Chapter 26

Adaptation and Evolution in a Gravitational Environment — A Theoretical Framework for the Limited Re-Generative Post-Natal Time Window of the Heart in Higher Vertebrates

Michele Mario Ciulla, Gianluca Lorenzo Perrucci and Fabio Magrini

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/55931

[Who are you who live in these many forms?]

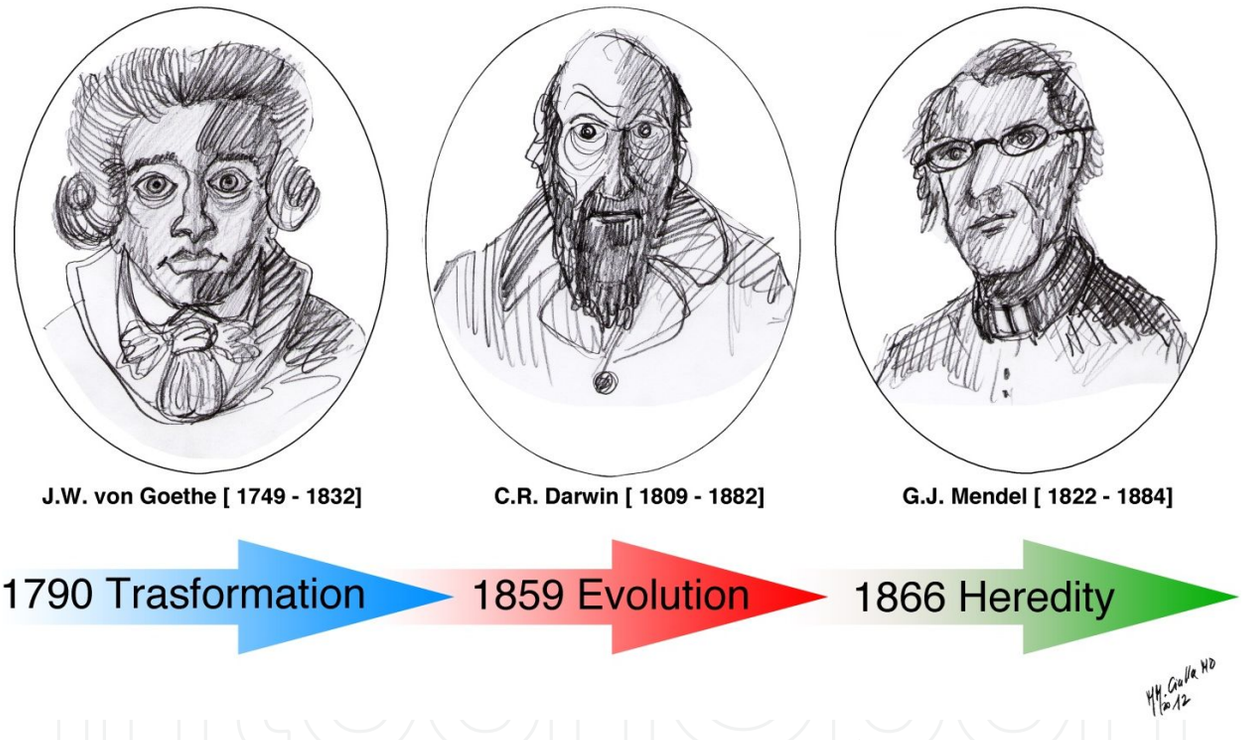
The Thin Red Line, 1998. Movie. Directed by Terrence MALICK. USA

1. Introduction

The origin and the meaning of life on the earth was traditionally attributed to an intelligent creator as an independent act until 1859 when Charles Darwin compiled the book The Origin of Species (Darwin, 1859). In this book Darwin introduced the *theory of evolution by natural selection* (Figure 1, central panel) opening a new perspective to read what looks like the *largest experiment on earth* called biological life. This new perspective has proposed a reversal of the traditional view where the intelligence is placed above the experiment by introducing the concept of *transformation or evolution* (Dennett, 2009). In this upside down view intelligence is not excluded but, rather, is within the experiment and drives the so called "struggle for life" in a dynamic planet where habitats are continuously destroyed and created.

Interestingly some years before, the *idea of transformation* was anticipated by the poet Johann Wolfgang von Goethe. In his book "The Metamorphosis of Plants" originally published in 1790, he wrote: *"Everyone who observes the growth of plants, even superficially will notice that certain*

external parts of them become transformed at times and go over into the forms of the contiguous parts" (von Goethe, 1790). What then seemed merely a poetic yearning on the wonder of nature, indeed, proposed the *transformation of the parties* (Figure 1, left panel) itself as a creative principle instead of a single external creative act. This *imaginative vision* provided by a poet shows how intuition and imagination can be a source of inspiration in the search for new knowledge and a place of convergence between literature and science (Pelaprat and Cole, 2011). The extension of the concept of transformation from the plant to the animal kingdom and the theory of evolution are further insights undertaken by non-poets with great imagination which certainly meets the definition of *creative scientists* (Boxenbaum, 1991). Thus, in the progress of human knowledge, the claim that science is superior to the literature, simply because it has to do with *facts* and the literature with *imagination*, has no basis because the idea behind every (great) scientific discovery is inspired by intuition, a kind of ability that does not use inference or reason (Beveridge, 1957).



Small cameos representing the faces of visionary scientists who introduced the concepts of transformation, evolution and inheritance.

Figure 1. The visionary scientists

Looking now at biological life with imagination, it is clear how it may seem the largest experiment, at least, on earth since, till now, we do not know whether there are other ongoing experiments like this in the *universe*. We know that many attempts to search for other forms of life in the universe have been made since the Sixties but, to date, without significant results (Wilson, 2001). Thus we cannot exclude that life on earth is, in fact, the *only* result of a larger experiment that we might call *life in the universe* (Aldiss, 2001).

http://dx.doi.org/10.5772/55931

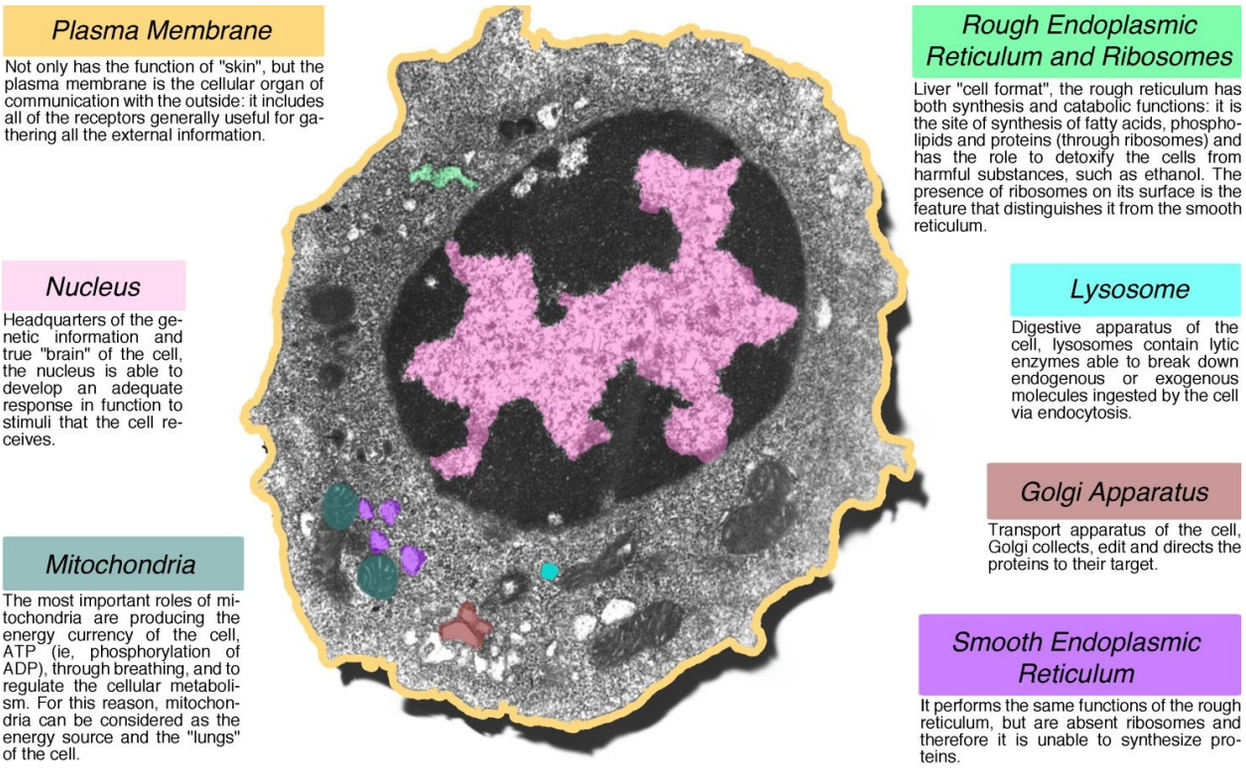
Returning back on earth, since here the experimental conditions vary continuously because of the regular and irregular environmental changes, there is no certainty about the results. If we try to define the experiment, this could be in summary to *assess life on earth*, and its process, through *trial and error*. Assuming that the experiment is started, to ensure its continuity in the presence of *errors* that can result from an *unfavorable interaction with the environment*, the method to explain how it works proposed by evolutionists implies a kind of continuous refinement of life through the *adaptation process* in order to get the possibility of a new trial with the environment. And it works since this challenge goes on from the evolution of the first *living organism*, represented by *ancestral bacteria*, dated about 3,500 millions of years ago till now (Kutschera, 2009).

Especially under adverse environmental condition, consisting mainly in climatic changes, a better adaptation to the environment obviously increases the chances of survival and gives continuity to the experiment. Therefore is the fittest organism that survives, which is to be considered a *prototype* that has passed the compatibility test with the environment, a process described by evolutionists as *natural selection*. In this framework it is logical to assume that allocating resources for adaptive processes in order to buffer environmental changes is an essential condition for life. The survival obtained through adaptation is temporary because it depends on each organism's life cycle and ends with death. To date the death still represents an essential phase in the experiment of organic life as it is the natural end of each life cycle; in addition, since the dead organism undergoes, under appropriate environmental conditions, to decomposition into basic elements, it can therefore be claimed that death, and after-death processes, also promote the accessibility of the basic elements for the vital functions of the other still living organisms that represent the ecosystem of the earth (Marschner and Kalbitz, 2003).

In order to overcome the time constraints imposed by the life cycle of individual organisms and ensure continuity to the experiment is required to introduce *the possibility of an offspring* and thus to apply the adaptation processes on a population consisting of copies (n>1) of the same organism.

This result can be achieved by duplication, a simple biosynthetic way to keep track of itself by division in use in *prokariotic* cells. Thus duplication ensures continuity to a single prototype, but this is not enough to respond to *major climate changes* of the earth, whose major effects can be deducted from the rate of extinction of living organisms (Jablonsky, 1994; Raup and Sepkoski, 1982).

In such dramatic context it is obvious that having more prototypes of living organisms to be tested provides more guarantees of continuity to the experiment. Therefore the *evolution of species* from a common ancestor, placed at the origin of what is commonly called the *tree of life*, is a way to adapt the biological life to randomly environmental changes (Kussell and Leibler, 2005) and must be seen as a *necessity* in evolution. Emerging of *diversity* is linked to the evolution of the *eukaryotic cell*, representing a real breakthrough in cell organization and function, which occurred about 2,500 million years ago. In this cell has its origin the *endosymbiosis*, an advanced form of *phagocytosis* that consists in *using the competence* of other organisms, instead of the energy, to re-organize cellular functions more efficiently, a starting point for the evolution of the cellular organization and *multicellularity* (Figura 2).



Electron microscopy image of a lymphocyte (courtesy of Paola Braidotti, BSc). The subcellular organelles with clear analogies with organs and/or apparati of complex multicellular organisms, such as humans, have been highlighted with pseudo-colors.

Figure 2. The cell: a body in miniature

Diversity is at the origin of the eukaryotic cell that adopts very early the *meiosis*, a new biosynthetic procedure evolved from the *mitosis* (Wilkins and Holliday, 2009) that allows *reproduction* instead of simply *duplication*. Intimately related to the development of *sexual reproductive cycles* (Antonovics et al., 2011) the *mitosis* generates more variability thus contributing to the overall *diversity*.

All these *adaptive responses* are coordinated by an *expert program* that enables living organisms to interact with the environment in an *active manner* ensuring at the same time *continuity* and *change* in the subsequent generations. This program, while remaining substantially the same over time, has ferried the biological life on earth through five *mass extinctions*, defined as times when the Earth loses more than three-quarters of its species, namely Ordovician, Devonian, Permian, Triassic and Cretaceous Periods. The *size of the experiment* has changed over time, from the first life forms to *complex organisms*, through the same basic mechanisms, showing the *major cellular evolution* at the origins followed by a very rapid expansion of life forms and a substantial stasis (Cavalier-Smith, 2006) but to understand the general principle by which the program reproduces itself, we will have to wait for some experiments on peas. A few years after the publication of The Origin of Species, Gregor Mendel, trying to understand with his experiments what any good farmer knows, which consists in the fact that through the selection of varieties of plants and their interbreeding is possible to obtain a better product, introduced

http://dx.doi.org/10.5772/55931

the general principles of heredity (1866). His remarks were neglected until the early twentieth century when they provided the inspiration for the birth of *genetics*, the study of *heredity in biology* (Figure 1, right panel).

