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Evidences For Lamarckism: A Review On Innate Mechanisms For Genome Modification, And Their Transgenerational Effects

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Abstract

Natural selection was established as the engine of adaptive evolution in the Modern Synthesis, owing to the elimination of alternative hypotheses. Lamarckism, particularly' mutational Lamarckism,' was one of the eliminated rivals, a theory that states that mutations may be directed toward developing phenotypes that increase an organism's performance in a certain environment. In contrast to this idea, the Modern Synthesis maintains that mutations are 'random,' despite the fact that the term's specific meaning has never been fully defined. Lamarck stated that evolution happened through the inheritance of acquired characters and traits. To put it in simpler terms, the theory states that changes are inherited through generations concerning the use and disuse of the organs or body parts of the organism. Lamarck was the first to provide a comprehensive theory of organic evolution, and he was the first to provide an elaborate explanation of it. This was an important moment in the museum's history as they had just lost the male elephant. The elephant's well-being had to do with Lamarck's findings, although it wasn't completely acknowledged at the point. We argue that the term "random mutation" refers to a triadic rather than a dyadic connection, present a new, formal, and exact definition based on the probabilistic idea of conditional independence, and lastly show how it might be used. The genetic specificity of the mutational process is not an essential requirement for the presence of mutational Lamarckism, according to our findings. So, the current review mainly focuses on innate mechanisms for genome modification, and their transgenerational effects.

Keywords: Lamarckism; innate mechanism; remodelling theory

1.Introduction

Darwin developed the theory of natural selection to better elaborate on the enormous diversity and adaptability of organisms. Darwin, through his findings, highlighted how organisms develop new or improved phenotypes to better adapt to the changing environment they live in, but even though Darwin put forward a fitting hypothesis, he failed to explain why in the first place the concept of natural selection arises in the first place. This gap or question was filled in Gregor Mendel through his mathematical model, which explained how the phenotype of an organism is linked to its genotype and how it is passed and inherited from parent to the offspring. Later, based on these findings in 1953 Francis Crick and James Watson published the Chromosome Theory of Inheritance, which explained how genes are copied and inherited. But this still did not solve the question of how the change was caused in the organism or the underlying cause for natural selection in organisms.

To address this question, Darwin put forward the theory of Pangenesis, which was later disregarded by scientists and classified as wrong. The theory stated how the changes occurring in an organism as a result of environmental influences could be passed on to the progeny without being encoded in the genetic material. But this concept of inheritance was widely disregarded. Even after a century or so, this question still remains unanswered of whether phenotypes that are not encoded in an organism's genome can be passed on to its progeny and how it is possible is still a great mystery. Hippocrates, "the father of medicine," who believed from his observations on a mythical race of people, the Macrocephali, firmly believed that characteristics were inherited by artificial means and later on it became an inherited character, and this practice wasn't necessary. Although various hypothesis has been put forward Darwin's theory of Natural Selection is one theory of evolution and inheritance that is widely accepted. (1) Recently, however, the name Lamarck has been making a gradual comeback into the scientific literature. The reason for this sudden burst is the emerging field of epigenetics, which is the study that deals with changes in gene expression that are not linked to changes in DNA expression. Some of these epigenetic alterations are passed on from one generation to another by violating the concepts of Mendel's model inheritance. It doesn't entirely support Lamarck's ideas, but it does state that epimutations can play a major role in evolution and in biology. Darwin did believe in the concept of inheritance of acquired characters, but the main difference between the views of Darwin and Lamarck was that Lamarck thought that evolution was initiated or driven by an inner need of an organism to adapt to its environment, such as the giraffe's neck whereas Darwin on the other hand stated that natural selection contributes to alterations rather than a vital inner force.

But as new theories and discoveries are made by the day science does raise the question of how Lamarck could be making a possible comeback and if so, could epigenetics be a deviation from the usual theory of Natural selection limiting the theories of Lamarckian ideas to merely concepts of Giraffes neck extension are not justified. Various claims state that Lamarckian theories hold good for many developments made in

the twenty-first century. Concepts and ideas of DNA methylation, histone modifications, and so on can be correlated to the Lamarckian idea of evolution. (2)

2.Theory of pangenesis

Through the years various evolutionary theories have been put forward by various scientists and researchers in order to provide a feasible explanation as to how and why life came into existence. The theory of Pangenesis was one such theory that accounted to fill a major gap in the evolutionary timeline. Proposed by Charles Darwin in the year 1868, the theory explains on the units of inheritance between parents and offspring and the processes which control the unit of inheritance.

