Epigenetics and the enlarged living world. On the interactions between organisms and their milieus

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Epigenetic and environmental factors might affect organisms either assuring health or causing diseases. It is now quite clear that some specific environmental, cognitive and social contexts might affect the response of the genome and the formation of the phenotype. In a post-genomic era, the importance of the organism/environment/culture interactions has become increasingly apparent. We argue that the study of these interactions could provide a key to our understanding of the development and evolution of higher organisms as well as of several mechanisms responsible for serious "multi-factorial" and "social" diseases.

Epigenetics and environment

The understanding of the amazing complexity and plasticity of high living organisms requires we investigate their organismal properties and their interactions with a more large, both natural and cultural environment. We are faced with the need of shifting from the local description of the molecular-genetic structure of DNA to the study of the networks of interactions between early development and evolution of complex living organisms, and of the way in which epigenetic, environmental and social factors affects the behavior and response of living beings. It is important to highlight the enormous impact of epigenetic and environmental phenomena on biological, cognitive and social processes. Another significant goal is to show that epigenetic, ecological and cultural effects can also be inherited across generations. This notably means that natural history and human evolution have been shaped by gene-culture and organisms-milieus interactions. Thus, our "living milieus", such as natural and urban landscapes, learning processes and cultural contexts, can have a profound effect on phenotypic variations and human evolution; conversely, human activities and cultural practices can modify organisms' metabolism and the contingent "history" of evolution's paths. We think that this cross-disciplinary dialogue may provide novel insights into how nature and culture are deeply interrelated and is essential for bringing biological sciences and social sciences together in a very new perspective.

Within this perspective, we specifically pursue a twofold objective. First, we want to show that positive selection of morphological and functional capabilities may have developed during evolution in response to human cultural practices. Next, that the organisms-milieus systems have co-evolved over evolutionary time through different interacting processes (for example: symbiosis as a source of novel traits; huge geographic migrations as a cause of genetic evolutionary and linguistic variation; radioactive large-rate pollution as a factor of genomic and phenotypic mutation) and niche-construction, that is the capacity of organisms to affect natural selection and evolution by modifications of their micro- and macro environments.

Environmental agents and genetic variants can induce heritable epigenetic changes that affect phenotypic variation and disease risk in many species. These trans-generational effects challenge conventional understanding about the modes and mechanisms of inheritance,[1] but their molecular basis is poorly understood. These heritable epigenetic changes persist for multiple generations and are fully reversed after consecutive crosses through the alternative germ-lineage.

Many environmental factors and genetic variants are known to induce heritable epigenetic changes that can persist for multiple generations, affecting a broad range of traits, and that often are as frequent and strong as direct environmental exposures and conventional genetic inheritance.[2] These trans-generational effects challenge our understanding of the modes and mechanisms for inherited phenotypic variation and disease risk, as well as the premise of most genetic studies in which causal DNA sequence variants are sought within the genome of affected individuals.

Reductionism and emergence

Biological complexity and specificity results from the way in which single components like molecules, genes and cells self-organize and function together when constituting a whole (a tissue, an organ, an organism), say a whole system including different subsystems. Not only the interactions between the parts and the influence from the environment (think of epigenetic factors, both chemical and spatial, that mediate the complex relationship between the genomes and the micro and macro biophysical environments), but also the systemic properties of the whole that exert an action on the components, give rise to new features, such as network behavior and functional properties, which are absent in the isolated components.[3] This means that we need to consider "emergence" as an effective new concept that complements "reduction" when reduction fails, and allow to take into account those specific systemic properties of the whole responsible for biological organization and regulation at higher levels.[4] Emergent properties do not result from properties pertaining to simple components of biological systems. They resist any attempt at being predicated or deduced by explicit calculation or any other analytical means. In this regard, emergent properties differ from "resultant" properties, which can be predicted from lower-level components. Advocating the reductionist idea of "upward causation" means to maintain that molecular components and states suffice to determine higher-level processes occurring in biological systems.[5] However, without denying a certain role of methodological reductionism in science, today we are led to recognize the important role played by the concept of emergence in many fields of the natural and life sciences, as well as to accept "downward causation" by which higher-level systems and processes influence lower-level configurations and entities. Emergence is essentially linked to the intrinsic and peculiar complexity of living systems. The existence of emergent properties is an outcome of the complexity of living systems. In other words, in order to solve the increasingly complexity linked to the stages of the developments of tissues and organs, and the construction of global physiological systems, self-organized living multicellular organisms give thus rise to newly, needed regulatory and functional properties.[6]

Conclusion

To conclude, we would like to stress the fundamental fact that organisms are more than, and a reality profoundly different from the genes that look after their assembly. Mechanical, chemical and cultural inputs from the environment, epigenetic cues, also have an effect on the final phenotype. In fact, continued environmental influences on the adult phenotype continue to affect its characteristics.[7] The open question is whether the epigenetic cues can become causative agents of phenotypic modifications. Within a biological multi-level, astonishing complex reality, higher levels result from lower-level processes (genes up to phenotype), and lower levels result from higher-levels processes (organism's properties to epigenetics mechanisms of genes expression and regulation), so that upward and downward causation are in different ways and in both directions deeply interlaced. Some epigenomic cues seem to be assimilated into the genome, as C. H. Waddington had already showed (1953).[8] The evolved genome therefore incorporates epigenomic cues or the expectation of their arrival. Genomes are more than linear sequence,[9] in fact, they exist as elaborate spatial and physical structures, and their functional properties are strongly determined by their cellular organization and by the interactions organisms develop with the environment.[10]

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[2] S. M. HO *et al.*, "Environmental epigenetics and its implications on disease risk and health outcomes", *Epigenetics* 53(3-4), 2012, 289-305.

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[4] M. POLANYI, "Life's irreducible structure", *Science* 160(3834), 1968, 1308-1312.

[5] F. H. C. CRICK, "The central dogma of molecular biology", *Nature* 227, 1970, 561-563. For an interesting criticism of the central dogma advocated by Crick and many other molecular biologist, see D. NOBLE, "A theory of biological relativity: no privileged level of causation", *Interfaces Focus* 2(1), 2011, 1-10 ; L. BOI, "Plasticity and complexity in biology: topological organization, regulatory protein networks, and mechanisms of genetic expression", in G. TERZIS, R. ARP (eds.), *Information and Living Systems: Philosophical and Scientific Perspectives*, Cambridge, The MIT Press, 2011, 287-338.

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[7] K. LORENZ, *Evolution and modification of behavior, Chicago*, Chicago University Press, 1965. See also M. SARÀ, "L'integrazione di genotipo e fenotipo alle soglie del 2000", *Systemæ Natura* 4, 2002, 181-208.

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[9] Cf. M. MCCLINTOCK, "The significance of responses of the genome to challenge", *Science* 226(4676), 1984, 792-801.

[10] R. C. LEWONTIN, "Gene, organism, and environment", in D.S. BENDALL (ed.), *Evolution from molecules to men*, Cambridge, Cambridge University Press, 1983, 273-285.