The term genetics was first used by William Bateson in 1905, but to identify the program code that at this point can be called *genetic program*, and how it is transmitted we should wait until 1953 in which the structure of DNA is discovered by other scientists with great imagination James D. Watson and Francis Crick. The rest is a more recent history. Having cracked the DNA code of humans and other living organisms, all scientists facing the incredibly high level of homology between different species have turned their interest towards the *proteome*, opening the so-called *post-genomic era* (Gromov and Celis, 2000). This new branch aimed at the analysis of the *functional state of the genome* has begun to develop. Unlike the genome, the proteome is much more complex and dynamic, and undergoes radical changes both in ontogeny and in different states. The proteome of any cell is unique and provides qualitative and quantitative information on proteins, thus giving a dynamic picture of genome expression under varying conditions (Gromov and Celis, 2000). The post-genomic era, in fact, strengthens the bonds of evolutionary biology with Darwin's theory of natural selection recovering the role of the environment in the experiment. But natural selection is still a mechanism at work? Yes it is, more in some geographical areas than in others (Stajich and Hahn, 2005), but is also working in a quite novel ways through the effects of changes in the environment caused by the so-called modernization (Hunter, 2007).

Although the question of the *origins of the life* after Darwin has been removed or limited in certain areas of science simply confining the *teleological question* to a purely human level (Ayala, 1999), we believe that the mission of modern science is still to find teleological explanations to everything that is humanly intelligible.

Even if none of us can be considered an expert on the origin of life on earth because of the lack of *fossil evidence*, the new synthetic view including *evolution* and *genetics* has contributed to define the main lines along which the *life experiment* on earth has evolved in a continuously *changing environment* (Graham, 2011). Trying to *conceptualize* the main steps in the evolution of *complex organisms*, we can identify three main lines, the first is the *organization* the second is the *diversity* and the third is the *adaptation*.

2. The organization

The *organization* or, better, the ability to organize itself, is the main feature of *living organisms*, but to date no one can state with certainty whether this property is intrinsic or acquired during evolution. Geological research has shown that the age of planet earth is about 4,560 million years (Dalrymple, 1991). Thus, as we saw earlier, we will have to wait about 1,000 million years from the origin of the earth for the evolution of the first living organism consisting in *ancestral bacteria* or *archaea*. In this somewhat *obscure* lapse of time, that have lasted at least 3,500 million years, much space is left to the imagination, but it is reasonable to assume that living organisms

are endowed with the ability of *self-organization* and that this capability has evolved from elementary properties of chemical compounds essential to kick off life on earth.

This obscure stage has possibly involved *abiotic molecules* slowly evolving towards self-replicating forms (Paragraph 1) in a kind of *chemical evolution* (Martin and Russell, 2003) that goes beyond this discussion. Self-replicating means keep track of itself and preserving memory of the experiment, but the question is, obviously, about the nature of the first self-replicating molecule; however, since replication is accomplished in modern cells through the cooperative action of *proteins* and *nucleic acids*, there is a general agreement on their essential contribution to the development and maintenance of any living organism. Hence at the origin of the cellular organization are elementary properties that, through self-replication, are transmitted to the offspring.

The appearance of the *prokaryotes* dating back approximately 3,500 million years ago represents the first remarkable result of this process, but is just a step towards the refinement of life. A real breakthrough in cellular organization is the advent of the *eukaryotes* where elementary properties are re-arranged to a higher level of complexity. But, how was it possible? Nobody knows, however this seems to be related to the endosymbiosis, an evolved form of phagocytosis that consists in using the competence of other organisms, instead of the energy. From this peculiar type of *symbiosis* (Mereschkowsky, 1926) derive certain essential properties of the cellular organization, such as *cooperation*, development of specific skills or *competence*, *complexity increase*, development of *interaction patterns* up to *multicellularity*.

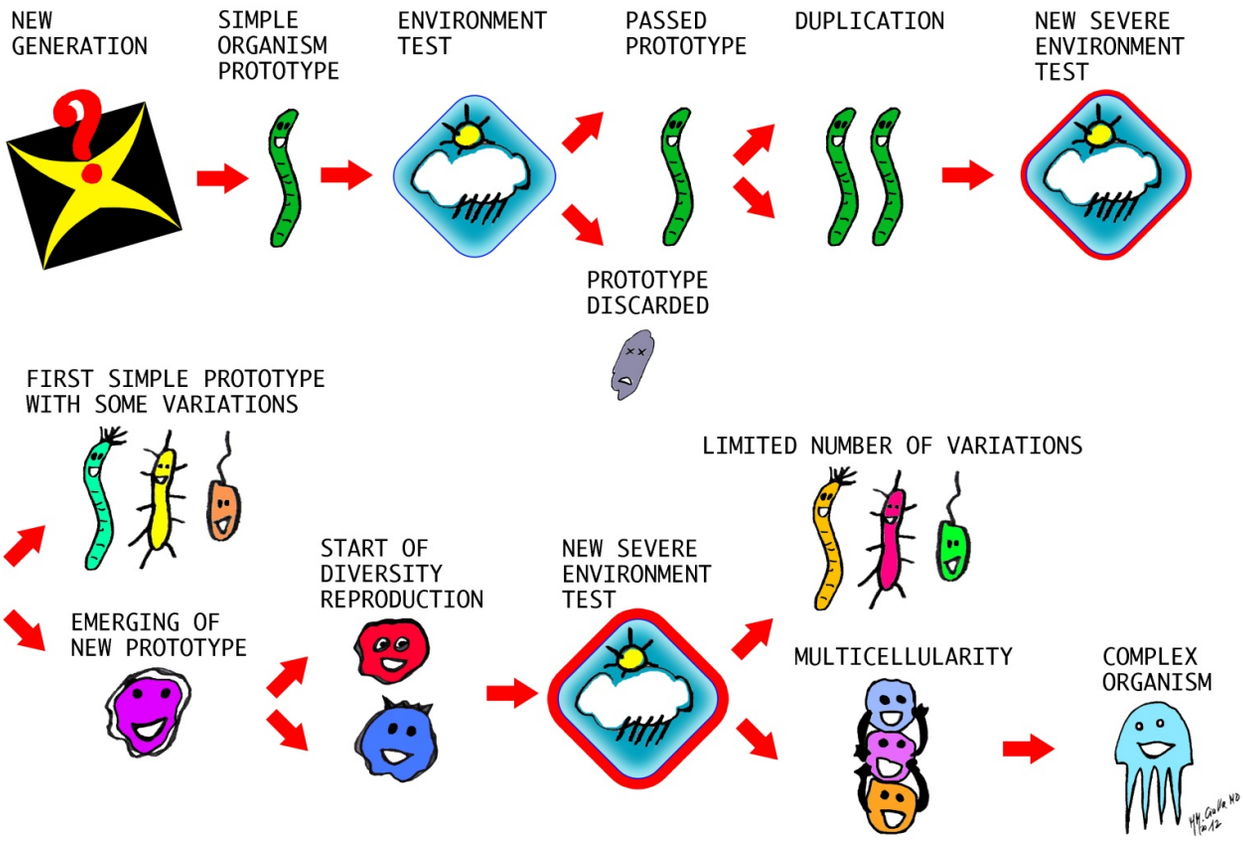
The appearance of multicellular organisms as occurred fairly rapidly in the experiment of life must be seen as an evolutionary stage that does not necessarily involve a significant increase in the complexity of the genetic program (Prochnik et al., 2010); this process has been reproduced recently in vitro by using an eukariotic model (Ratcliff et al., 2012).

Furthermore, since the evolution of multicellularity has not resulted in the replacement of the *prokaryotic prototype* that is still alive, for example, in *modern bacteria*, it seems logical to assume that this stage represents a necessity in evolution (Furusawa and Kaneko, 2000) for *some* living organisms expecially when exposed to highly selective environmental conditions. These extreme conditions on earth are possibly responsible for the *evolutionary peaks* recorded after long periods of stasis (Eldredge et al., 2005) and thus for the evolution of multicellularity. At this regard it is noteworthy that archaea and bacteria, in spite of their early evolution, exibit a very small number of species (about 5,000) if compared with multicellular organisms, and are associated with a high level of resistance in all ecosystems (Staley, 2006). Therefore, it is plausible to assume that bacteria are a *source of backup* capable of restarting the experiment of life on earth even after catastrophic climate change or, possibly, in other places in the universe (Wickramasinghe, 2004).

Returning to the metaphor of the *tree of life*, having a common trunk or origin means to share, at least, some features and/or functions, and in multicellularity some properties of unicellular organisms are reallocated on a larger scale with the evolution of *cellular differentiation* and *specialization*. This new kind of cooperation establishes *functional hierarchies* and leads from the development of *finely detailed pattern* up to the evolution of fully developed *complex organisms*(Furusawa and Kaneko, 2000).

http://dx.doi.org/10.5772/55931

The evolutionary stages, from the development of the first prototype to multicellular organisms, are conceptualized in the block diagram in Figure 3.



The black box [*new generation* machine] represents the obscure stage of the experiment of life, originating the first prototype [*single organism prototype*]. The environmental tests are possibly responsible for the evolutionary peaks, generating others prototypes [*variations, diversity*] up to multicellular and complex organisms.

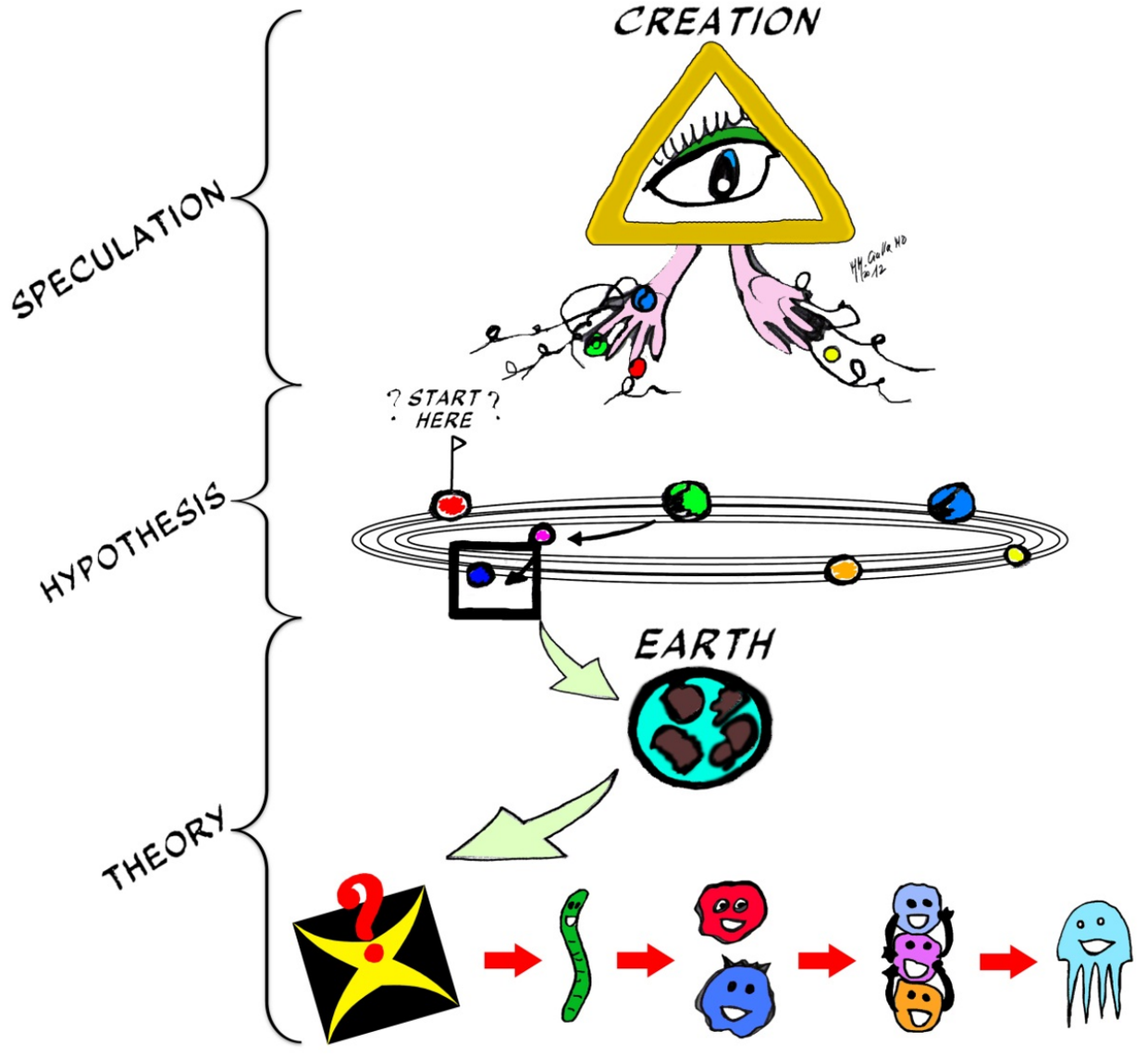
Figure 3. Conceptualization of evolutionary stages

3. The diversity

The *diversity* in biology is "...the variety and variability among living organisms and the ecological complexes in which they occur." (Assessment., 1987). The diversity can also be calculated as the *number* of different items and their *relative frequency*; these items are organized at many levels, ranging from entire ecosystems to the chemical structures that are the molecular basis of heredity (Paragraph 2).

As we have seen before, the diversity originated very early in the tree of life with a very rapid expansion characterized by the evolution of an extraordinary variety of living organisms in a relatively short time followed by a long lasting substantial stasis (Eldredge et al., 2005). This expansion phase is possibly the second *obscure stage* in the experiment of life, after the initial

one (Figure 3), since it is really hard to imagine a cause-effect relationship during those phases beyond the theories of transformation-evolution (Figura 4).



Schematic representation of the origin of life and diversity. The upper part is a speculation and represent an intelligent creator above the experiment of life in the universe. The intermediate part is a representation of the hypothesis that life on Earth has an extraterrestrial origin thanks to space vectors such as meteorites or asteroids. The lower part recalls the second obscure stage [generation machine] and the evolutionary theory explaining the origin of diversity.

Figure 4. On the origin of life

The road to the diversity is marked by milestones including the transition from *duplication* to *reproduction* and this innovation is believed to coincide with the evolution of the *eukaryotic* cell that adopts the *meiosis*. This peculiar form of cell division produces greater variability contributing to increase the diversity of living organisms.

http://dx.doi.org/10.5772/55931

But writing of diversity in biology can be complicated, precisely because of different points of view covering the whole scenario; indeed, from a purely *descriptive* point of view, there are both visible and invisible differences. Focusing on a *population* represented by all the living organisms that belong to the same species and live in the same geographical area, since individuals are not identical, some visible differences are expected and these differences are even more noticeable when taking into account *different populations* or species.