In this theory Darwin proposed a new method in addition to cell division for the transfer of information. He introduced a new molecule known as "gemmules". He defined gemmules as molecules which are diffused and united with somatic as well as germ cells, these gemmules can be transmitted from parent to offspring (immediate generation). These gemmules may be activated or inactivated in the immediate progeny these gemmules are activated based on how they are united with other gemmules. it can also remain dormant and can be expressed as per the changing conditions of the environment, thus the composition of gemmules mirrors the changing environment of the organism. (3)

The theory of pangenesis provided an extension towards explanation regarding various theories of inheritance including Gregor Mendel's theory of dominance and inheritance of dominant characters. The theory of pangenesis also provided support towards Lamarckian theory of inheritance of acquired characters and the influence of the environment. Even though the theory put forward by Darwin supported Mendelian and Lamarckian views it was later disregarded due to lack of evidence. These molecules (gemmules) were not visible under the microscope and furthermore the pangenesis theory was replaced by August Weismann's Germ plasm theory which stated that information is transmitted from germ cells to somatic cells and not vice versa. (4)

The following review will focus on innate mechanism capable of restructuring genomes and their transgenerational effects.

3.Environmental influences on sex determination- Charnov bull model

In genotypic sex determination, the sex of the fetus is solely dependent on the chromosome or the genes present. Non genetic mechanisms of sex determination on the other hand includes the influence of external environmental factors such as temperature, chemicals, humidity and social interaction during a sensitive period in development. Temperature dependent sex determination is a widespread method of sex determination in reptiles such as crocodiles, turtles and a few species of lizards. The influence is the enzyme aromatase is one mechanism by which this phenomenon is explained. Aromatase plays an important role in the conversion of sex steroids from male to female. Low levels

of aromatase during the temperature sensitive period will induce male characteristics while high levels of aromatase will increase the production of female hormones. (Bull n.d.)

The Charnov-Bull model proposes the evolutionary significance of temperature dependent sex determination. The differential reproductive success rate influences TSD to evolve. The warmer temperatures cause the eggs to hatch earlier than normal. Therefore, the individuals tend to be bigger than average by the end of their first reproductive season. Young females are benefited from this as they may be able to lay eggs and are at an advantage over other females due to their increased reproductive potential. Young males, on the other hand exhibit no such advantage over others. (5)

4.Phenotypic plasticity in social insects

Phenotypic plasticity refers to the biological phenomenon where individuals with the same genotype exhibit variable phenotypes depending on their adaptability to varying external factors. (Baltimore and Press. n.d.) (5(1):9–1 n.d.) Eusocial insects such as those from the order Hymenoptera (ants, bees and wasps) and Isoptera (termites) exhibit caste polymorphism, which is defined as the precense of two or more morphologically different individuals of the same sex and genotype. (Gadagkar n.d.)

In bees, there exist a division of labor between the reproductive queens and the non- reproductive workers. In spite of sharing the same genotype, the diverse morphology and role in the hierarchy can be attributed to the difference in their nutrition at the larval stage. The nurse bees produce glandular secretions called jelly which contains all the macro and micronutrients required for larval development. The queen destined larvae is given the riyal jelly which is qualitatively superior to the worker jelly provided to the rest of the larvae. (2. Winston ML. 1991. The biology of the honey bee. Cambridge n.d.) (3. Haydak MH. 1970. Honey bee nutrition. Annu. Rev. Entomol. 15 n.d.)

