

Supercellular patterns of information processing

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The ability to produce two identical copies of itself to be replaced by them is the most universal functional feature of each single cell. Just this feature suggests the mechanism of formation and the nature of an universal life pattern: the progressive cell propagation produces what can be called a cell progression. At the base of the cell progression, one cell grows and divides giving rise to two daughter cells. These newly formed cells themselves grow and divide producing four daughter cells which then give rise to eight cells and so on. In growing cell progression, the number of progeny cells redoubles after each round of cell divisions. The cell progression is an universal life pattern in principle. It is essentially a four-dimensional pattern of information processing. The implication of the well-known feature of the single cell to recognize an universal life pattern has been overlooked completely. Here, I draw attention to this implication and show that it yields a powerful conceptual framework suited very well to strongly integrate known life phenomena and to reveal their novel emergent features.

The whole cellular world is only one cell progression which arose from one single primordial cell and has 3 or 4 billions years of uninterrupted history. It can be called a general cell progression. The present-day biosphere is merely a tiny slice from it, a visible top of iceberg in ocean of time. The ancient part of this gigantic life pattern leaves very scarce traces. In the known universe, it is the most complex structure. The ultimate goal of biology is to understand its spatio-temporal organization as completely as possible.

Although all cells of the general cell progression should be theoretically identical to each other genetically, this is not the case in the nature. Rather, the general cell progression consists of numerous cell subprogressions which can be distinguished from each other just by different DNAs. In the general cell progression, DNA undergoes not only a multiplication but also a diversification. Each cell subprogression which is specified by a particular individual DNA can be referred to as an individual cell progression. The general cell progression can be considered as a growing composition of an increasing number of individual cell progressions.

Generally, the life history of an individual cell progression begins with a founder cell. In the founder cell, the DNA can be either monogenomic or digenomic. Digenomic DNA contains two non-identical genomes. Both monogenomic and digenomic cells can exhibit high level of ploidy which refer to the number of genomes without distinguishing between identical and non-identical.

If founder cell is monogenomic, the life history of the individual cell progression is simple.

Monogenomic DNA remains the same in all its cells beginning with founder cell. All members of such cell progression are genetically identical with one another and with the founder cell: each cell is considered to be a clone of the founder cell.

If in any cell the DNA will be significantly altered in any way, this cell becomes a new founder cell giving rise to a new individual cell progression.

One way to alter the monogenomic DNA is a sequence mutation which arises either spontaneously or as a result of exposure to mutagenic agents in environment. While sequence mutation is only the way to produce variants of the same gene, called alleles, it is considered as an ultimate source of gene diversification. Whether a mutation is good, neutral, or harmful depends on how it affects survival of the individual cell progression.

The other way to alter the monogenomic DNA is a sequence transfer that can be either intragenomic or intergenomic. There are a large number of extraordinarily specialized mechanisms of sequence transfer. Some mechanisms require more or less extensive sequence homology, the others do not.

If founder cell is digenomic, the life history of the individual cell progression becomes more complex.

The digenomic founder cell, a zygote, is a product of syngamy of two monogenomic cells, gametes. By syngamy, gametes first unify physically their complete matrices and then combine their complete DNAs. Both DNAs are usually homologous in the sense that, although differing in deoxyribonucleotides sequences, they show the same genome composition. Consequently, the zygote receives one allele of the gene from each gamete and contains two alleles of the same gene. If both its alleles are alike, the gene is homozygous. If its alleles are different, the gene is heterozygous. When the gene is heterozygous, one allele may be dominant and the other recessive since only one allele of the same gene can be expressed in digenomic cell. Only eukaryotic cells are able to form completely digenomic founder cell. The digenomic cell can be either in monokaryotic or in dikaryotic state.

Commonly, newly formed zygote progressively propagates producing cell subprogression which cells remain all digenomic. This digenomic cell subprogression can be called a zygotic cell progression.