Nonetheless the visible differences give way to *basic similarities* when are taken into consideration the internal features, invisible at naked eyes. These common features include the general *molecular structures* and principles that are the basis of *biochemical functions* in all living organisms and clearly demonstrate the concept of *branching of the tree of life* starting from a *common ancestor*.

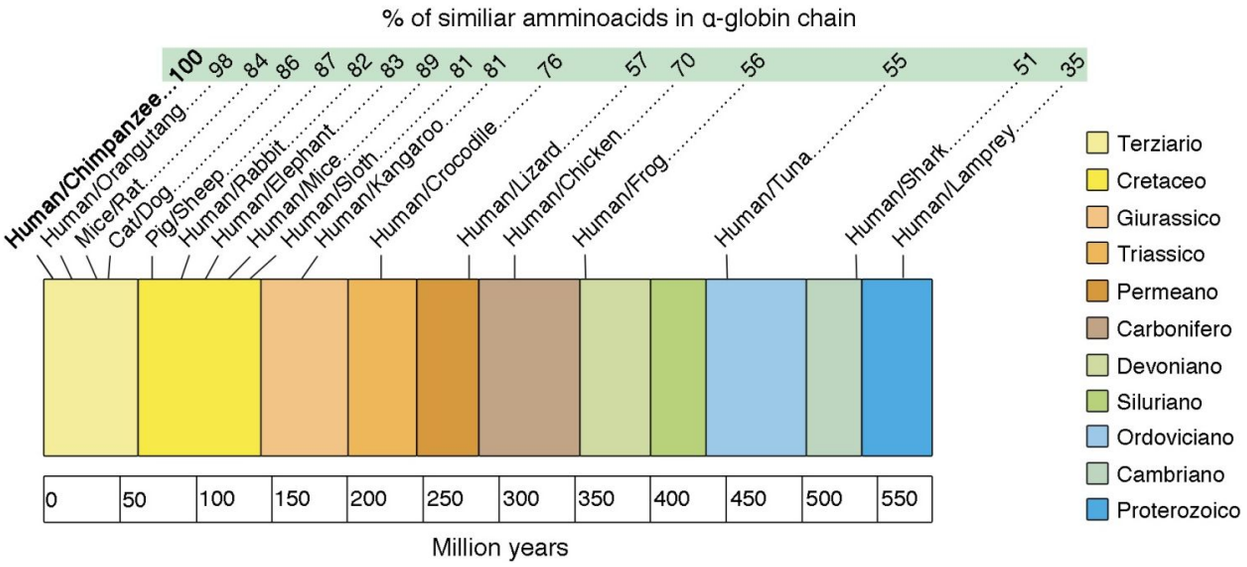
Thus the biological life is characterized by a *partial and transient independence* as the result of the dynamic interaction between the environment and the biochemical function of some *common macromolecules* such as lipids, nucleic acids, namely DNA and ribonucleic acid (RNA), proteins and carbohydrates reallocated on a larger scale with the evolution of *cellular differentiation* and *specialization*.

The *nucleic acids* of all organisms are constituted by the same set of nucleotides and the proteins blocks are almost made by the same amminoacids. Moreover, several *cellular events* share the same mechanisms and machinery; events like mitosis, DNA duplication, protein syntesis are indeed based on the same molecular steps and the molecular structures involved are the same both in prokayotes and eukaryotes, such as histones for chromatin packing, polymerase for DNA duplication, ribosomes for protein syntesis and so on.

From a molecular point of view, only the analysis of structures, such as the analysis of how many and which amino acids compose a protein with a similar function in two different species, can state the diversity, assess the *phylogenetic proximity* between species and outline the branches of the tree of life (Figure 5).

Looking now at the *genetic program* that determines the shape and the function of living organisms, it is represented by different *gene sequences* that, because of *diploidy*, in humans consists of two or more copies of genes called *alleles*. Thus the *gene pool* of a population is made by the totally of alleles, their *combination* or *aplotype* and their *relative frequencies* among the individuals. Thus the *genetic diversity* describes the existence of many different versions of the same individual, a *different phenotype* is the result of a genetic variation in a specific environment and is called *variant*. As stated before, the *genetic diversity* among individuals in a given population and even more between species, increases the chances of survival in case of highly selective environmental conditions; thus *evolution* takes place when there are *any* changes in the genetic pool that increase the adaptation process (Paragraph 1). There are few processes that can lead to *new genetic combinations* and the most relevant for this discussion are *mutation*, *recombination* and *natural selection*, therefore we do not take into account the effects of *migration* into a population from another one, with different gene frequencies, as a *source of variation*.

Essentially these processes can be *random*, meaning that they take place independently of the needs of the organism, *probabilistic* and *directional*; mutations are random, recombination is



The picture shows the estimated geological age of the last common ancestor of each pair of specified animals. Each time estimate is based on comparisons of amino acid sequences of orthologous proteins; more time had a pair of animals to evolve independently, smaller is the percentage of amino acids remaining identical. The final estimates and the time scale has been calibrated to match the fossil evidence that the last common ancestor of mammals and birds lived 310 million years ago. Numbers in the top bar gives data on sequence divergence for a particular protein chosen arbitrarily, i.e the α-chain of hemoglobin. The clear irregularities in growing divergence with increasing time reflect the randomness of the evolutionary process and, probably, the action of natural selection, which drives particularly rapid changes in some organisms subjected to special physiological requirements.

Figure 5. Phylogenetic proximity

probabilistic, depending on the distance between genes (Russell, 1998), and natural selection is directional since it follows a direction which favors the survival of the fittest organism.

Both mutation and recombination define the *allelic variability*, which determines a difference between the genotypes of individuals; this variability will be further shaped by the environment, that ultimately determine the presence of different *phenotypes*, based on instructions dictated by the *genotype* (Russell, 1998). Mutations, as source of variation, are quite limited since their rates are very low. On the other side, recombination is a primary source of variation; most of the attention of evolutionary geneticists has focused on the extensive *genetic recombination* that takes place during meiosis and, in particular, during pairing of sisters chromatides and its significance as a generator of genetic diversity in organisms with sexual reproduction (Charlesworth, 1988; Edwards, 2000).

In organisms with asexual reproduction, such as bacteria, recombination is very limited since mutations are the only source of gene combinations, thus, asexual organisms may evolve more slowly, under natural selection, than sexual ones (Griffiths et al., 1999). Although the mutations play a more limited role as a source of variability in multicellular organisms with sexual reproduction, together with the effects of gene recombination, they can still be transmitted to offspring only by the *germ cells*.

In multicellular eukaryotes these cells are the connection between the different generations since they are the only ones that undergo *meiosis*, as well as *mitosis*, in contrast to *somatic cells*,

http://dx.doi.org/10.5772/55931

practically all the others, that divide only by mitosis. In organisms that have evolved forms of *sexual reproduction*, the life cycles start through the union of two germ cells, male and female, and their nuclear fusion originates the *zygote*. Several reasons support the evolutionary necessity and the benefits of sexual reproduction in multicellular organisms (Roze, 2012; Wong and Wessel, 2006) and their prevalence in animals (Engelstadter, 2008).

Thus the zygote is a *diploid cell* resulting from the mating of two *haploid cells*, that gives rise, after three cell divisions, to the first *stem cells*. These cells are the only ones capable of differentiating into all cell types that make up a multicellular organism. This extreme versatility is known as *potency*, it is maximal during the pre-natal life in the *embryonic stem cells*, and progressively decreases in post-natal life remaining confined within the *adult stem cells*.

With regard to the definition given at the beginning of the paragraph, it should be remarked that the *biodiversity* implies the overall biological variability, including both genetic and environmental features. Environmental changes, both cyclic and irregular ones, may be a serious challenge for the experiment of life causing usually a *switch* in the phenotype. There are two opposite types of switching of the phenotype: the *reactive type*, which occurs as a direct response to an external cause detected by a *sensory mechanism,* such as a receptor, and the *stochastic type*, which occurs without the mediation of a sensory mechanism (Kussell and Leibler, 2005).

The *phenotypic diversity* is generated by *phenotype switching* caused mainly by stochastic mechanisms; thus the *population diversity* and the coexistence of subjects differently adapted to a certain environment, can be a way to respond to *irregular environmental changes* (Soll and Kraft, 1988; Perez-Martin et al., 1999; Bayliss et al., 2001; Lachke et al., 2002; Bonifield and Hughes, 2003; Kearns et al., 2004; Balaban et al., 2004).

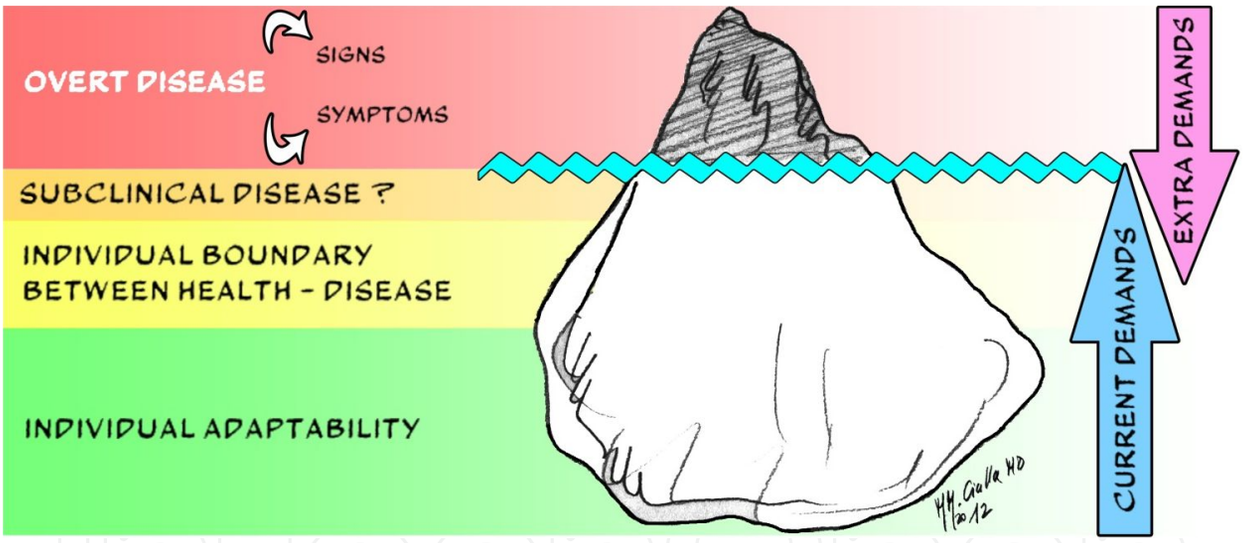
4. The adaptation

It is impossible to speak of life in a biological sense without postulating a *certain degree of independence* from the environment where life itself takes place. Whatever its level of complexity, a living organism is a *biological system* delimited by a kind of boundary to face the *external environment* and capable to maintain a stable, constant condition by regulating himself and the *internal environment*.

The demarcation of self with a *membrane* and the establishment of an *internal environment*, opposed to the external one, is a formal requirement to any living organism and the condition of *relative equilibrium* called *homeostasis* (Cannon, 1929) provides the biological system an appropriate level of independence from the environment that allows to acquire other essential properties such as response to stimuli, development, growth and reproduction.

Any change, either decremental or incremental, in the internal/external environment of the cell/organism such that it requires an active response from the cell/organism can be termed demand (Ciulla et al., 2011). By using the simplified approach *demand-response*, it is possible to classify the demand as a function of its *type*, *intensity* and *duration*. Since the possible responses

of the cell/organism are limited and fall within the *adaptive processes*, the demands can be further classified in current or extra according to the efficiency with which they can be handled. Current demands can be adequately dealt with in a physiological context, even though some degree of cell/organism injury can still occur; extra demands cannot be sufficiently buffered, and lead to functional impairment and, eventually, to disease or, as the last resort, to death. Anyhow the final outcome of the changes imposed on living organisms depends on the *ratio demand-response*; an excess in demand and/or a defect in the response for the lack or depletion of adaptive resources, can represent a serious problem for the survival of the organism. In such view, *disease* is the result of an *unfavorable interaction* between the cell/organism and the environment or, by simplifying, between the genetic resources and the environment. The succession of cyclical and stochastic environmental changes suggests that, during the life cycle, the current demands represent the bulk of all demands while extra demands are more often occasional. The relation between current and extra demand can be depicted by using the iceberg metaphor (Figure 6). Thus, the *possibility of damages* and *disease* caused by *unfavorable interactions* with the environment are foreseen and their occurrence is managed by coping biological resources involved in tissue maintenance and repair of damages.