5.Epigenetic mechanism for genome modification

The theory of transmission of acquired characters received a new strong ground by the advancement in the study of epigenetics. The term was first coined by Conrad Waddington who had been a keen supporter of the theory of acquired characters. He defined epigenetics as the interactions of genes with their environment which bring the phenotype into being" (Waddington, 1942). Epigenetic marks are modifications in the DNA or post- translational modifications in the histone proteins that can influence the activity or inactivity of a particular gene. These modifications make it possible for the single-celled zygote to differentiate into different types of cells and perform specific functions. The 25000-30,000 genes present in the DNA are selectively expressed based on the function performed in a particular tissue type. The main types of epigenetic modifications include DNA methylation, post translational histone modifications, Chromatin remodeling complexes, Histone variants and non-coding RNA's. In this review, the scope of DNA methylation is explored as a mechanism of inheritance and maintenance

of acquired characters. DNA methylation involves the addition of methyl group the 5' position of cytosine to form 5-methyl cytosine.

These methylated sites recruit additional proteins or factors that can affect the transcriptional activity of the particular sequence. This transfer is facilitated by a class of enzymes called DNA methyl transferases The methylation of a particular site is associated with its inactivity or silencing. Methylation plays an important role in development and exists as a dynamic process alternating between de novo DNA methylation and demethylation. (6)

6.Epigenetic inheritance in colorless non-ripening tomatoes (Cnr tomato)

Recorded case of epigenetic inheritance (transgenerational inheritance) of colorless non-ripening tomato or Cnr tomato. The Cnr "mutation" was first characterized at the phenotypic level: it inhibits normal ripening and fruits develop a colorless mealy fruit wall. This alternative phenotype is hereditarily transmitted following a Mendelian pattern, and as such was thought to be the consequence of a classical genetic mutation. But surprisingly it was shown that there were no sequence differences between mutant and wild-type DNA at the Cnr locus. The mutant phenotype is indeed the consequence of a hypermethylation of the gene that becomes inactivated. Such a hypermethylation, associated with gene silencing, is heritable and thus biologists' term "epimutation" those processes responsible for the creation of "epialleles".

7.Epigenetic reprogramming in mammalian embryos

In mammals, zygote formation is followed by an extensive period of epigenetic reprogramming that ensures the reestablishment of cellular totipotency. In the zygote, the male pronuclei undergoes rapid active demethylation with the help of TET enzymes which aid base excision repair to substitute and un-methylated cytosine. However, the female pronuclei undergoes demethylation in a gradual, passive fashion in a cell division dependent manner. These marks are re-established after implantation to aid gene regulation and cell differentiation. (Fraser R, 27601712 and PMC5097126. n.d.). Alterations in DNA methylation caused by varying environmental conditions such as food scarcity, tobacco smoke, pollution, stress, metals, chemicals, microbiome, etc. can result in hyper or hypo methylation. (1, 30388784 and PMC6275017. n.d.). These defects in methylation have been observed to be associated with various pathological conditions like cancer, elevated stress levels, diabetes. Various human epidemiological studies were conducted to understand the influence of environment on the physiology and state of an individual.

8.Dutch hunger winter- exposure to nutritional deficiency during early embryonic development

The first example is the Dutch famine or the Dutch hunger winter. Towards the end of the second world war, food supplies to the Netherlands were halted and lead to severe food

scarcity. By the time Netherlands was liberated, 20,000 people had already died and those that survived carried the scars of the famine. Pregnant women were especially vulnerable and children they gave birth to suffered the ramifications throughout their lifetime. (3. Roseboom T and Scholar] n.d.) A 10 percent increase in mortality rate was observed 68 years after the famine. Further investigation of this statistical discovery showed that exposure to the famine during preconceptional period had resulted in individuals born during the famine to suffer from increased metabolic and mental disorders such as coronary artery disease (CAD), schizophrenia, diabetes and obesity as compared to those born before the famine or after the famine. (9. Stanner SA and Scholar] n.d.) (sheep. n.d.) However, these parents produced normal healthy offspring in the next generation. These effects have been linked to altered DNA methylation at various locus when compared to the control group. (Tobi EW n.d.). (7)