Soon or later, any cells of zygotic cell progression deviate from normal sequence of stages in cell life history. First signs of such deviation occur during prophase, where homologous chromosomes recognize each other and become physically paired along their length. So, the two couples of chromatids are juxtaposed making a bundle of four, called a tetrad. At each tetrad, a remarkable process occurs: paired non-sister chromatids exchange homologous fragments of DNA through breakage and reunion of their arms at points called crossovers. During prometaphase, tetrads are released in the cytosol and captured by the spindle apparatus. During metaphase, they are aligned appropriately at the middle plane between the two poles of the spindle. During anaphase, homologous chromosomes are segregated by spindle apparatus, whereas sister chromatids of each chromosome remain joined together. Because of recombination the sister chromatids are strongly speaking not identical but rather different. Additionally, while the spindle apparatus segregates chromosomes randomly to either of a two poles, the distribution of

homologous chromosomes between two nuclei is also random. After cell division is complete, the cell is replaced by two cells which do not need to double their DNA and immediately undergo cell division to segregate sister chromatids. The series of these two cell divisions is collectively called meiosis. Meiosis replaces one digenomic cell, a meiocyte, by four monogenomic cells, unluckily designated tetrads. Genomes of tetrads differ not only from each other but also from two genomes of the meiocyte. Totally, a zygotic cell progression can produce $4N$ different genomes, where N is a number of cells that undergo meiosis, a meiocytes. The meiosis is the main source of DNA diversification in eukaryotic cells.

Each tetrad progressively propagates and so the zygotic cell progression branches into a multitude of monogenomic cell subprogressions which can be called tetradic cell progressions.

Thus, if the founder cell is digenomic, the individual cell progression contains one zygotic cell progression and $4N$ tetradic cell progressions.

In tetradic cell progressions, any monogenomic cells soon or later become gametes which can take part on syngamy to form new zygotes. Usually, gametes forming a zygote originate from different individual cell progressions. Alternatively, zygote can be formed by autogamy if gametes originate from the same individual cell progression or even from the same meiocyte. Very often, gametes exhibit female-male dimorphism. The female gamete, an egg, is usually non-motile and is said to be fertilized by a motile male gamete, a sperm. The same individual cell progression can produce either both gamete types, eggs and sperm, or only one of both gamete types, eggs or sperm.

In one extreme case, the zygote does not propagate but immediately undergo meiosis which products then propagate progressively. In this case, individual cell progression only consists of a zygote and of four tetradic cell progressions. The number of tetradic cell progressions can be reduced even to two if the zygote does not replicate DNA but immediately segregates non-sister chromatids randomly to either of a two daughter cells.

In other extreme case, the zygote progressively propagates, but tetrads do not. They immediately become gametes and take part in production of new zygotes and thus leave individual cell progression that therefore does not branch into tetradic cell progressions.

In an individual cell progression, not all cells necessarily have an equal chance of surviving and propagation. Many of them may die away. Immortality must be considered as a feature of an individual cell progression, not of a single cell. However, the immortality is rather a potential feature: despite the ability to persist forever by progressive cell propagation, no one individual cell progression becomes really immortal.

Thus, an individual cell progression is a primary source of genome multiplication and diversification.

Within the general cell progression, one individual cell progression gives rise to many new individual cell progressions which in turn give rise to the next generation of individual cell progressions and so on. A pool of homologous genomes arises. In this pool, genome variants are produced rather randomly without any confident expectation on future needs. However, some of them can make their individual cell progressions better suited to given environmental conditions. These individual cell progressions are more likely to survive and to produce next generation of new individual cell progressions than others. Changes in genome that can pass through more than one generation of individual cell progressions making them better suited to particular environment are called adaptations. Because the environment is always in changing, there is no one perfectly-adapted genome in pool. When previous adaptations are no longer suitable to new environmental conditions, extinction of such genomes from the pool occurs. Thus, genomes obey natural selection by changes in environment. Natural selection is made tougher by a constant struggle for limited resources of mass, impulse, and energy. Only the fittest survive a struggle for existence.

