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Opinion

Genes, genome and Gestalt

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ABSTRACT. According to *Gestalt* thinking, biological systems cannot be viewed as the sum of their elements, but as processes of the whole. To understand organisms we must start from the whole, observing how the various parts are related. In genetics, we must observe the genome over and above the sum of its genes. Either loss or addition of one gene in a genome can change the function of the organism. Genomes are organized in networks of genes, which need to be well integrated. In the case of genetically modified organisms (GMOs), for example, soybeans, rats, *Anopheles* mosquitoes, and pigs, the insertion of an exogenous gene into a receptive organism generally causes disturbance in the networks, resulting in the breakdown of gene interactions. In these cases, genetic modification increased the genetic load of the GMO and consequently decreased its adaptability (fitness). Therefore, it is hard to claim that the production of such organisms with an increased genetic load does not have ethical implications.

Key words: Gene network, Genetically modified organism, Gestalt, Genetic load, Bioethics

INTRODUCTION

From macrocosm to microcosm, all systems are organized in levels. The systems make up the whole, and each of them can be considered as a *Gestalt.* The German term *Gestalt* means form or figure, and *Gestalt* thinking views phenomena as indivisible organized totalities, articulated in configurations. Descartes' scientific method advocated that, in order to understand nature, it is necessary and sufficient to have a detailed understanding of the function of the parts that are the fundamental elements. In contrast, *Gestalt* theory involves a perception as a whole rather than as a juxtaposition of parts. Therefore, as *Gestalten*, the systems cannot be observed separately.

Seen like this, physiological processes cannot be viewed as simply a sum of elements, but rather as processes of the whole. The whole must be considered as something different from the mere sum of the parts, since no part of the system can change without changing the system in its entirety. These are the principles of *Gestalt* theory, as established by Max Wertheimer, Wolfgang Köhler and Kurt Koffka in early nineteenth-century Germany. According to them, perception is a combination of individual sensations, in which we perceive the environment in terms of its organizational structure, through related properties. To understand organisms we start from the whole, observing how the various parts are related. The removal or functional loss of one of the parts compromises the organism (Engelmann, 2002).

In genetics, the thousands of genes that make up organisms must act as an entirety (genome) so that the organism may function normally. Either loss or addition of one gene in a system (organism) can change the function of the whole. The composition of a phenotype is governed by the interaction of different genes with the environment. There is interaction on two levels: interaction between the genes within the organism, and the integrated expression of these genes with the effect of environment.

What is vital is the total form rather than the elements that can separate themselves from the being they belong to. Genetically, organisms are organized in networks of genes. They are separate networks, and for organisms to function properly, these networks need to be well integrated. Networks work at a variable equilibrium. In the human organism, there are genes that act alone in the determination of phenotype, genes that can be turned off and many other genes with extremely varied levels of expression.

The variations in the levels of gene expression occur in accordance with various factors, including temporal, metabolic and hormonal differences. One example of how networks function is the circadian cycle or biological clock, which controls our biological rhythm in accordance with day and night signals. This mechanism modulates arterial pressure, mental performance, hormonal secretions, etc. It is known that modifications in the genes that control the circadian cycle alter the homeostasis of the individual, making them more susceptible to infections, changing their mood, their ability to reason, etc. Many blind individuals experience sleep disturbance because their circadian system for light and dark is not synchronized with day and night (La Fuente et al., 2002). Taking this and other examples of how gene networks function into account, genomic analysis truly merits a *Gestalt*-based approach as much as one based on elements.

Biological systems are orchestrated by means of selective expression of genes. Levels of gene expression may vary, depending on various endogenous and exogenous factors. Studies using the DNA microarray technique, which simultaneously analyzes the pattern of expression of many genes, show how some genes control the expression of other genes. This tech-

nique allows us to simultaneously quantify the content of different messengers RNA (mRNA), so that genetic activities may be measured. It also allows the expression of the functional genome to be analyzed, and by understanding the profile of gene expression we may understand how metabolic pathways behave. A disturbance in a metabolic pathway caused by a variation in the expression of a gene can be detected by the DNA microarray technique. This is the most sensitive technique for finding gene expression variations associated with changes in biochemical pathways.

Indeed, in contrast to the traditional reductionist analysis of gene function, DNA microarray technique permits *genomic* analysis, raising genetic analysis to a holistic level or to a systemic vision of biology, putting the genomic picture above the functioning of genes or networks of genes. Another useful procedure is metabolic control analysis, which uses biochemical reactions to measure the metabolic state of the cell at any determined moment. By combining these two types of analysis, the cell's state of activity can be deduced. By disturbing the cellular system, modifications in mRNA concentrations can be observed, which point to a change in the gene expression pattern. Thus, mRNA concentrations are measured for different genes in two different metabolic states of the cell. Before applying metabolic stress, the microarray plate supplies a matrix for the state of gene activity. After stress, another matrix is obtained, and the two are compared. Differences in mRNA concentration levels before and after stress for the genes in question are then compared, as well as making comparisons with the other genes in the matrix.

Mendonza (1999) have shown that the process of morphogenesis in flowers of *Arabidopis thaliana* takes place via an integrated network of genes, following the principle of biochemical kinetics. As indicated by *Gestalt* theory, two or more stimuli may interact and produce effects that cannot be predicted from our knowledge of the action of components acting in isolation. This same reasoning can be extrapolated for two or more genes, which may interact to give unforeseen phenotypes.