9.Influence of maternal care on rat stress response

A similar case can be observed in the case of rats exposed to poor maternal care during early childhood. Mother rats spend a lot of time licking, grooming and nursing their pups and this plays a crucial role in their development. (Bridges n.d.) The well nurtured pups grew up to be calm adults. Rat pups grown by a stressed mother grew up to be anxious adults. (Champagne n.d.) (Liu n.d.). The absence of the nurturing environment caused by the methylation of certain regions of the DNA resulting in its silencing. These silenced regions interfered with the production of a glucocorticoid receptor which binds to the steroid cortisol. A stress response elicits the production of cortisol which binds to GR in the hippocampus. When enough number of receptors are occupied, the stress response is switched of. However, in these rats, the malfunctioning receptors prevent effective binding with the steroid resulting in anxious behavior. The role of methylation was confirmed by injecting mice with a chemical called methionine which reverses methylation. The administration of methionine tends to calm the mice down, thereby confirming the association of hyper methylation to the stress response. (American College of Neuropsychopharmacology. "High levels of maternal care has life-long impact on vulnerability to stress n.d.) (8)

10.Liver damage in mice

A study was conducted in rats that suffered liver damage. Liver damage in rats elicits a certain wound healing mechanism which involves histone modifications such as methylation in genes linked to fibrosis. (Hardy T, 27624887 and PMC5099193. n.d.) Such changes were also observed in sperms and thus the offspring of such organisms were better adapted to surviving liver damage. This study also produced another interesting observation linked to the effect of serum transfer from animals exposed to liver damage to a control group. The control group expressed the same transgenerational phenotypes. (Hardy T, 27624887 and PMC5099193. n.d.) This suggested that a factor present in blood must be responsible for mediating epigenetic changes in the germ cell. (9)

All these case studies have succeeded in showing the role of the environment in the phenotype of an organism. But if we look closely, we can see that these modifications in response to the changing environmental conditions have also shown to be advantageous. Sometimes, the altered environmental conditions stimulate better adaptive capabilities which helps in surviving the new unfamiliar or unfavorable environment. In the first case, it was observed that the individuals exposed to the severe famine at preconceptual stage was more likely to survive if they were to be exposed to these adverse conditions again. Their bodies are accustomed to functioning at low nutritional levels. The thrifty phenotype hypothesis was put forward to explain this phenomenon. The food scarcity during embryonic period encourages the body to store energy for later use. When exposed to large amounts of food, the body stores it rather than using it leading to obesity and other related conditions.

Similarly, the anxious mice are more likely to survive in an environment plagued by food scarcity and danger from predators. The anxious rat is always on its guard and respond quickly to stress and maintain a low profile whereas the relaxed rat is more likely to be attacked by predators. These observations point to the fact that organisms are capable of adapting their physiologies to survive an adverse situation or a change in habitat. These variations that make them better suited to survive in this new environment may not be entirely random as proposed by Darwin but a more complex survival mechanism triggered by need.

11.Assisted reproductive technology

Assisted reproductive technology involves medical procedures that are used to treat infertility, and involves handling of gametes or embryos using techniques such as In-vitro fertilization (IVF), Intra-cytoplasmic sperm injection (ICSI), embryo culture and embryo cryo-preservation. More than 5 million children are born worldwide with the assistance of ART and it accounts for roughly 0.3% of the total births. The high success rates of ART have lead more people into seeking it as a first line of therapy in cases of infertility or reproductive disorders.

ART treatments are considered safe, however certain adverse obstetric and perinatal outcome such as low birth weight, small for gestational age, diabetes and CVD risks, and obesity have been associated with its use. Children born by ART has also been shown to be at a higher risk of developing imprinting disorders such as Beckwith-Wiedmann syndrome (BWS), Angelman syndrome (AS) and Silver Russell-syndrome (SRS). These aberrant phenotypes have been linked to the altered culture environment and improper handling of the gametes and embryos. (DeAngelis AM and 30866009. n.d.). The genome undergoes several rounds of epigenetic remodelling during gametogenesis and the early embryonic period. These are key points in development and any alteration in the environment, external or internal can lead to aberrations during zygote and embryo formation. Assisted reproductive technology involves the manipulation of the embryo or the germ cells during these crucial stages to artificially produce a zygote. (10)