Some changes in genome can make it no more homologous to other genomes in pool. A new genome pool and, consequently, a new type of individual cell progressions arise. However, there is a great deal of convenience by definition of boundaries between different pools of genomes.

The genome multiplication and genome diversification seems to be the ultimate aim in the life history of an individual cell progression. Just these both events ensures the continuity of life from one generation of individual cell progressions to the next and so secures the immortality of the general cell progression and so the immortality of the Life on the Earth.

Thus, the genome multiplication and diversification provide raw material for evolution of types of individual cell progressions.

Different individual cell progressions display broad variability according to the temporal organization.

Within some individual cell progressions, all cells divide symmetrically so that two sister cells are always identical in their potential. If any cell differentiates in any direction of specialization, it retains the ability to de-differentiate or even to re-differentiate in other direction.

Within other individual cell progressions, some cells divide asymmetrically so that two sister cells are not always identical in their potential and may adopt distinct fates. Asymmetric cell division is a source of the cell diversification within the same individual cell progression. Although genetically identical, two sister cells produced by asymmetric cell division give rise to the cell subprogressions which differ from one another by differential DNA expression. Therefore, they can be called differential cell progressions. An individual cell progression can contain a large number of differential cell progressions which sometimes may be in complex interrelation to each other since asymmetric cell division can occur also within a differential cell progression itself.

Within some individual cell progressions, asymmetric cell divisions occur occasionally so that the cell diversification is rather a random.

Within other individual cell progressions, asymmetric cell divisions occur rather regularly so that the cell diversification is an established process during which the cell potential usually decreases sequentially. The progressive propagation of the initially totipotent founder cell produces a number of pluripotent cells. The totipotentiality of the founder cell is usually owed to a unique set of the cell fate determinants which becomes simply exhausted even if cells divide symmetrically. After a critical number of pluripotent cells is reached, they may divide either symmetrically or asymmetrically. Each asymmetric division produces one pluripotent cell and one multipotent cell. In turn, after a critical number of multipotent cells is reached, they also may divide either symmetrically or asymmetrically. The sequential diminishing of the cell potential ends with production of unipotent cells which fate is usually a division arrest and a terminal differentiation. A terminally differentiated cell can not de-differentiate. On the contrary, non-terminally differentiated cells may alternatively de-differentiate and even re-differentiate into other direction of specialization. In each newly formed founder cell, the totipotentiality is restored.

Asymmetric cell division is associated with either symmetric or asymmetric kinetics of cell propagation. Cell progression generally tends to grow exponentially when the kinetics of cell propagation is symmetric. On the contrary, the asymmetric kinetics of cell propagation can pose a fundamental barrier to exponential growth.

Asymmetric cell division associated with asymmetric kinetics of cell propagation is generally appreciated as an essential property of the so called stem cell. Stem cell divides very rarely. If it divides, only one daughter cell inherits stem cell property. On the contrary, the other daughter cell becomes a non-stem cell but propagates rather quickly giving rise to a large number of progeny cells. So, the stem cell gives rise to a differential cell progression that consists of a stem cell lineage and a number of differential cell subprogressions each of which has a non-stem daughter cell at the base. Whereas the potential to divide seems to remain unlimited throughout the whole stem cell lineage, the propagation of each non-stem daughter cell is accompanied by a sequential restriction of the division capacity down to the division arrest, terminal differentiation, and death. Thus, each non-stem cell gives rise to the differential cell subprogression with a limited number of progeny cells.

The differential cell progression with a stem cell at the base can be called an asymmetric cell progression and the differential cell subprogressions within it can be called limited cell progressions.

An asymmetric cell progression is a steady state system.

