DNA polymorphism.

Please, insert Figure 3 somewhere here.

Any bimodular hereditary factor (BHF), in which ED is associated with DNA, obligatorily possesses DD. Moreover, any BHF, in which ED is associated with a particular RNA or protein, reflects the existence of the corresponding DNA region, otherwise this molecule could not have arisen. Thus, the role of DNA is fundamental for all kinds of hereditary factors

including those involved in epigenetic inheritance and IAC. This means that the Lysenko's doctrine has nothing to do with epigenetics and should be rejected.

The features of any BHF depend on both its DD and ED. Meanwhile, some EDs can be definitely affected by the environment resulting in the arising of novel BHFs (Figure 3). In this regard, the IAC conception, being adequately rethought, becomes a full-fledged element of modern biology.

We rethink Lamarck's Second Law in the following way: *Some acquisitions or losses determined in living organisms by the environment through induction or repression of specific molecular processes can be preserved in the progeny*. This effect can be underlain by definite changes in DNA sequences, host-microbe interactions, EDs of some BHFs, or, in theory, both determinants of some BHFs. Depending on additional circumstances, such changes may vary in their modes of transmission, up to unfading universal IAC.

In good agreement with the Lamarckian conception, induction of unfading IAC requires prolonged exposure to the environmental influence. This is experimentally proven in many plant species (Durrant, 1962; Hill, 1965; Zubko and Day, 1998; Bogdanova, 2003; Henderson et al., 2003). In addition, to promote unfading IAC in yeast at least several cell generations should be exposed, otherwise the effect is indefinite or quickly reversible (Goldring et al., 1970; Wergzin et al., 2001; Tikhodeyev et al., 2017).

Ability of a particular species for IAC, even asexual-only, can be a significant benefit. This is evident in case of adaptive dauermodifications in ciliates (Jollos, 1921) or vernalization in vegetatively propagated plants (Henderson et al., 2003). Moreover, even fading IAC, if adaptive for sub-lethal environmental influence, might allow several generations to survive and thus improve the features of canonical natural selection. Thus, all the kinds of adaptive IAC could be regarded as the elements of natural selection (Stajic, 2019), though non-canonical in their origin and molecular nature. This is a probable way towards synthesis of the Lamarckian and Darwinian conceptions.

In particular, the updated view on IAC explains possible molecular basics of the Baldwin effect, an old idea claiming that acquired behavioral traits can be transformed into instinctive (i.e. heritable) ones by means of natural selection (Baldwin, 1896; Simpson, 1953).

10. Practical issues of IAC

These issues are presently evident in three areas. First, IAC can be applied in agriculture for obtaining new variants with improved characteristics like enhanced resistance to extreme environmental conditions in wheat genotroph induced by niacin acid (Bogdanova, 2003). Such variants might be especially helpful in vegetatively propagated plants, particularly as some EDs are effectively transmissible through regeneration from calli (Nakamura and Hennig, 2017).

Second, environmentally regulated genetic constructs with alternative hereditary states of expression, like digenic engineered system in *E. coli* (Tchuraev et al., 2000), could be applicable in microbial biotechnology, if periodical switching of these states is needed. Such a scheme does not require long-term supply of the stimulant agent (the chosen state will display unlimited heritability) and thus possesses significant benefit comparing to continuous stimuli usage.

Third, numerous environmental agents have been shown to promote Inter-I or probably Trans-I in humans (for a review see Shukla et al., 2019; Sun et al., 2019; Xavier et al., 2019), and the list of these permanently expands. Therefore, elaboration of test systems to assess potential risks of IAC induction is required. This task seems to be particularly relevant due to the problem of missing heritability: the impact of whole-genomic sequence polymorphism on various human traits is just a modest portion of that of the genotype (Zuk et al., 2012; Mayhew and Meyre, 2017). Missing heritability could be theoretically underlain by epistatic interactions between different polymorphic sites (Zuk et al., 2012), stochastic molecular processes affecting phenotype formation (Tikhodeyev and Shcherbakova, 2019), and epigenetic heredity (Bourrat et al., 2017). If the impact of the latter is significant, the environmental agents potentially causing IAC should become a new limelight in genetic toxicology.