In-vitro fertilization involves multiple procedures such as superovulation, manipulation of the embryo, embryo culture and transfer, embryo and gamete exposure to altered hormonal environments, oxygen tension and Ph. These exposures occur at sensitive periods in epigenetic reprogramming. Epigenetic reprogramming involves removal of existing epigenetic marks and establishment of new ones which are maintained in the dividing embryo and persist through adulthood. Some genes within the genome are expressed in a parent of origin specific manner. The selective expression of genes depending on the sex of the parent from which its passed on is called genomic imprinting. Genomic imprinting doesn't affect the sequence of DNA itself, but rather, the expression is regulated by chemical modifications such as methylation, acetylation, histone modifications or via long non-coding RNA's. Mutations resulting in improper imprinting can lead to various imprinting disorders. Angelman syndrome and Prader-Willi syndrome are two distinct diseases caused by mutations in the same part of chromosome-15. When the deletion occurs in the chromosome 15 that came from the mother, the child develops Angelman syndrome and when the deletion occurs in the chromosome 15 that came from the father, it's called Prader-Willi syndrome.

Beckwith-Wiedman syndrome is the most widely studied imprinting disorder and is characterized by macroglossia, macrosomia, abdominal wall defects and a predisposition to tumorigenesis. A vast majority of BWS is caused by the dysregulation of imprinted genes on chromosome 11p15 consisting of two imprinting domains, IGF2/H19, CDKN1C/KCNQ1OT1. The epigenetic and genetic causes of BWS includes loss of methylation, gain of methylation, paternal uniparental disomy, mutations and chromosomal rearrangements. (11)

Somatic cell nuclear transfer, commonly referred to as cloning is a technique in which the nucleus of a somatic cell is transferred to an enucleated oocyte, after which the somatic nucleus is reprogrammed by the egg cytoplasmic factors to produce the zygote. This technology has attracted great interest worldwide because of its potential applications in biomedicine and animal husbandry. However, the occurrence of genetic abnormalities such as low birth rate, large offspring syndrome and placental dysfunctions appear to be in the way of efficient cloning. SCNT involves remodelling and dedifferentiation of highly differentiated somatic cells to a totipotent embryonic cell. Defects in reprogramming has been associated with the decreased efficiencies and developmental abnormalities.

12.Cancer epigenetics

Drug resistance is a major challenge in the treatment of cancer. It is seen that in patients suffering from cutaneous melanoma tumours carry BRAF mutations which result in the activation of the mitogen-activated protein kinase which helps in the survival and rapid multiplication of the cell. In a study conducted in 2011 it was seen that vemurafenib, a drug that targets the cells with BRAF mutations. Suggestively improved progression-free survival over the conventional chemotherapy drug dacarbazine However, resistance

soon evolved in patients treated with this drug and with another BRAF targeting drug, dabrafenib, due to continued activation of the MAPK pathway through downstream targets of BRAF such as MEK. In 2015, another multicentre, double-blind clinical trial showed the improved efficacy of combined therapy with dabrafenib and trametinib, resulting in related BRAF and MEK inhibition, over treatment with dabrafenib alone. Nevertheless, about half of patients treated with this combination drug therapy still progress after 12 months. How does this resistance develop and why?

The current model proposed to determine tumour drug resistance is a mutational model, this model states that the cells on treatment or before treatment acquire additional genetic alterations that provide them with the capacity to outgrow their neighbours become immune to therapy and thereby also escape immune surveillance. Studies have shown that once resistance is obtained in BRAFi or MEK-treated tumours the MAPK pathway is seen to be reactivated. This occurs through mechanisms such as BRAF amplification, mutations in MEK and oncogenic mutations in NRAS. But it was seen that the resistance still developed even though the somatic mutations were targeted sequentially. This led the researchers to discover that there must be more to this than the mutational model. The mutational model isn't representing the entire concept, there are other mechanisms through which the resistance develops. (12)

The study seeks to study the mechanisms of acquisition of therapy resistance in BRAF V600E/K-mutant melanomas treated with BRAFi/MEKi. The method used was patient- derived xenograft models of BRAF V600E/K-mutant melanomas and exposed mice to BRAFi/MEKi treatment with the drug combination of dabrafenib/trametinib combination. Three phases of treatment responses were involved. Phase one involved a rapid tumour shrinkage phase, phase two consisted of a phase where the tumour became impalpable and phase three consisted of a phase where the tumour relapsed. However, it was seen that the cells sampled from phase two where the minimal residual disease/MRD remained did not show significantly different genomic profiles from cells taken before the tumours were exposed to BRAFi/MEKi. This result led the researchers to come to conclusion that the MRD was established in this model through means of non- mutational mechanisms.