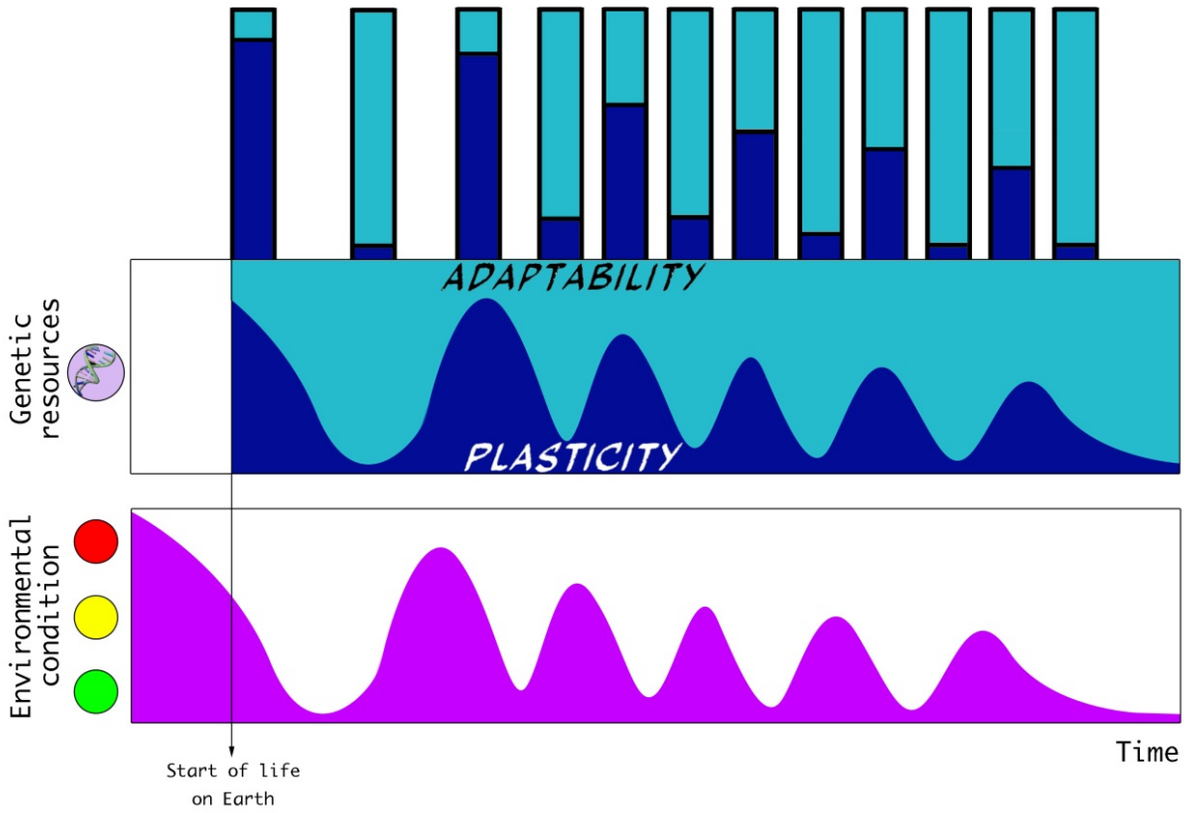
Representation of the iceberg metaphor, illustrating the boundary between health as a result of *individual adaptability* and disease. The tip of the iceberg corresponds to overt disease; the huge part below the water line is where individual adaptability successfully buffers environmental demands; just below the surface is the grey zone of subclinical disease. Demands are defined as current or extra according to how efficiently they can be handled by the single organism.
Modified from an Open Access source: http://www.intechopen.com/books/advances-in-regenerative-medicine/inflammation-angiogenesis-cross-talk-and-endothelial-progenitor-cells-a-crucial-axis-in-regenerating.

Figure 6. The iceberg metaphor to understand diseases

Therefore, as changes in the internal/external environment occur continuously, it is evident that *allocating biological resources* in order to buffer changes is an essential requirement for life and living organisms have, indeed, evolved specific *adaptive processes* to meet the demands imposed by changes in the environment. In this context, it is therefore not superfluous to

http://dx.doi.org/10.5772/55931

remind that the *availability of resources* is only possible if there is a corresponding *genetic resource*. The *genetic program* that governs *genetic resources* is a *finite sequence of instructions* whose possible combinations are somehow limited by the same program. Furthermore, especially in complex organisms that require *stages of development* to reach a final *adult form* and a *full functionality*, genetic resources are not only quantitatively limited but also *temporally regulated* by the constraints of the life cycle. Thus in the same manner will also be limited the *adaptive processes*, including *organism adaptation* or *plasticity* and *adaptability* (Kutschera, 2009). The *plasticity* is the ability to express a broad variety of phenotypes in response to environmental changes and, in complex organisms with sexual reproduction, is at a maximum during *embryogenesis* and *early extrauterine life*. The *adaptability* could instead be applied to the more limited process of adaptation which occurs in adult life and varies between organs and species (Figura 7).



The lower panel shows the environmental fluctuations as result of temperature changes (street light colors) during the history of Earth. The upper panel shows how genetic resources respond accordingly to these fluctuations by tuning adaptability and plasticity. The bars depict which resource is mainly involved in each time points.

Figure 7. Relationship between plasticity and adaptability in a changing environment

But why are these processes limited in adult life? In this regard, it should be remembered that in complex organism the evolution towards multicellularity is a form of adaptation to the environment that involves a high cost in terms of biological resources; in other words,

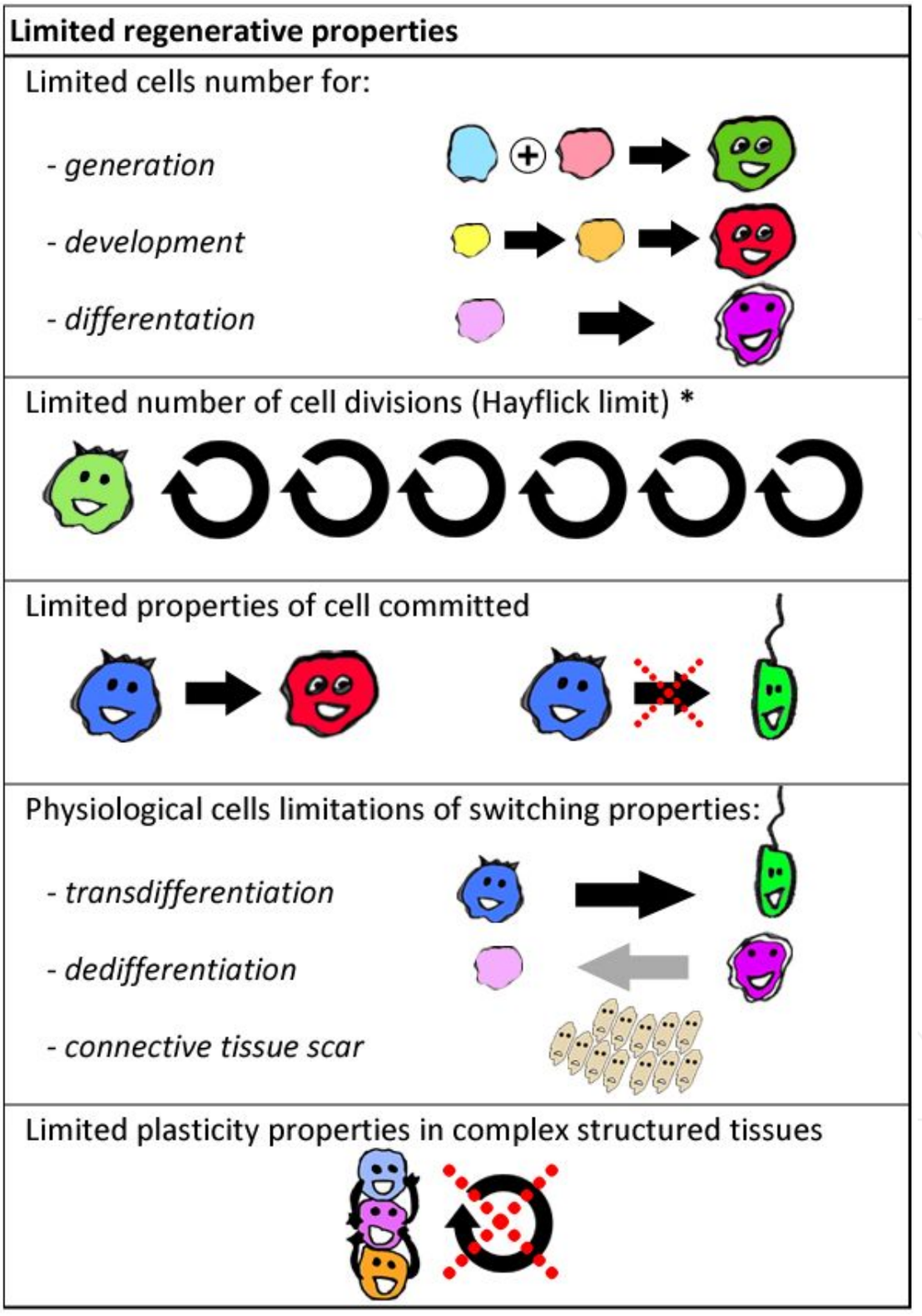
differentiation, specialization, establishment of functional hierarchies and development of a *fully developed complex organisms* implies a considerable expense of biological resources, thus reducing the availability of resources for other forms of adaptation in adult life such as the *re-generation* process.

Therefore in the presence of an *extra demand* causing a damage the response of complex organisms in adult life mainly consists in *functional* and *structural adaptation* since *re-generation* processes after *injury* are limited. Indeed in such organisms, *generation* and *re-generation* are capabilities shared by the same deputy cells named *stem cells*, the only ones capable of differentiating into all cell types that make up a multicellular organism (Paragraph 2). The number of stem cells is limited and, as we saw earlier, their *potency* is maximal during the pre-natal life in the *embryonic stem cells*, and progressively decreases in post-natal life remaining confined within the *adult stem cells*.

These cells are therefore to be understood as a kind of *functional reserve*, restricted to a *specific tissue*, that could be recruited to support adaptation processes that allow the organism to better fit in with the changed environment and, thus, attain a new equilibrium. At this regard the *functional hierarchy* of complex organisms allocates *functional reserve* where it is needed and establishes the *distribution of the available resources*. In complex organisms such as mammals, many adult tissues contain populations of adult stem cells that have the capacity for *renewal after disease* or *aging*; these tissues include brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis. Thus, the primary role of adult stem cells in a living organism is to *maintain* and *repair* the tissue in which they are found. Unfortunately there is a very small number of adult stem cells in each tissue, with large numerical differences between a tissue and another, and, therefore, the *re-generative potential* is unevenly distributed and, in any case, is very limited. The reason why some *highly specialized tissues* have limited regenerative capacity is not yet known, but we can not exclude that the extreme structural and functional specialization reached by some tissues is an inherent limit to regeneration (Table 1).

Recently a number of experiments have reported that certain adult stem cell types can differentiate into cell types seen in organs or tissues other than those expected from the cells' predicted origin or *lineage*; for example, brain stem cells that differentiate into blood cells or blood-forming cells that differentiate into cardiac muscle cells, suggesting the idea that cells might have an *alternative fate* after maturation according to their specific identity. The two known processes by which cells are able to turn into other cell types are: *trans-differentiation*, consisting in the direct conversion from one cell type to another, and *de-differentiation*, or the reversion to a less-differentiated cell type and the subsequent maturation to a different lineage. Thus the *cell identity*, which had so far been considered a rigid and durable characteristic involving a one-way process from precursor to mature cell, was shown to exhibit not only intrinsic plasticity (Scadden, 2007) but also a certain degree of adaptation depending on the interplay between genome and microenvironment. In fact it was demonstrated that mature cells are able to switch not only their functional phenotype but also their gene expression profile into that of stem cells, thereby acquiring pluripotent plasticity (Ciulla et al., 2011). The

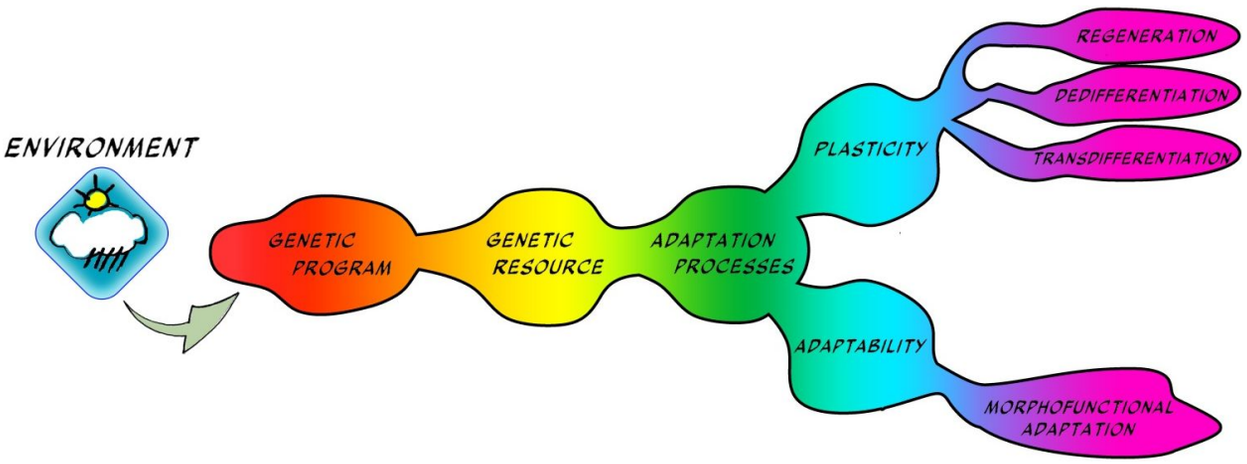
http://dx.doi.org/10.5772/55931



* Hayflick demonstrated in 1965 a limited number of cell division (Hayflick, 1965)

Table 1. Limited regenerative properties of cells in complex organisms

alternative fate has indeed opened a new window of opportunity revealing the significant opportunities that may arise from *engineering of adaptive processes* (Figure 8).



Representation of biological resources allocation by genetic program in order to buffer changes in the internal/external environment. All living organisms have evolved specific *adaptive processes* to meet the demands imposed by environment.

Figure 8. Allocation of biological resources for adaptation processes

In the last decade the topic of *adult stem cell repair* of the infarcted myocardium was among the most popular in the scientific community and has gained growing popularity among top scientific journals. The objective of these studies is, therefore, to optimize the adaptive processes by probing the possibility of *manipulating the cellular identity*. By suggesting possible *alternative fates* for the cells, this research model clashes with the *dogma of the cell cycle* and is faced with the problem of how to ascertain the identity of the cells in a context in which the identity itself is no longer a certainty but, rather, a dynamic concept (Ciulla et al., 2011).