10. Conclusions

IAC is a real biological phenomenon described in bacteria, protists, plants, fungi and animals. Probably, it also occurs in humans but to prove the definite nature of the induced characteristics additional thorough studies are required. IAC represents a specific case of genotype×environment interactions requiring certain genotypes and prolonged exposure to the inducing influence, as usual.

The mechanisms of IAC are highly diverse: they include various epigenetic ones as well as alterations in DNA sequences and host-microbe interactions. Notably, most of these mechanisms are involved in common DNA-mediated or epigenetic inheritance; thus, the only principal specificity of IAC is the definite origin of the environmentally induced changes. Depending on numerous additional circumstances, the same mechanism may promote different modes of IAC.

Basing on the aforementioned data, the IAC conception may be synthesized with canonical molecular genetics as well as with environmental and evolutionary biology. We propose that such synthesis will significantly enrich current biology with new fundamental and applied issues.

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Figure Legends

Figure 1. The principal scheme of intergenerational and transgenerational inheritance. The examined organisms/cells are shown as gray circles. In F0 female, the exposed ovum or F1 embryo is shown as an oval. In case reproduction is sexual, the same kinds of inheritance can be promoted by a mutation which is present in F0 individual but absent in the descendants.

Figure 2. The digenic system with two alternative hereditary states of expression due to the competition between the encoded transcription factors (modified from Tikhodeyev, 2018; the general idea is from Tchuraev, 2006). *lacI* and *cI* are open reading frames regulated by promoters, P_L and P_{trc}, respectively. The protein encoded by *lacI* represses transcription from P_{trc}. In its turn, the protein encoded by *cI* represses transcription from P_L. In this bistable system, simultaneous expression of both *lacI* and *cI* is impossible.

Figure 3. Possible changes of bimodular hereditary factors (BHFs).

A – BHFs, in which an epigenetic determinant (ED) is a specific mark covalently or non-covalently associated with a DNA determinant (DD).

B – BHFs, in which ED is a specific mark associated with the RNA/protein encoded by DD.

1 – initial BHF; 2 – its epigenetic null-allele; 3 – novel BHF due to alteration of ED; 4 – novel BHF due to alteration of DD; 5 – novel BHF due to alteration of both determinants. Alterations in DD are shown as black squares; the corresponding changes in RNA/protein sequences are shown as black circles. Other designations are as in Table 2.

Table 1. Modes, inducing influences, and mechanisms of IAC

Modes of IAC[1]	Examples of heritable ACs	Species	Inducing influences	Mechanisms of AC induction	References
Unfading universal	Altered morphology	*Linum usitatissimum*	Specific combinations of mineral fertilizers	DNA rearrangements, induction of non-coding RNAs	Chen et al. 2005; Melnikova et al. 2016
	Resistance to extreme environmental conditions	*Triticum aestivum*	0.1% niacin acid	Unknown	Bogdanova, 2003
	albino phenocopies[2]	Various plants	Streptomycin	Inactivation of plastid translation	Zubko and Day, 1998; 2002
	[*prion*$^-$] state for various amyloid prions	*Saccharomyces cerevisiae*	5 mM Guanidine-HCl	Inactivation of HP104 chaperone	Wergzin et al., 2001
	[*prion*$^-$] state for non-amyloid prion *C*	*Podospora anserina*	37°C	Unknown	Silar et al., 1999
	Respiratory deficiency	*Saccharomyces cerevisiae*	Ethidium bromide	Elimination of mtDNA	Goldring et al., 1970
Fading universal	Alteration of metabolism	*Caenorhabditis elegans*	Starvation	Induction of non-coding RNAs	Rechavi et al., 2014
	Shortened longevity	*Drosophila melanogaster*	Low-protein early-life diet	Increased level of H3K27me3	Xia et al., 2016
			High-protein early-life diet	Unknown	Xia and de Belle, 2016
	Deprivations in bone integrity	*Danio rerio*	Benzo[a]pyrene	Decreased DNA methylation	Knecht et al., 2017
	Decreased sperm number and motility	*Rattus norvegicus*	Vinclozolin	Alterations in DNA methylation	Anway et al., 2005
			Methoxychlor	Alterations in DNA methylation	Manikkam et al., 2014