The next step done was that the researchers expansively considered the MRD cell population by single cell RNA sequencing and pseudo-time analysis. The result showed "starved-like melanoma cells" or SMCs which showed that the drug exposure brought about transcriptional state characterized by an intermediate MITF or Melanocyte Inducing Transcription Factor activity and a gene profile remainder of nutrient deprived cells. The cells were observed to move along a differentiation trajectory to become either a pigmented subpopulation. It was characterized by elevated MITF activity and markers of differentiation and pigmentation or take up a de-differentiated state which has the ability to either become an invasive phenotype which is marked by the expression of epithelial to mesenchymal transition markers or the cells have the ability to become a neural crest stem cell/NCSC population which is marked or characterized by high

expression of NCSC markers. All the subpopulations were drug tolerant and it was observed that all these different states were seen to co-exist in MRD.

The NCSC subpopulation was a noteworthy one as it increased dramatically as the tumour was shrinking during the course of drug exposure. The cells had the property of being able to reversibly transition into the desired state through phenotypic switching. It was also analysed that the cells initially did not display NCSC markers but upon drug exposure it was seen to exhibit NCSC markers and the marker expression was lost upon drug removal. This supports the theory of how a non-mutational phenomenon is involved in the case of these tumours. It also seemed to be independent of genetic background and mutational state, as it was seen both in NRAS-mutant and triple wild-type melanoma cell cultures. It was also identified the retinoid X receptor Y (RXRG) as a key driver of the NCSC state through a gene regulatory network analysis and showed that targeting it together with BRAFi/MEKi can significantly delay the development of resistance. (13-20)

These results highlight a non-mutational mode of drug tolerant or resistant state in cells, this is further followed by acquisition of somatic mutations that provide the drug tolerant state of cells with a growth advantage. It can be said that drug resistance takes a path of both Darwinian selections powered by somatic mutations and moreover a strong path of Lamarckian induction driven by epigenetic changes and transcriptional plasticity. It can be concluded that a better adapted cell state comes as a result of the environmental influences and changes, these are then inherited by daughter cells. These theories revealed that in this study of how NCSC population emerged independently without regard for genetic background and at a specific phase tumour i.e. phase three tumours after relapse carried resistance associated mutational events.

Drug resistance is a major challenge in cancer treatment. Although there hasn't been a clear-cut understanding of why this happens, studies and cases such as these could provide a better understanding to this phenomenon. Epigenetic changes as part of theories put forward by Lamarck hold good while examining cases such as these and do provide possible understandings and explanations. This mechanism may represent a non- mutational mode of inheritance which differs from the usual mutational model of inheritance.

13.Conclusion

It was Jean Baptiste Lamarck who first proposed a fully thought theory regarding evolution, but it didn't hold good for long it was disregarded by various scientists and researchers. Through the course of this review, the scope of Lamarckism has been reconsidered under the light of modern-day evidences and theories concerning evolution. Three separate mechanisms of non-genetic genome modification under the influence of the environment has been analyzed and discussed. The Chernov bull model for TSD has also successfully incorporated the importance of natural selection in the maintenance of environmentally determined characters. Instances through the years such as the Dutch famine shows us how the environment has drastically influenced

organism's development and the characteristics of their offspring's. This leads us to the question of whether there was more to the Lamarckian theory than what was interpreted, could it easily be neglected in a period where the field of epigenetics is highly developing? It may be highly possible that there is more to explore and understand on a concept Lamarck had once put forward. What was once just an observation and one of the first evolutionary theories that was put forward may pave the way forward to obtaining answers to concepts such as drug resistance, cancer treatment, genetically inherited diseases and so on. It is possible that a once neglected theory can hold great importance in answering many questions in the coming generations.

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