Thus the issue of cell identity or phenotype led to develop alternative techniques to direct visualization of histological structures; among them the refined, however complex, techniques of *fluorescence microscopy* based on the confocal representation of *fluorochromes* visible at different wavelengths. The employment of these laboratory techniques in the belief that *methodological complexity* equates to biological soundness has produced a paradox culminated in a scientific nonsense: the same experiment, carried out by different investigators, produced discrepant findings, as illustrated by an article on Nature (Orlic et al., 2001). After this setback the isolated instances of *trans-differentiation* observed in some vertebrate species following transplantation of adult stem cells have been debated by the scientific community and the observations so far made have been explained alternatively as a result of the fusion of a donor cell with a recipient one; in addition, even when trans-differentiation has been detected, only a small percentage of cells undergo to this process. This episode, seen as a drama by the scientific community, points out that as the complexity of a study increases its informative content paradoxically deteriorates. The scientific basis for this type of reasoning can easily be found in the field of mathematics, according to Gödel's Incompleteness Theorem: *a great complexity is a source of incompleteness because it increases the likelihood that true sentences cannot*

be proved (Calude and Jurgensen, 2005). In this regard it should be emphasized that the direct visualization of histological structures across a large number of fields coupled with immunohistochemistry assay on contiguous slices in clear guarantees, in any case, a high spatial resolution (Kwok et al., 2010; Ciulla et al., 2013).

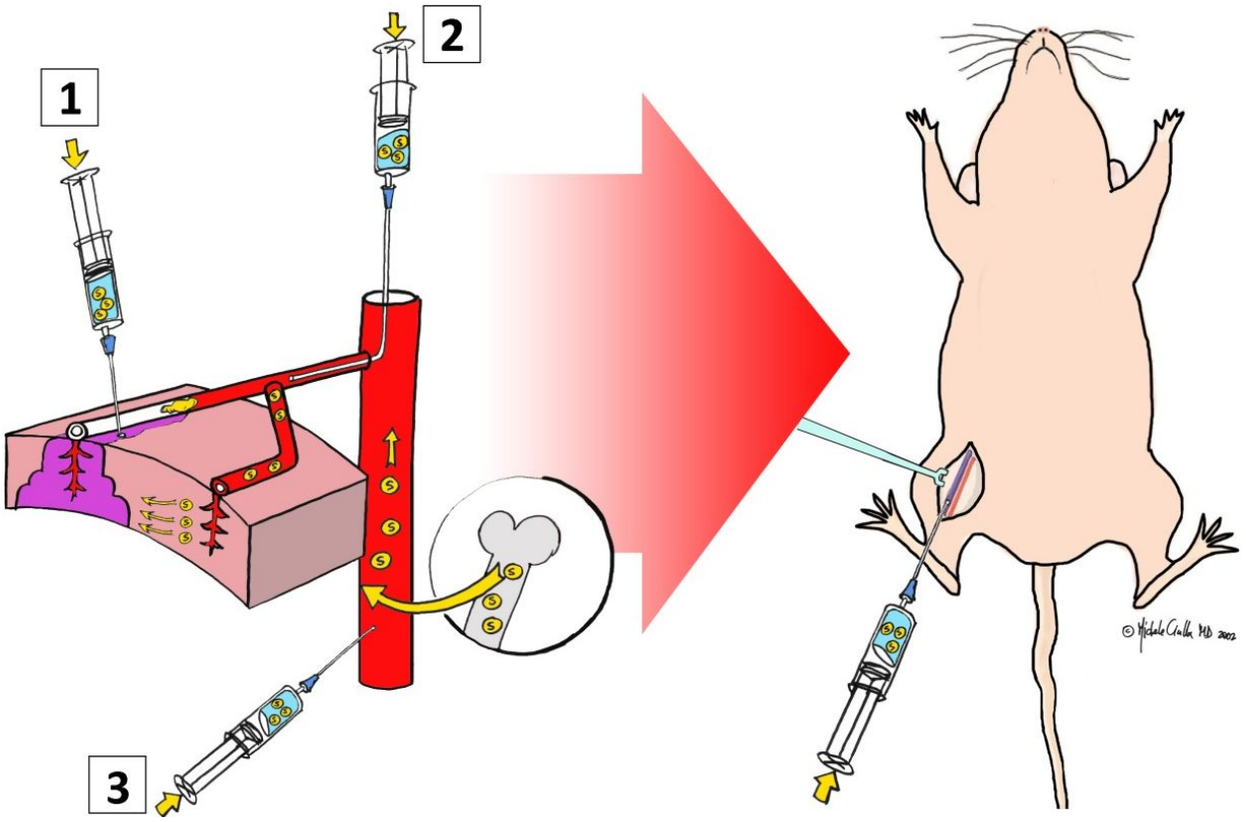
Nonetheless research on adult stem cells continues to generate great enthusiasm and has led researchers and clinicians to ask whether adult stem cells could be used for transplants. In the era of biomedicine, transplantations and tissue engineering, an emerging practical issue, however, is what kind of adult stem cells should be used to optimize the adaptive processes after tissue damage. Pioneering studies have focused on the most versatile adult stem cell such as the *hematopoietic* one that, starting from a common precursor, is able to give rise to very different cell lines. It must be remembered that adult hematopoietic stem cells transplantation has been used as a medical procedure in the field of hematology and oncology since the fifties (Rebulla and Giordano, 2004).

Once collected from a donor and administered peripherally to a recipient, the ability of these hematopoietic precursors, identified as *bone marrow mononuclear cells*, to travel through the circulation and to selectively targeting an area of *experimental myocardial damage* produced by means of *cryoinjury* (Ciulla et al., 2004b) has been demonstrated in rats (Ciulla et al., 2003) (Figure 9).

Furthermore, the study of the *mechanisms of homing* of these cells, also showed that this phenomenon is proportional to the extent of the damage (Ciulla et al., 2004a) and, finally, their contribution consists mainly in giving rise to new, actually working, vessels (Ciulla et al., 2006; Ciulla et al., 2007). Another instance is that transplanted cells might have also a *paracrine effect* such as to modulate the response to injury (Ciulla et al., 2008). In the perspective of the autologous infusion, it has been shown that adult stem cells, once removed from the body, have very limited ability to divide, making generation of large quantities of stem cells difficult (Ciulla et al., 2006). Despite these limitations, with a view to improve the healing process in humans, the advantages of using adult stem cells should be remarked as they allow to avoid the ethical and political issues associated with the use of embryonic stem cells.

5. Evolution in a gravitational environment or gravity as an evolutionary force

The gravity of the Earth refers to the *acceleration* that the Earth imparts to any given body on its surface by virtue of its *mass*; this acceleration is directed toward the center of the Earth and is approximately 9,81 m/sec^2. More precisely, according to the law of gravitation formulated by Isaac Newton to 1665, the attractive force between two bodies, in this case the earth and any object, is directly proportional to the product of the masses and inversely proportional to the square of their distance. The *mass* is an intrinsic property of any body and is a constant in classical physics, on the contrary the *weight* varies and *on Earth* is the result of *mass* for *Earth's gravitational acceleration*. Gravity or, better, the Earth's *gravitational field* hasn't significantly changed since the origins and is considered a *constant* although there are some differences in



The main routes used for the administration of hematopoietic precursors. Left drawing, 1) direct injection in the infarcted area; 2) direct coronary injection and 3) peripheral injection. Right drawing, peripheral injection in vivo in the femoral vein in rat.

Figure 9. Administration of adult stem cells in experimental model of myocardial injury

its distribution since the Earth is not a perfect sphere with a constant density and, due to its rotation, is subject to the *inertial force*.

By virtue of the gravity of the Earth, also living organisms have a weight that affects every aspect of life including biological ones. The life originated from the sea, landing on the ground of certain organisms and the experience of gravity has, therefore, required the development of specific mechanisms to counteract the effects of gravitational acceleration. Subsequently for some species the transition from the horizontal position to the vertical one has required the adoption of *sensors for the gravity* and of systems to allow the movement and the fine adjustment of the displacement of body fluids. (Table 2).

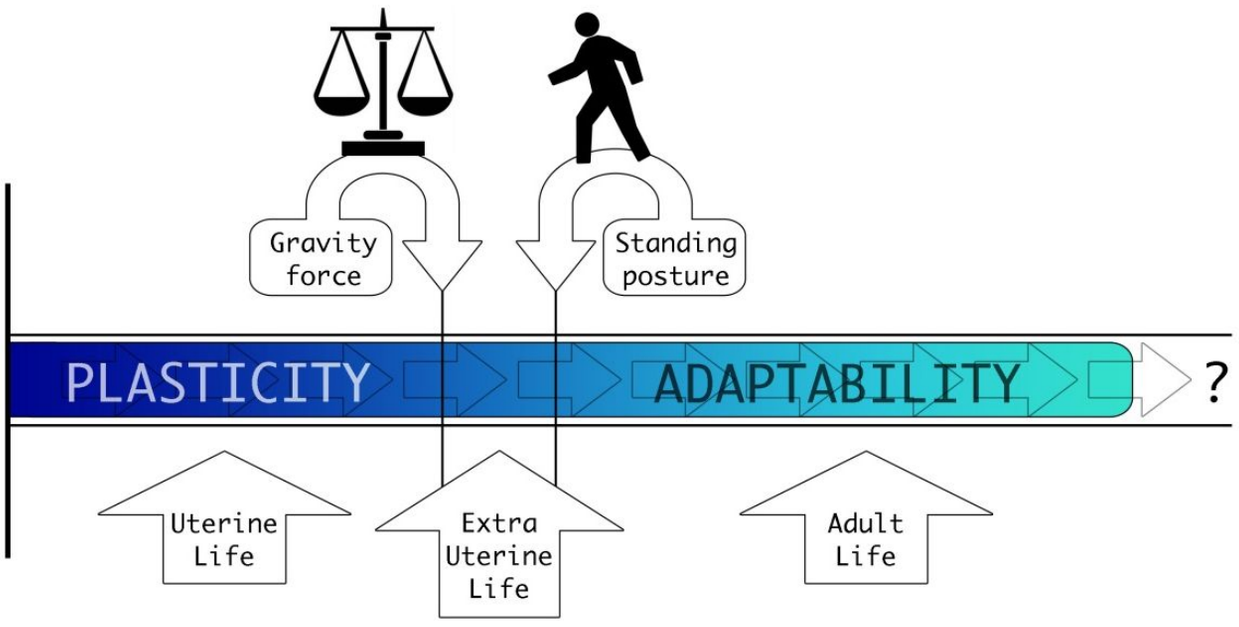
These postural changes from the horizontal position to the vertical one are cyclical and mainly related to the rhythms of activity and rest that are typical of each species. Furthermore, especially in placental mammals such as humans, for *n* months, first the embryo and then the fetus, are immersed in a fluid and compressed by a capsule that exerts a counter-pressure that diminishes the direction and the force of gravity creating a *microgravity environment*. This exposure to microgravity cause changes in gene expression in a variety of developing organ systems in live embryos (Shimada et al., 2005) thus the meaning of *prenatal life* goes beyond

http://dx.doi.org/10.5772/55931

Evolution in a gravitational environment
Sensors *Sensors for the gravity*
Standing and locomotion *Structural support* *Postural stability*
Fluid and Flow regulation *Fine adjustment of the displacement of body fluids*

Table 2. Requirements for the evolution of a complex organism in a gravitational environment

the simple effect of *mechanical protection* played by amniotic fluid as it covers an essential role in initiating the processes of long-term expression of the genetic program of the embryo. These different developmental pathways are ultimately triggered by the *external environment* through the maternal mediation (Fligny et al., 2009); the shift from uterine life to extra uterine life is concurrent with the progressive decrease of plasticity in favor of adaptability (Figure 10).



The transition from a microgravity environment (uterus) to a gravitational one and the assumption of standing posture in humans are potential stimuli shifting adaptive resources from plasticity to adaptability.

Figure 10. Gravity challenges and adaptive resources allocation during human life

The effects of gravity on organisms can be studied easily by varying the *gravity level* by simulating microgravity on the earth or in flight. The *simulated microgravity* is commonly

obtained on Earth by *head down tilt*, *prolonged bed rest* or *dry water immersion* (Magrini et al., 1992), in flight, during the fall phase of *parabolic flight in jet aircraft* or in orbit around the Earth with *spacecraft* (Table 3).

Simulated microgravity
On Earth - *Head down tilt* - *Prolonged bed rest*
In flight or in orbit around the Earth - *Parabolic flight in jet aircraft* - *Orbit flight in spacecraft*

Table 3. Experimental approaches to simulate microgravity

Since these techniques counteract some of the effects of gravity, it is believed they can provide important information relevant to biology in a gravitational environment.

Unfortunately the precise role of gravity on evolution is difficult to determine in complex organisms because, until now, the stay in a *microgravity environment* has been too limited and no higher vertebrate has passed at least one life cycle in microgravity to see the effects on subsequent generations. These simulations, even if limited in time, may nevertheless provide useful information on *adaptive processes* to counteract the force of gravity in different organisms and, in such sense, the responses of the cardiovascular system are paradigmatic. Previous observations suggests that prolonged dry water immersion after birth in rats is able to dissociate the effects of body growth and aging on systolic blood pressure since the microgravity reduces the needing for load-bearing structures and then the body weight, temporarily blunting systolic blood pressure rise (Magrini et al., 1992).

It should be remarked that the ability to survive in a gravitational environment is inversely proportional to the size, in other words unicellular organisms such as bacteria are much less sensitive to gravity when compared to complex organisms with blood circulation and subject to cyclical postural changes. These observations are derived from the study of extremophiles, i.e organisms capable of surviving in extreme environments and similar to those that are supposed to exist on other planets (Rothschild and Mancinelli, 2001; Brack and Pillinger, 1998).

Due to this lower sensitivity to changes in gravity, as demonstrated also by the growth at hyper-accelerations (Deguchi et al., 2011) and also to the high level of resistance in all ecosystems, bacteria have indeed the potential to travel in space and colonize planets with different gravity levels. This theoretical possibility, and some studies on meteorites, have led to the suggestive hypothesis that life on Earth has an extraterrestrial origin thanks to space vectors such as meteorites or asteroids (Mautner, 2002). This kind of exogenesis, challenged at the

http://dx.doi.org/10.5772/55931

theoretical level (Di Giulio, 2010), moves indeed elsewhere the problem of the origin of life but, at the same time, is in line with the concept of a solid common trunk for the tree of life which possibly consists in extremophile bacteria.