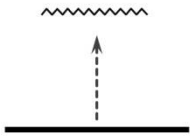
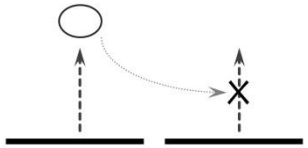
	Cognitive improvement	*Mus musculus*	Physical exercises	Unknown	McGreevy et al., 2019
	Decreased size[3]	*Mus musculus*	*In utero* undernourishment	Decreased DNA methylation	Radford et al., 2014
Unfading asexual-only	Switched state of expression	*E. coli*	42°C	Competition of transcription factors	Tchuraev et al., 2006
	Vernalization	Various plants	Prolonged chill	Increased level of H3K27me3	Henderson et al., 2003
Fading asexual-only	Tolerance to heat	*Paramecium*	Moderate heat	Unknown	Jollos, 1913
	Tolerance to salinity	*Paramecium*	Moderate salt concentrations	Unknown	Orlova, 1941
	Altered morphology	*Daphnia*	Maternal starvation	Unknown	Woltereck, 1919

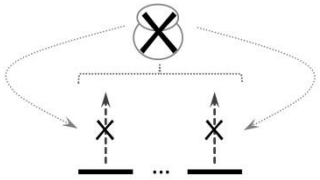
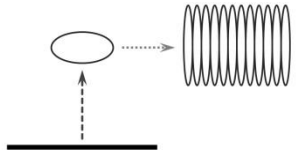
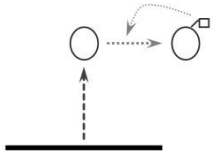
[1] In theory, unfading sexual-only and fading sexual-only modes of IAC might also be suggested. They would be possible if a certain environmental influence affected a higher eukaryote, causing definite transmissible changes in its gametes but not in somatic cells. Presently, such cases are unknown.

[2] Transmissible through ova

[3] Transmissible through spermatozoa

Table 2. Various types of bimodular hereditary factors (BHFs) which mechanisms relate to IAC

Type of BHFs	Certain example	DNA determinant[1]	Epigenetic determinant	Graphical designation of the BHF[2]	Generalized designation[3]
epialleles possessing chemical groups covalently associated with DNA	the *NMR19-4* epiallele in *Arabidopsis* (He et al., 2018)	genomic region *PPH*	certain distribution of 5-methylated cytosines		
epialleles possessing chemical groups non-covalently associated with DNA	the *FLC* epiallele gained through vernalization in *Arabidopsis* (Heo and Sung, 2011)	genomic region *FLC*	tri-methylated H3K27		
transgenerationally heritable small RNAs	starvation-induced microRNAs in *Caenorhabditis elegans* (Rechavi et al., 2014)	genomic regions encoding the microRNAs	synthesis of the starvation-induced micro-RNAs		
alternative states of a bistable digenic network	the *lacI*-expressing state of the bistable network in	P_L*::lacI*, P_{trc}*::cI*	*lacI* expression		

	E. coli (Tchuraev et al., 2000)				
self-reproducing absence of plastids ribosomes	hereditary *albino* phenocopy in tobacco (Zubko and Day, 1998)	plastid genes coding for plastid ribosomal proteins	the absence of the pre-existing plastid ribosomes		
alleles of amyloid hereditary prions	prion [PSI^{+}] in yeast *Saccharomyces* (Derkatch et al., 1996)	*SUP35*	certain amyloid form of SUP35p		
alleles of hereditary prions possessing chemically modified prion protein	prion *C* in *Podospora anserine* (Silar et al., 1999)	*PaASK1*, *PaMKK1*, *PaMpk1*[4]	the phosphorylated state of the PaMpk1-cascade proteins		

[1] determines the sequence(s) of the encoded protein(s) and/or RNA(s);

[2] black lines are DNA determinants; dark-gray arrows designate gene expression; light-gray arrows are alterations in the gene-product states, or the effects of epigenetic determinants; zigzag line is the encoded small RNA; various ovals are the encoded proteins and their aggregates;

[3] a DNA determinant is designated as a rectangle; an epigenetic determinant is shown as an asterisk; the encoded product (either RNA or protein) is shown as a wavy line; gene expression is designated as arrow;

[4] the listed genes code for three protein kinases of the PaMpk1 MAPK-cascade.