GENETICALLY MODIFIED ORGANISMS

In the evolutionary history of species, spontaneous mutations that give rise to new allelic forms submit the organism to a period of adaptation to this new gene, which may be favorable or unfavorable to the previous form. The transformation of a single element reflects on the group as a whole. In the case of genetically modified organisms (GMOs), where an exogenous gene has been inserted into a receptive organism, this network of genes is disturbed by the integration and expression of the exogenous gene. This disturbance modifies the orchestration of the network, resulting in the breakdown of epistatic relations, provoking alterations in feedback mechanisms that regulate gene expression, in the occurrence of mutations by inactivating other genes, and other interactions that may turn genes in the host genome on or turn off.

One example of this adaptation to a new gene among transgenic plants is the genetically modified soybean. Inserting the gene CP4-EPSPS from *Agrobacterium* destroyed the harmony between gene networks and changed the metabolism and production of lignin, a substance that physically sustains the plant. This has meant that when this genetically modified soybean is planted in soils where temperatures go over 45°C, the stem cannot withstand the heat and breaks down. In addition, the metabolism of phytoestrogen is also altered, implying that at least two gene networks have been disturbed.

The insertion of an exogenous gene by biolistics provoked a disturbance in one of the networks of the gene system, which was reflected in the network system as a whole, i.e., in the functional genome. Biolistics is one of the most frequently used techniques in the production of GMOs, and consists of coupling DNA (the gene) with particles of gold or tungsten, which are then inserted in the receptor genome. This method has some disadvantages: its results are unpredictable, since multiple integrations can be randomly generated in the receptor cell genome, both of the gene and of the DNA fragments. This can provoke other alterations in the way the genome functions in the receptor cells, such as the silencing of certain genes and the excessive expression of the exogenous gene, causing unforeseen consequences for the receptor organism's metabolism. When the integrated functioning of the genes in an organism is changed, this alteration is probably much more disadvantageous than advantageous, since it involves the modification of a biological model that was the result of a long evolutionary process. In other words, the consequence of genetic modification is an increase in the plant's genetic load. We know that there is an inverse correlation between the genetic load and the adaptive value (fitness). This means that GMOs tend to have less adaptability in proportion to their increased genetic load. These are classic evolutionary concepts that should be considered when GMOs are produced. These methods can be seen as a violation of genetic integrity, because they involve an unpredictable manipulation of living organisms.

In genetically modified rats, DNA microarray technique has confirmed that the introduction of an exogenous gene induced an unexpected expression of a group of genes involved in the cellular response to stress (Panda et al., 2003). The development of genetically modified *Anopheles stephensi* mosquitoes, in an attempt to prevent malaria transmission, was only successful in the laboratory. This is because in the wild this genetically modified mosquito has a reduced capacity for survival and reproduction, being less adaptable than wild mosquitoes. Tests demonstrated that the insertion of the exogenous gene blocked the expression of an important *Anopheles* gene (Catteruccia et al., 2003). One of the first reports exposing welfare problems associated with the use of biotechnology is the case of the "Beltsville pig". The Beltsville pig, which had human growth hormone genes to accelerate growth, suffered from health problems, such as lameness, ulcers, cardiac diseases, and reproductive problems (King, 1996; Rollin, 1997). Currently, safe manipulation techniques are already being developed, which involve precise and predictable manipulations, with minimum perturbation of the long-established systems. One of these new techniques of DNA insertion, based on the natural mechanism called transposon movement, allows plants to relocate their DNA, reducing the disruption caused by genetic manipulation.

Genetically modified organisms are constructed to meet a human need for production of some kind of protein or hormone, to express a certain resistance or some other type of desirable phenotype. This raises an ethical problem, since in carrying out this biotechnological process the organism *per se* is not considered. What is important is the added value given by the genetic modification. In accordance with *Gestalt*-based thinking, we should look at the strength in the grouping of genes, functioning together to give harmony to the genome, as in an orchestra. Each gene network is a *Gestalt*, and the genome is thus composed of *Gestalten*, each with its own strength. Inducing a mutation or artificially introducing an exogenous gene weakens a *Gestalt* and therefore also the genome, assuming that most mutations are generally disadvantageous and that genetic modification disrupts the systems. Spontaneous mutations test new alleles, and thus *Gestalten* are dynamic. In order to understand the new genome of a GMO, we

must strive for a *Gestalt*-based vision of the process, which is an ability to see the complexity of how the genome functions, over and above understanding how its genes and its gene networks function. And we must take into account that deliberately increasing the genetic load of an organism, and therefore endangering that organism, raises ethical implications.

This can be clearly seen in the case of inherited metabolic diseases. Such diseases demonstrate another good example of integration between functional and structural gene networks, since it is only when a failure in one of the network nodes occurs that we can, through its consequences, see the degrees of interdependence. These generally monogenic and recessive autosomic diseases involve a mutation in only one allele, but when they occur in homozygosis they interrupt or reduce one step in the multiple-step metabolic pathway. This unique event is already enough to provoke metabolic disturbances and morphophysiological alterations in individuals. Mutation in just one gene locus is enough to provoke the outbreak of a syndrome. When a mutation generates a new and unfavorable allele, the individual, and thus its genome as a whole, comes under the pressure of selection.

This is the ethical question that faces those who change the genomic system: what becomes of the previously adapted and complete individual when its gene network is disturbed? A deleterious mutation in a single gene can harm or even eliminate that individual, however, "good" the other thousands of genes in its genome may be.

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