Since the bacteria are *single-celled organisms*, in assessing the effects of gravity a point that deserves emphasis is the impact of the microenvironment in which the cells are suspended which affects nutrient supply and disposal of waste with potential cumulative effects (Klaus et al., 1997).

6. The heart of the matter: Circulation of blood in a gravitational environment

Despite little changes over time in the Earth's gravitational field, the effects of gravity on living organisms cannot be properly appreciated without taking into account some factors related to the development of multicellularity that have introduced significant changes in the experiment of life on earth. Among these factors, the development of blood circulation and the propensity to postural change have certainly contributed to substantially increase the role of gravitational factors.

In complex organisms the development of a cardiovascular system fulfills the need for transport of nourishment, oxygen and metabolic waste as well as the need for communication between distant districts (Ciulla et al., 2011). The impacts of the *assumption of standing position* in mammals during evolution may have represented a real challenge for the cardiovascular system and, certainly a step forward in the freedom to move in space (Gisolf, 2005). This challenge presents itself in every individual after birth when the assumption of the upright position translocates the intravascular volume from the cardiopulmonary area to the periphery eliciting appropriate *neuro-humoral responses* whose objective is to control the dynamics of body fluids and blood pressure in a gravitational environment (Magrini et al., 1989). It should be recalled at this point that the heart of higher vertebrates is a quite complex multi-chambered pump that contracts synchronously; for its function, a number of components have to be generated; thus not surprisingly, several factors are involved in regulating the target genes responsible for both morphogenesis and function (Hoogaars et al., 2007).

Indeed the cardiovascular system begins to adapt to the gravitational loading before birth and, in particular, when the fetus, growing, begins to come into contact with the amniotic sac (Sekulic et al., 2005). This takes place towards the end of the pregnancy and is essential for the proper development of *sensory receptors* (Bradley and Mistretta, 1975) thus the microgravity resulting from immersion in the amniotic fluid does not mask the effects of gravity on the fetus. After birth, the newborn is immediately exposed to the gravitational load that, as we have seen, also varies depending on the posture. Exposure to gravitational stimuli may also have played a key role in the evolution of the position of the heart in relation to the circulation; taking, for example, three types of snakes that live in different environments, such as trees, land and sea, it was noticed that the position of the heart is closer or more distant from the head as a function of the gravitational load, being more distant in water snakes (Lillywhite,

1988). Therefore, even if gravity is a rather constant parameter on earth, it conditions the development of living organisms, before and after birth, with an increasing impact depending on having a blood circulation and, at the same time, on the propensity to postural change, and both of these characteristics are typical of higher vertebrates.

Finally, several findings suggest that gravity continues to play a decisive role *during aging*, since the reduction of loading conditions that characterizes the more sedentary life typical of the elderly has important effects on the organism that resemble, in many respects, to what happens in microgravity environment during prolonged space flight (Vernikos and Schneider, 2010). In particular, the reduction of motion and acceleration typical of *aging* and of the *prolonged space flight*, can decondition the cardiovascular reflexes, altering the control of blood pressure with *orthostatic hypotension*, and lead to a reduction of muscle mass and the loss of calcium from the bones.

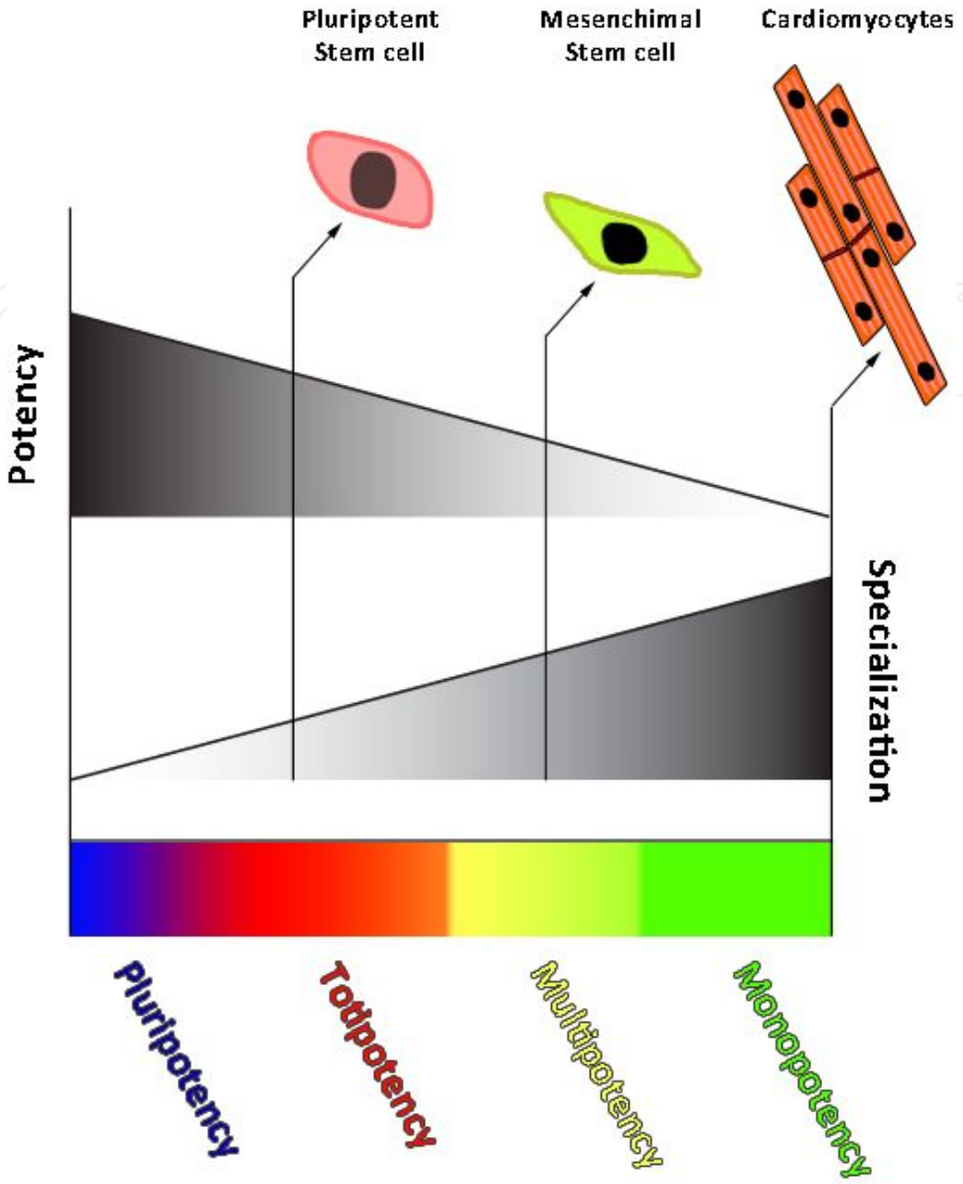
7. Generative and re-generative time windows: Definition and meaning

As we saw earlier, *generation* and *re-generation* are capabilities shared by the same deputy cells named *stem cells*, the only ones capable of differentiating into all cell types that make up a complex organism. The number of stem cells is limited as well as the number of generations, and their *potency* is maximal during the pre-natal life in the *embryonic stem cells*, and progressively decreases in post-natal life remaining confined within the *adult stem cells*. These processes have very tight *time constraints* to allow the *harmonious development* and *maintenance* of a very complicated structure such as a higher vertebrate; thus generative and re-generative processes are only possible at the opening of a *specific time-window* that coordinates them through the activation of specific gene sequences. In this respect, the evolution towards multicellularity is a form of adaptation to the environment that involves a high cost in terms of biological resources to handle *differentiation, specialization*, *establishment of functional hierarchies* and development of a *fully developed complex organisms* (Figure 11).

It is therefore evident that the availability of resources for other forms of adaptation in *adult life* such as the *re-generation* process for *maintenance* or *repair* is limited, especially if we take into account the complex organisms. These *time-windows* have very different characteristics, the *generative time-window* close formally when the organism reaches its full development, although with large time differences between the various tissues. On the other hand, the *re-generative time-window* differ depending on the tissue and on the functional hierarchy that it covers; more precisely, in *permanent tissues*, the re-generative time window is *formally closed* and the cells that compose them cannot divide after generation; in *stable tissues* the window *can be re-opened* in the event of a *limited damage* to allow the *repair*; finally, in *labile tissues*, the window *remains open* almost throughout the life cycle for maintenance and repair (Figure 12).

It should be recalled, therefore, that the experiment of life on earth includes the *possibility of damages* caused by *unfavorable interactions* with the environment and, above all, that there are also some solutions to fix them (Ciulla et al., 2011). These solutions range from the optimal one which consists, obviously, in the re-generation, to that of lower efficacy such as the replacement

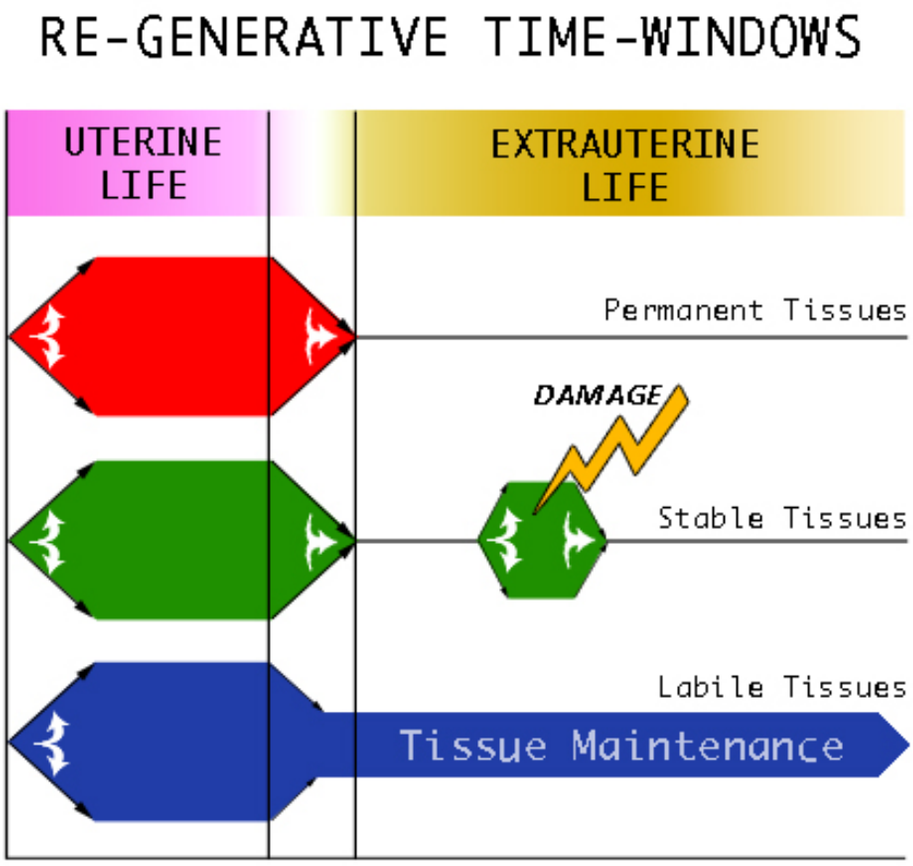
http://dx.doi.org/10.5772/55931



The number of stem cells and their replication cycles are limited; their potency is maximal during pre-natal life (embryonic stem cells) and progressively reduces in post-natal life (adult stem cells). Generative and re-generative processes are possible only at the opening of a specific time-window (Figure 12). The potency of the cells is inversely proportional the degree of cellular specialization, that is thus maximal at monopotency.

Figure 11. Relationship between potency and specialization of cells

of damaged tissue with *scar tissue*, a process known as *scarring*. Thus, the primary roles of *adult stem cells* in a living organism is to support the *functional reserve* by *maintaining* and, eventually, *repairing* the tissue in which they are found, according to a specific re-generative time window. Unfortunately there is a very small number of adult stem cells in each tissue, with large numerical differences between a tissue and another, and, therefore, the *re-generative potential* is unevenly distributed and, in any case, is limited. It should be remarked that in the *vascular system* a vast reservoir of adult stem cells is maintained for *renewal processes* including



Master plan of re-generative time-windows in the three main tissues, according to the cell replication capabilities during human life. The white arrows indicate the opening and the closing of each window.

Figure 12. Re-generative time-windows

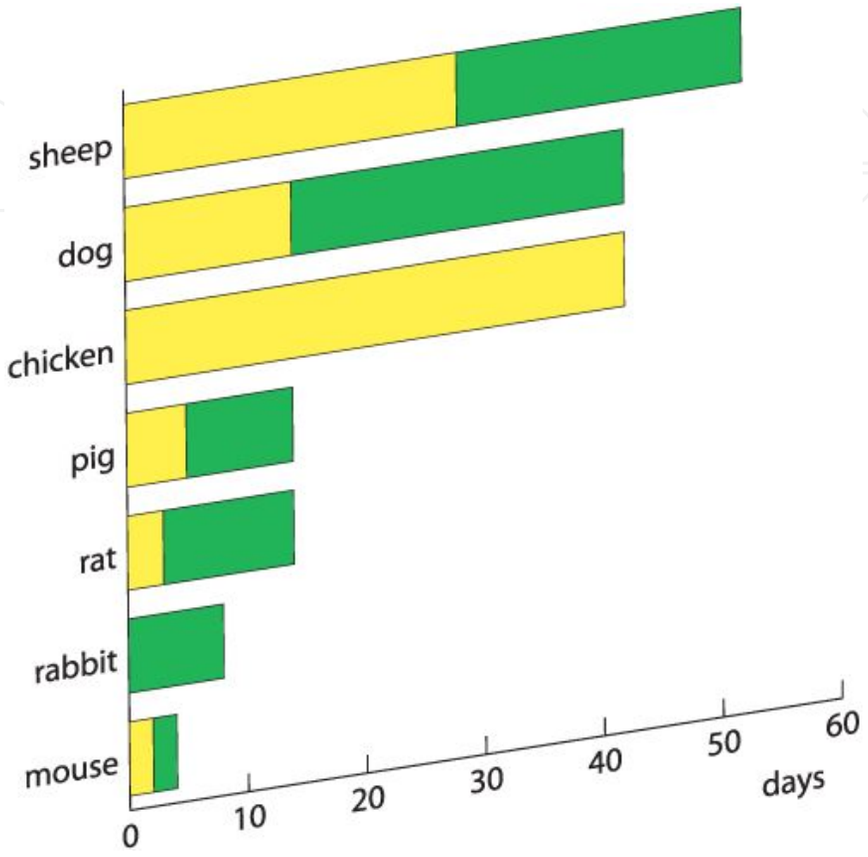
the continuous production of the endothelial cells lining the vessel wall and of the circulating blood elements.