Highlights

- The Lamarckian concept of inheritance of acquired characteristics (IAC) is not outdated
- The mechanisms of IAC are predominantly epigenetic
- Any epigenetic hereditary factor (EHF) possesses bimodular structure
- Some EHFs can be definitely altered by certain environmental influences

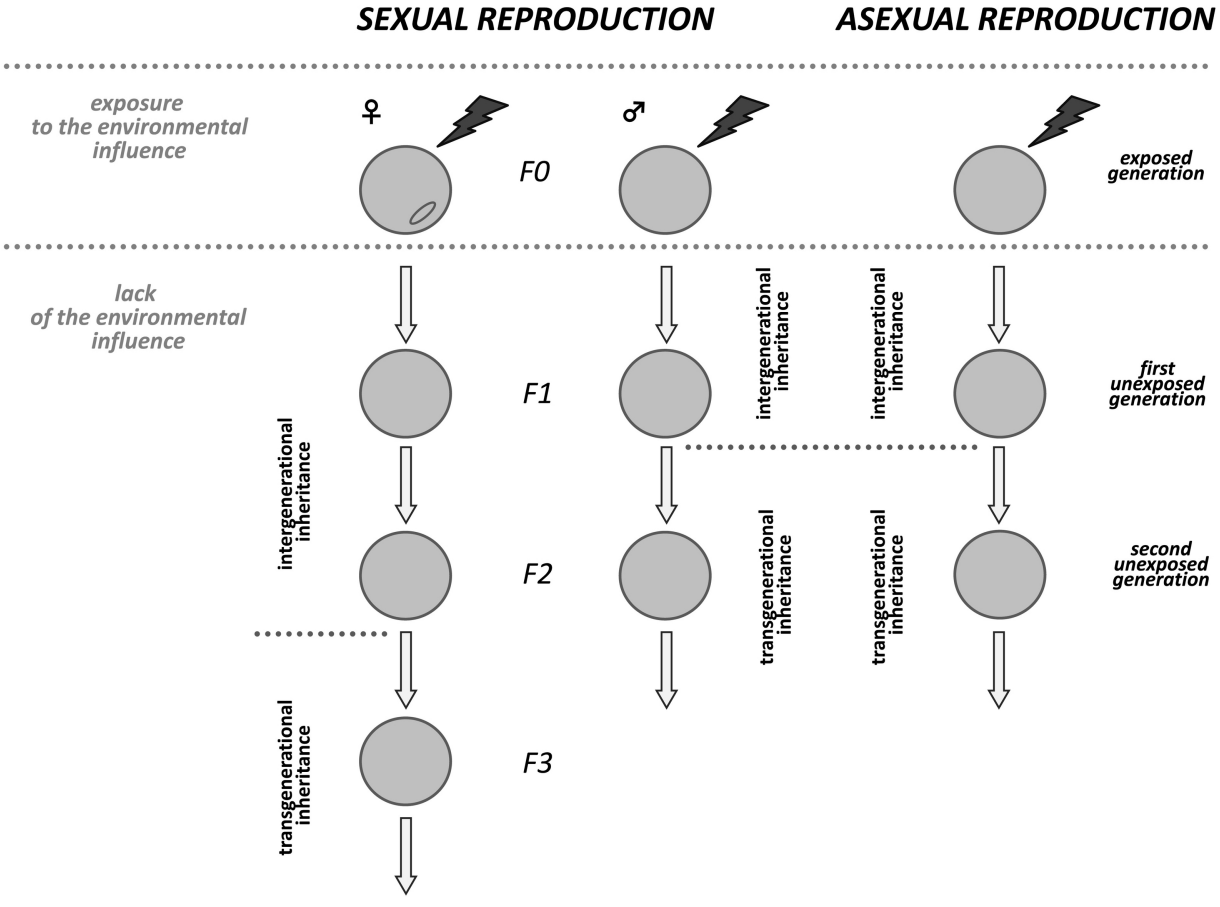
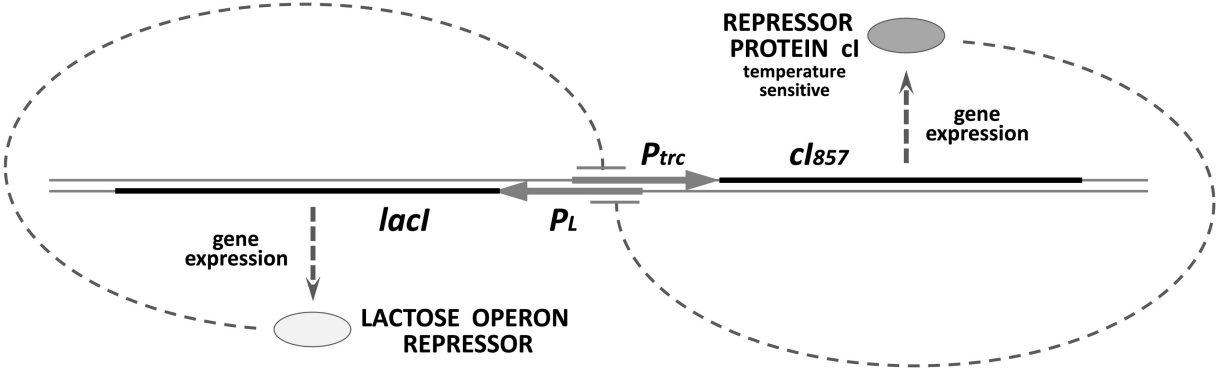