At the base of this system, the asymmetric division of the first stem cell yields the second stem cell and the first non-stem cell. The newly formed second stem cell remains inactive for a long period of time during which the first non-stem cell progressively propagates producing the first limited cell progression. Within a limited cell progression, the cells first propagate at the fastest rate producing a growing number

of so called transit amplifying cells. After a critical number of division rounds is reached, the cells become committed to undergo differentiation into one or more directions of specialization. Differentiating cells propagate at the lower rate and, when a critical number of division rounds is reached, they become mature specialized cells which do not divide and become exhausted by performing their special functions. At certain critical point of the history of the first limited cell progression, the second stem cell divides producing the third stem cell and the second non-stem cell so that the exhausted first limited cell progression becomes replaced by the newly formed second limited cell progression. Since the potential to divide remains unlimited throughout the stem cell lineage, the asymmetric cell progression produces unlimited number of limited cell progressions which replace each other in consecutive order. So, an asymmetric cell progression can maintain near a constant number of cells.

Different individual cell progressions display broad variability according to the spatial organization too.

Within some individual cell progressions, the cells will be rather randomly dispersed in space and each cell seems to become autonomous in behavior.

Just the individual cell progressions with this type of cell arrangement are poorly studied while most attention usually was paid solely the single cell. This type of cell arrangement allows different individual cell progressions to superpose each other in space.

Within other individual cell progressions, the cells will remain in an association, a cell colony, held together in any way.

In the individual cell progressions with this type of cell arrangement, the founder cell first gives rise to primary cell colony which body plan is usually a filamentous chain, a hypha, or a globular body, a sphaera. By further cell propagation, an initial primary cell colony usually clones itself giving rise to a number of primary cell colonies respectively. Within a growing individual cell progression, these primary cell colonies may be either dispersed in space or held together in association forming a secondary cell colony of any kind and size and for any period of time under specific environmental circumstances. In turn, an initial secondary cell colony can give rise to a number of secondary cell colonies. Within a growing individual cell progression, also the secondary cell colonies may be either dispersed in space or held together in larger cell association. So, different individual cell progression can superpose each other even at the level of the secondary cell colony.

Generally, the cell association has advantageous ability to carry out activities with a complexity not possible by single cell.

Within an association, many cells come together to collectively respond to environmental conditions. This collective respond is usually more effective than by a single cell.

Some cell associations are continuously growing systems, the others are rather steady state systems which cell number is balanced in any ways.

The balance between cell propagation and cell elimination may be secured by DNA-orchestrated set of homeostatic mechanisms so that the cell association becomes able to maintain near a constant number of cells. This ability seems to be advantageous since some cell associations evolve homeostatic mechanisms which even involve a programmed cell death, the cell apoptosis, eliminating not only damaged cells but also superfluous healthy cells.

Different cell associations show a significant variation of degree of integration and coordination among cells.

Within an association, the cells will either remain similar or become different.

Progressive cell propagation may be accompanied by cell differentiation creating the diversity of specialized cells. The number of specialization directions can range from 1 to more than 200. Specifically designed to perform different functions, the cells may collectively respond to brighter spectrum of environmental conditions. This differential collective respond is usually more effective than by an association of similar cells.

Within an association, the cell differentiation will be either a random or an established process.

Progressive cell propagation may be accompanied by the establishment of an amount of differential cell progressions that may be asymmetric cell progressions. As a result, the cell association can contain a number of regions each of which is occupied by particular asymmetric cell progression. Within such region, stem cell is usually located in especially carefully protected area, a stem cell niche. If the stem cell divides, one daughter cell is retained as a stem cell but the other becomes non-stem cell and must leave the stem cell niche to enter an area occupied by limited cell progressions. Since limited cell progressions replace each other in consecutive order, near constant number of cells can be maintained within their area. The newly formed non-stem cell first enters a section occupied by a pool of transit amplifying cells and proceeds through a number of division rounds at the fastest rate providing a renewal of this pool. The transit amplifying cells are regularly committed to enter the next section occupied by a pool of differentiating cells which propagate at the lower rate. Finally, the differentiating cells are regularly committed to enter a section occupied by a pool of mature specialized cells which become inevitably exhausted by performing their functions.