In complex organisms the functional hierarchy is paramount in allocating this functional reserve where it is needed establishing the priorities in the *distribution of the available resources*. In mammals many adult tissues contain populations of adult stem cells that have the capacity for *renewal after disease* or *aging* but some *highly specialized tissues* -such as heart and brain- have a very limited re-generative potential. At this regard, we cannot exclude that the extreme structural and functional specialization reached by some tissues is a further and, possibly, inherent limit to re-generation.

Thus, returning to a broader view, it is a matter of fact that in the complex interplay between organization of the living matter, natural selection and adaptation, mammals have evolved with limited or no re-generative capabilities of the heart after birth and the reasons for this apparent flaw have to be sought in organization and allocation of resources in a hierarchically structured multi-cellular organism with an evolved system of transport and communication, such as the circulation of blood.

http://dx.doi.org/10.5772/55931

Focusing on *adaptive resource allocation*, it is widely acknowledged that during the post-natal development of the heart in higher vertebrates there exists a limited generative time-window. In figure 13 we show the upper limit of such time-window for different animal species.



During the post-natal cardiac development exists a limited time-window of potential tissue regeneration; the graph shows the lower (yellow) and the upper (green) length of this period. The data were taken from the following references: (Li et al., 1997; Brodsky et al., 1988; Hoerter et al., 1981; Clubb and Bishop, 1984; Burrell et al., 2003; Morgan and Beinlich, 1997; Bishop and Hine, 1975). Data collected by courtesy of Paola Nicolini, MD.

Figure 13. Limited generative time-window of the heart in higher vertebrates

Since generation and re-generation of the heart rely on the same physiological reserve consisting in proliferating cardiomyocytes, is logical to assume that the generative and re-generative time-windows coincide, but the questions on re-generative potential still open are:

1. *Why the limited re-generative capacity of the heart is a current problem?*

2. *What is the physiological significance of this post-natal time-window?*

3. *What are the clinical implications of this last re-generative chance for the heart?*

1. *Why the limited re-generative capacity of the heart is a current problem?*

In humans what appears to be a flaw may not have been a problem for thousands of years until, in the twentieth century, the increase in *life expectancy* (Burger et al., 2012) has given rise

to diseases generally less frequent in the first three or four decades of life. Therefore, the significant increase in *morbidity* and *mortality* related to cardiovascular disease, seen mainly in Western countries in the last years (Smil, 1989; Ramsden et al., 2009), has brought to the foreground the problem of *cardiac damage* and of its repair. According to this broader view of the problem, the limited regenerative capacity should be read in the context of the processes associated with aging (Frangogiannis, 2012). At this point it should be emphasized that in Western societies cardiovascular disease have a cost and this cost is fully or partly covered by the community; therefore, as economic resources are finite and health care costs are programmed at the political level on the basis of emerging issues, the new opportunities arising from research on adult stem cells have represented in recent years an attractive location for public and private funds. As in the overall budget military spending represents an item in competition with those of health, research on adult stem cells has the great merit to redirect spending towards scientific research in the biomedical field.

2. *What is the physiological significance of this post-natal re-generative time-window?*

Some studies have tried to characterize the post-natal re-generative window by using its potential to repair a myocardial damage. Among them, one of the most impressive for the scientific community was conducted a few years ago on the zebrafish with the amputation of a limited portion of the cardiac apex (Poss et al., 2002). The results were in line with the expectations since this kind of injury is coherent with the pathophysiology of teleost fish and urodele amphibians which are known to regenerate body parts, and the resected ventricle was regenerated (Poss et al., 2002; Neff et al., 1996). More recently, a similar experiment was conducted on mice achieving a similar regenerative result (Porrello et al., 2011) even if the resection of about 15% of the ventricular myocardium has a poor clinical applicability to humans. Unfortunately the goal of both these studies, was not to elucidate the physiological significance of this re-generative time-window but, rather, to evaluate its potential under *extreme experimental conditions* far from a clinical setting, even if hypothetical.

In this regard, the limited duration of the re-generative cardiac time-window and its placement between fetal and postnatal life clearly argues for its physiological function linked to the development of the cardiovascular system in a gravitational environment whose impact grows, indeed, after the birth. The plasticity of the heart is therefore required in mammals to support the new load conditions: birth is an event that carries great challenges for the heart, not only because there is a change from the fetal to the neonatal circulation which imposes haemodynamic stresses on the ventricles but also because it is marked by a transition from a microgravitational to a gravitational environment, with gravity playing a key role in the maturation of the cardiovascular system (Magrini et al., 1989).

Thus it cannot be excluded that the use of this post-natal potential for *re-generative purposes* that go beyond the physiology, such as the repair of a myocardial damage, would interfere with normal cardiac development.

About the mechanism by which myocytes proliferate, the proliferation of cardiomyocytes implies their dedifferentiation and the previous cited study (Porrello et al., 2011) provided evidence of sarcomeric disassembly, but this is somewhat far from a biological point of view. Indeed, with

http://dx.doi.org/10.5772/55931

the sole exception of cancer stem cells it is generally accepted that cell division does not require the cell to move backwards along its differentiation pathway. Other authors (Bersell et al., 2009) suggest that sarcomeric disassembly occurs in *differentiated* cardiomyocytes and is the process by which the cell reorganises its contractile apparatus to avoid interference with karyo- and cytokinesis. But the most likely hypothesis is that the replicating cells belong to an earlier stage of differentiation since possibly are adult cardiac stem cells committed to the myogenic lineage. There is convincing data that in vitro *c-kit+* stem cells show an immature morphological and functional phenotype, including sarcomeric disassembly (Beltrami et al., 2003).

Finally, as it is known that the physiological processes taking place during postnatal cardiac growth lie along a continuum in time (Ahuja et al., 2007) it is reasonable to suppose that the proliferative response to amputation, in terms of intensity and duration, would also exhibit a temporal gradient. Unfortunately it is not possible to track its dynamics since none of these studies investigate multiple time-points and neglect the intermediate time-window. In future studies aimed to the characterization of this re-generative time-window valuable information might be obtained by exploring earlier time-points around the time of birth, possibly including the late prenatal period. Moreover, considering that physiological reserves are finite, to exclude that the use of these resources does not interfere with cardiac development, both the contractility and the residual proliferative potential of the heart should be evaluated carefully.

3. *What are the clinical implications of this last re-generative chance for the heart?*

As we have seen, this time-window that appears to be the last post-natal re-generative "chance" of the heart argues for a function that seems to be closely linked to the development of the cardiovascular system in a gravitational environment and, in particular, to support the new load conditions at birth. Thus it is difficult hypothesize its role in a specific clinical scenario. Assuming a clinical role for this time-window restricted to the neonatal period, it is possible to take into consideration neonatal acute myocardial infarction (AMI) as clinical scenario, but AMI is rare, usually due to congenital heart disease, paradoxical coronary artery thromboembolism or perinatal asphyxia in premature newborns with severe respiratory distress (Poonai et al., 2009), and is often extensive (Fesslova et al., 2010; Abdurrahman et al., 1999; Iannone et al., 1975) and with an extremely high mortality rate, approaching 90% (Poonai et al., 2009). This, of course, raises questions about the possibility to use the re-generative resources for reparative purposes in this context. On the other hand, if applied to the clinical setting of adult AMI, it would be more appropriate since, according to recent epidemiological data, the last few decades have witnessed a marked decrease in infarction severity, with a growing predominance of non-ST elevation AMI (NSTEMI) over transmural AMI (Roger et al., 2010). Unfortunately this time-window is almost completely closed soon after birth in mammals, therefore his only possible clinical use in adults requires the exact knowledge of the mechanisms that control its opening and closing in order to re-open it when necessary as to repair a myocardial damage. Finally, it is possible to speculate that further experiments in microgravity environment, such as prolonged space flight, can provide further information on the functioning of the post-natal re-generative time-window of the heart.

8. Concluding remarks

This text traces its origin in the lectures given to students, in the discussions held with PhD students and in some years spent in cardiovascular research, and more precisely, in hematopoietic adult stem cells. All it has been then placed in an evolutionary perspective that has helped to give the text a teleological perspective; however, being the territory of the origins and evolution of life on earth almost without scientific evidences, the text leaves wide space for the imagination of the authors.

The text was then carefully reviewed to avoid repetitive forms that relate to citations; unfortunately, in some cases, this may have led to borderline syntactic forms, so we apologize to our readers. Finally, the images, with some exceptions, are an attempt to conceptualize the evolution and the adaptive processes and, therefore, do not have a data base to which to refer, however, we believe that they can illustrate complex phenomena not yet completely known.

9. Summary

In the complex interplay between organization of the living matter, natural selection and adaptation, mammals have evolved with limited or no re-generative capabilities of the heart after birth.

The reasons for this apparent flaw is far from being understood, however, they are closely related to the concept of organization and allocation of resources in a hierarchically structured multi-cellular organism with an evolved system of transport and communication, such as the circulation of blood. In humans this flaw may not have been a problem for thousands of years until, in the twentieth century, the increase in life expectancy has given rise to diseases generally less frequent in the first three or four decades of life. Therefore, the significant increase in morbidity and mortality related to cardiovascular disease, seen mainly in Western countries in the last years, has brought to the foreground the problem of cardiac damage and of its repair. In order to develop new therapies for cardiovascular damage aimed at reawakening and, possibly, expanding the limited re-generative capabilities of the heart is necessary to reconsider the basic concept on adaptation and functional reserve allocation in complex organisms.

In this regard, the demonstration of a temporary re-generative window in the post-natal heart of higher vertebrates may provide an opportunity to investigate when, why and how the re-generative capabilities are self-limited in some organs by the genetic program.

Therefore in this chapter we will consider this window that appears to be the last post-natal re-generative "chance" of the heart and try to place it in the general context of the adaptation by assuming that its meaning is, at least in part, related to the cardiovascular adjustment in a gravitational environment.

Author details

Michele Mario Ciulla*, Gianluca Lorenzo Perrucci and Fabio Magrini

*Address all correspondence to: michele.ciulla@unimi.it

Department of Clinical Science and Community Health, Laboratory of Clinical Informatics and Cardiovascular Imaging, University of Milan, Milan, Italy

References

[1] Abdurrahman, L, Schwartz, S M, & Beekman, R H. rd (1999). Thrombotic occlusion of the main stem of the left coronary artery in a neonate Cardiol Young , 9-189.

[2] Ahuja, P, & Sdek, P. and MacLellan W R (2007). Cardiac myocyte cell cycle control in development, disease, and regeneration Physiol Rev , 87-521.

[3] Aldiss, B W. (2001). Desperately seeking aliens Nature , 409-1080.

[4] Antonovics, J, Boots, M, Abbate, J, Baker, C, Mcfrederick, Q, & Panjeti, V. (2011). Biology and evolution of sexual transmission Ann N Y Acad Sci , 1230-12.

[5] Assessment, U. S C O o T (1987). Technologies to Maintain Biological Diversity, OTA-F-330 (Washington, D.C.: U.S. Government Printing Office)

[6] Ayala, F J. (1999). Adaptation and novelty: teleological explanations in evolutionary biology Hist Philos Life Sci , 21-3.

[7] Balaban, N Q, Merrin, J, Chait, R, Kowalik, L, & Leibler, S. (2004). Science, (United States , 1622-1625.

[8] Bayliss, C D, Field, D, & Moxon, E R. (2001). The simple sequence contingency loci of Haemophilus influenzae and Neisseria meningitidis J Clin Invest , 107-657.

[9] Beltrami, A P, Barlucchi, L, Torella, D, Baker, M, Limana, F, Chimenti, S, Kasahara, H, Rota, M, Musso, E, Urbanek, K, Leri, A, Kajstura, J, Nadal-ginard, B, & Anversa, P. (2003). Adult cardiac stem cells are multipotent and support myocardial regeneration Cell , 114-763.

[10] Bersell, K, Arab, S, Haring, B, & Kuhn, B. (2009). Neuregulin1/ErbB4 signaling induces cardiomyocyte proliferation and repair of heart injury Cell , 138-257.

[11] Beveridge, W. I B (1957). The art of scientific investigation (New York: W W Norton & Company Inc.)

[12] Bishop, S P, & Hine, P. (1975). Carciac muscle cytoplasmic and nuclear development during canine neonatal growth Recent Adv Stud Cardiac Struct Metab , 8-77.

[13] Bonifield, H R, & Hughes, K T. (2003). Flagellar phase variation in Salmonella enterica is mediated by a posttranscriptional control mechanism J Bacteriol , 185-3567.

[14] Boxenbaum, H. (1991). Scientific creativity: a review Drug Metab Rev , 23-473.

[15] Brack, A, & Pillinger, C T. (1998). Life on Mars: chemical arguments and clues from Martian meteorites Extremophiles , 2-313.

[16] Bradley, R M, & Mistretta, C M. (1975). Fetal sensory receptors Physiol Rev , 55-352.

[17] Brodsky, V, Carlson, B M, Arefieva, A M, & Vacilieva, I A. (1988). Polyploidization of transplanted cardiac myocytes Cell Differ Dev , 25-177.