SEXUAL REPRODUCTION
ASEXUAL REPRODUCTION
exposure to the environmental influence
lack of the environmental influence
♀
♂
F0
F1
F2
F3
exposed generation
first unexposed generation
second unexposed generation
intergenerational inheritance
intergenerational inheritance
intergenerational inheritance
transgenerational inheritance
transgenerational inheritance
transgenerational inheritance

Figure 1


REPRESSOR
PROTEIN cI
temperature
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lacI
PL
gene
expression
LACTOSE OPERON
REPRESSOR

Figure 2

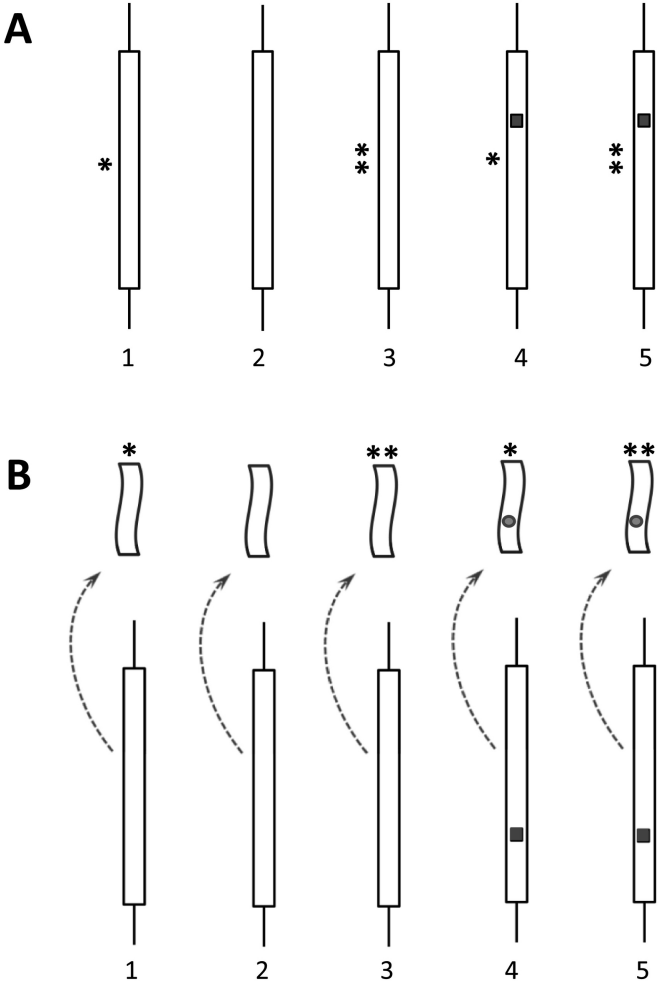

Figure 3