Thus spatially, each region occupied by an asymmetric cell progression consists of two areas: a stem cell niche with one stem cell and an area occupied by limited cell progressions. In turn, the area occupied by limited cell progressions consists of three sections: a section occupied by a pool of transit amplifying cells, a section occupied by a pool of differentiating cells, and a section occupied by a pool of mature specialized cells.

The cells of an asymmetric cell progression put together a well-proportioned unit. This unit is a very stable dynamic system being able to exist eternally owing to the very fine co-ordination of the whole hierarchy of the cell propagation, cell elimination, and cell differentiation events. Using inflow of negative entropy from environment this unit can maintain sufficiently high level of hierarchy organization, so ensuring endless self-renewal. Since the asymmetric cell progression is potentially immortal, the cell association establishing a superposition of asymmetric cell progressions is therefore potentially immortal as well and can persist forever maintaining near a constant number of cells.

Stem cell lineage plays a key role in this hierarchy. It is namely the source of preservation of genetic fidelity and the source of self-renewal of the whole asymmetric cell progression. Stem cells remain undifferentiated while simultaneously producing highly specialized cells. The splitting of the stem cell progeny into two separate cell groups that drastically differ in division frequency and division number is assumed as a consequence of a selective pressure in evolution of cell association types to avoid the negative results of mutations. On the one hand, this splitting allows to reduce the division frequency of just those cells that reside permanently in cell association and so ensures the protection against accumulation of mutations. The division of these cells is very rare and is protected so sufficiently that they may divide unlimited number of times. On the other hand, the splitting allows to reduce the number of cell division rounds in the group of intensively proliferating cells and therefore to minimize the rate of malformation arising out of deleterious mutations. Also non-deleterious mutations in intensively proliferating cells do not accumulate since this progeny of the stem cell soon or later leaves the cell association. So, the splitting provides asymmetric cell progression with the property to exist beyond the number of cell divisions that leads to a significant risk in deleterious mutation.

Stem cells that acquire a mutation or are damaged by injury are to be culled from the cell association and therefore either undergo apoptosis or become directly a transit amplifying cells so that these asymmetric cell progressions soon or later become completely exhausted. In cell association, the number of asymmetric cell progressions is however maintained since each stem cell, if necessary, can alternate from asymmetric to symmetric cell division which results into two stem cells as well. While cell association can maintain stem cells as reservoirs for genetic fidelity, deleterious mutation spectrum could still arise.

The evolution brought into being an extensive diversity of cell associations with asymmetric cell progressions and their combinations.

Thus, some individual cell progression may have very regular spatio-temporal organization.

In conclusion, the proposed conceptual framework strongly integrates known life phenomena each of which can be described as a particular four-dimensional pattern of information processing within the related four-dimensional whole. This is advantageous while revealing novel emergent features and thus providing more insights into understanding of these phenomena. The whole cellular world is only one cell

progression which arose from one single primordial cell and has 3 or 4 billions years of uninterrupted history. This general cell progression can be considered as a growing composition of an increasing number of individual cell progressions each of which is specified by a particular individual DNA. Individual cell progressions are ultimate sources of genome multiplication and diversification. Different individual cell progressions display a broad variability in spatio-temporal organization which mostly depends upon whether the cells divide symmetrically or asymmetrically, whether the asymmetric cell divisions occur occasionally or regularly, whether the asymmetric cell division is associated with symmetric or asymmetric kinetics of the cell propagation, whether the cells will be rather randomly dispersed in space to become autonomous in behavior or remain in an association to form cell colony (primary, secondary, etc.), whether the cell association grows continuously or is a steady state system. The most regular spatio-temporal organization of an individual cell progression involves establishment of numbers of asymmetric cell subprogressions each of which has a stem cell at the base.

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