[18] Burger, O, Baudisch, A, & Vaupel, J W. (2012). Proc Natl Acad Sci U S A,

[19] Burrell, J H, Boyn, A M, Kumarasamy, V, Hsieh, A, Head, S I, & Lumbers, E R. (2003). Growth and maturation of cardiac myocytes in fetal sheep in the second half of gestation Anat Rec A Discov Mol Cell Evol Biol , 274-952.

[20] Calude, C, & Jurgensen, H. (2005). Is complexity a source of incompleteness? Adv Appl Math , 35-1.

[21] Cannon, W B. (1929). Organization For Physiological Homeostasis. Physiological Review , 9-399.

[22] Cavalier-smith, T. (2006). Philos Trans R Soc Lond B Biol Sci, (England , 969-1006.

[23] Charlesworth, B. (1988). Science, (United States , 1072-1073.

[24] Ciulla, M M, Acquistapace, G, Perrucci, G L, Nicolini, P, Toffetti, L, Braidotti, P, Ferrero, S, Zucca, I, Aquino, D, Busca, G, & Magrini, F. (2013). Immunohistochemical Expression of Oncological Proliferation Markers in the Heart of Rats during Normal Pregnancy Biomarker in Medicine, 119-129

[25] Ciulla, M M, Ferrero, S, Gianelli, U, Paliotti, R, Magrini, F, & Braidotti, P. (2007). Micron, (England , 321-322.

[26] Ciulla, M M, Ferrero, S, Lazzari, L, Pacchiana, R, Paliotti, R, Gianelli, U, Busca, G, Esposito, A, Bosari, S, Magrini, F, & Rebulla, P. United States , 239-244.

[27] Ciulla, M M, Ferrero, S, Montelatici, E, Gianelli, U, Braidotti, P, Calderoni, S, Paliotti, R, Annoni, G, De Camilli, E, Busca, G, Magrini, F, Bosari, S, Lazzari, L, & Rebulla, P. (2006). Assessment of selective homing and contribution to vessel formation of cryopreserved peripherally injected bone marrow mononuclear cells following experimental myocardial damage Cardiovasc Hematol Disord Drug Targets , 6-141.

[28] Ciulla, M M, Lazzari, L, Pacchiana, R, Esposito, A, Bosari, S, Ferrero, S, Gianelli, U, Paliotti, R, Busca, G, Giorgetti, A, Magrini, F, & Rebulla, P. (2003). Homing of peripherally injected bone marrow cells in rat after experimental myocardial injury Haematologica , 88-614.

[29] Ciulla, M M, Montelatici, E, Ferrero, S, Braidotti, P, Paliotti, R, Annoni, G, De Camilli, E, Busca, G, Chiappa, L, Rebulla, P, Magrini, F, & Lazzari, L. (2008). J Transl Med, (England , 30.

[30] Ciulla, M M, Nicolini, P, Perrucci, G L, Benfenati, C, & Magrini, F. (2011). Advances in Regenerative Medicine, ed S W-G (Ed.)

[31] Ciulla, M M, Paliotti, R, Ferrero, S, Braidotti, P, Esposito, A, Gianelli, U, Busca, G, Cioffi, U, Bulfamante, G, & Magrini, F. (2004). b J Surg Res, (United States , 91-97.

[32] Clubb, F J. Jr. and Bishop S (1984). Formation of binucleated myocardial cells in the neonatal rat. An index for growth hypertrophy Lab Invest 50 571-7, 1984.

[33] Dalrymple, G B. (1991). The Age of the Earth (California: Stanford University Press)

[34] Darwin, C R. (1859). On the origin of species by means of natural selection, or the preservation of favoured races in the struggle for life (London: John Murray)

[35] Deguchi, S, Shimoshige, H, Tsudome, M, Mukai, S A, Corkery, R W, Ito, S, & Horikoshi, K. (2011). Proc Natl Acad Sci U S A, (United States , 7997-8002.

[36] Dennett, D. (2009). Proc Natl Acad Sci U S A, (United States , 10061-10065.

[37] Di Giulio M (2010). J Theor BiolEngland: 2010 Elsevier Ltd) , 569-572.

[38] Edwards, A W. (2000). The genetical theory of natural selection Genetics , 154-1419.

[39] Eldredge, N, & Thompson, J N. Brakefield P M, Gavrilets S, Jablonski D, Jackson J B C, Lenski R E, Lieberman B S, McPeek M A and Miller W I (2005). The dynamics of evolutionary stasis Paleobiology , 31-133.

[40] Engelstadter, J. (2008). Constraints on the evolution of asexual reproduction Bioessays , 30-1138.

[41] Fesslova, V, Lucci, G, Brankovic, J, Cordaro, S, Caselli, E, & Moro, G. Massive myocardial infarction in a full-term newborn: a case report Int J Pediatr (2010).

[42] Fligny, C, Hatia, S, Amireault, P, Mallet, J, & Cote, F. (2009). Mammalian prenatal development: the influence of maternally derived molecules Bioessays , 31-935.

[43] Frangogiannis, N G. (2012). Regulation of the inflammatory response in cardiac repair Circ Res , 110-159.

[44] Furusawa, C, & Kaneko, K. (2000). Complex organization in multicellularity as a necessity in evolution Artif Life , 6-265.

[45] Gisolf, J. (2005). Postural changes in humans : effects of gravity on the circulation. (Amsterdam: University of Amsterdam)

[46] Graham, A. (2011). Am J Bot, (United States , 336-351.

[47] Griffiths, A, Gelbart, F, Miller, W M, & Lewontin, J H. R C (1999). Modern Genetic Analysis (New York: W. H. Freeman)

[48] Gromov, P S, & Celis, J E. (2000). From genomics to proteomics] Mol Biol (Mosk) , 34-597.

[49] Hayflick, L. (1965). THE LIMITED IN VITRO LIFETIME OF HUMAN DIPLOID CELL STRAINS Exp Cell Res , 37-614.

[50] Hoerter, J, Mazet, F, & Vassort, G. (1981). Perinatal growth of the rabbit cardiac cell: possible implications for the mechanism of relaxation J Mol Cell Cardiol , 13-725.

[51] Hoogaars, W M, Barnett, P, Moorman, A F, & Christoffels, V M. (2007 T). box factors determine cardiac design Cell Mol Life Sci , 64-646.

[52] Hunter, P. (2007). EMBO Rep, (England , 316-318.

[53] Iannone, L A, Duritz, G, & Mccarty, R J. (1975). Myocardial infarction in the newborn: a case report complicated by cardiogenic shock and associated with normal coronary arteries Am Heart J , 89-232.

[54] Jablonsky, D. (1994). Extinctions in the Fossil Record [and Discussion] Philosophical transactions- Royal Society. Biological sciences , 344-11.

[55] Kearns, D B, Chu, F, Rudner, R, & Losick, R. (2004). Mol Microbiol, (England , 357-369.

[56] Klaus, D, Simske, S, Todd, P, & Stodieck, L. (1997). Investigation of space flight effects on Escherichia coli and a proposed model of underlying physical mechanisms Microbiology 143 (Pt 2) 449-55

[57] Kussell, E, & Leibler, S. (2005). Phenotypic diversity, population growth, and information in fluctuating environments Science , 309-2075.

[58] Kutschera, U. (2009). Charles Darwin's Origin of Species, directional selection, and the evolutionary sciences today Naturwissenschaften , 96-1247.

[59] Kwok, T C, Rakha, E A, Lee, A H, Grainge, M, Green, A R, Ellis, I O, & Powe, D G. (2010). Histopathology, (England , 212-219.

[60] Lachke, S A, Joly, S, Daniels, K, & Soll, D R. (2002). Phenotypic switching and filamentation in Candida glabrata Microbiology , 148-2661.

[61] Li, F, Mcnelis, M R, Lustig, K, & Gerdes, A M. (1997). Hyperplasia and hypertrophy of chicken cardiac myocytes during posthatching development Am J Physiol 273 R, 518-26.

[62] Lillywhite, H. (1988). Snakes, blood circulation and gravity Scientific American , 256-92.

[63] Magrini, F, Reggiani, P, Ciulla, M, Meazza, R, & Branzi, G. (1992). Prolonged water immersion. Effects on blood pressure maturation in normotensive rats Hypertension , 19-482.

[64] Magrini, F, Roberts, N, Branzi, G, Mondadori, C, Reggiani, P, Meazza, R, & Ciulla, M. (1989). Cardiac responses to head up tilt during early extrauterine life: relevance of active acquisition of erect posture Cardiovasc Res , 23-460.

[65] Marschner, B, & Kalbitz, K. (2003). Controls of bioavailability and biodegradability of dissolved organic matter in soils Geoderma , 113-211.

[66] Martin, W, & Russell, M J. (2003). On the origins of cells: a hypothesis for the evolutionary transitions from abiotic geochemistry to chemoautotrophic prokaryotes, and from prokaryotes to nucleated cells Philos Trans R Soc Lond B Biol Sci discussion-5, 358-59.

[67] Mautner, M N. (2002). Planetary resources and astroecology. Planetary microcosm models of asteroid and meteorite interiors: electrolyte solutions and microbial growth--implications for space populations and panspermia Astrobiology , 2-59.

[68] Mereschkowsky, K. (1926). Symbiogenesis and the Origin of Species

[69] Morgan, H E, & Beinlich, C J. (1997). Rapid cardiac growth--mechanical, neural and endocrine dependence Jpn Circ J , 61-645.

[70] Neff, A W, Dent, A E, & Armstrong, J B. (1996). Heart development and regeneration in urodeles. The International journal of developmental biology , 40-719.

[71] Orlic, D, Kajstura, J, Chimenti, S, Jakoniuk, I, Anderson, S M, Li, B, Pickel, J, Mckay, R, Nadal-ginard, B, Bodine, D M, Leri, A, & Anversa, P. (2001). Bone marrow cells regenerate infarcted myocardium Nature , 410-701.

[72] Pelaprat, E, & Cole, M. (2011). Minding the gap": imagination, creativity and human cognition Integr Psychol Behav Sci , 45-397.

[73] Perez-martin, J, Uria, J A, & Johnson, A D. (1999). Phenotypic switching in Candida albicans is controlled by a SIR2 gene EMBO J , 18-2580.

[74] Poonai, N, Kornecki, A, Buffo, I, & Pepelassis, D. (2009). Neonatal myocardial infarction secondary to umbilical venous catheterization: A case report and review of the literature Paediatr Child Health , 14-539.

[75] Porrello, E R, Mahmoud, A I, Simpson, E, Hill, J A, Richardson, J A, Olson, E N, & Sadek, H A. (2011). Science, (United States , 1078-1080.

[76] Poss, K D, Wilson, L G, & Keating, M T. (2002). Science, (United States , 2188-2190.

[77] Prochnik, S E, Umen, J, Nedelcu, A M, Hallmann, A, Miller, S M, Nishii, I, Ferris, P, Kuo, A, Mitros, T, Fritz-laylin, L K, Hellsten, U, Chapman, J, Simakov, O, Rensing, S A, Terry, A, Pangilinan, J, Kapitonov, V, Jurka, J, Salamov, A, Shapiro, H, Schmutz, J,

Grimwood, J, Lindquist, E, Lucas, S, Grigoriev, I V, Schmitt, R, Kirk, D, & Rokhsar, D S. (2010). Science, (United States , 223-226.

[78] Ramsden, C E, Faurot, K R, Carrera-bastos, P, Cordain, L, De Lorgeril, M, & Sperling, L S. (2009). Dietary fat quality and coronary heart disease prevention: a unified theory based on evolutionary, historical, global, and modern perspectives Curr Treat Options Cardiovasc Med , 11-289.

[79] Ratcliff, W C, Denison, R F, Borrello, M, & Travisano, M. (2012). Proc Natl Acad Sci U S A, (United States , 1595-1600.

[80] Raup, D M, & Sepkoski, J J. Jr. (1982). Science, (United States , 1501-1503.

[81] Rebulla, P, & Giordano, R. (2004). Int J Cardiol, (Ireland , S38-S42.

[82] Roger, V L, Weston, S A, Gerber, Y, Killian, J M, Dunlay, S M, Jaffe, A S, Bell, M R, Kors, J, Yawn, B P, & Jacobsen, S J. (2010). Trends in incidence, severity, and outcome of hospitalized myocardial infarction Circulation , 121-863.

[83] Rothschild, L J, & Mancinelli, R L. (2001). Life in extreme environments Nature , 409-1092.

[84] Roze, D. (2012). PLoS Biol, (United States , e1001321.

[85] Russell, P J. (1998). Genetica. Edises) , 804.

[86] Scadden, D T. (2007). The weight of cell identity J Clin Invest , 117-3653.

[87] Sekulic, S R, Lukac, D D, & Naumovic, N M. (2005). Med Hypotheses, (Scotland , 221-228.

[88] Shimada, N, Sokunbi, G, & Moorman, S J. (2005). BMC Dev Biol, (England , 10.

[89] Smil, V. (1989). Coronary Heart Disease, Diet, and Western Mortality Population and Development Review , 15-399.

[90] Soll, D R, & Kraft, B. (1988). A comparison of high frequency switching in the yeast Candida albicans and the slime mold Dictyostelium discoideum Dev Genet , 9-615.

[91] Stajich, J E, & Hahn, M W. (2005). Mol Biol Evol, (United States , 63-73.

[92] Staley, J T. (2006). Philos Trans R Soc Lond B Biol Sci, (England , 1899-1909.

[93] Vernikos, J, & Schneider, V S. (2010). Gerontology, (Switzerland: 2009 S. Karger AG, Basel.) , 157-166.

[94] Von Goethe, J W. Versuch die Metamorphose der Pflanzen zu erklären

[95] Wickramasinghe, C. (2004). Cryobiology, (United States , 113-125.

[96] Wilkins, A S, & Holliday, R. (2009). Genetics, (United States , 3-12.

[97] Wilson, T L. (2001). The search for extraterrestrial intelligence Nature , 409-1110.

[98] Wong, J L, & Wessel, G M. (2006). Curr Top Dev Biol, (United States , 1-151.

IntechOpen

IntechOpen