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THE MOLECULAR TSUNAMI¹

Jean-François Nicolas et Jean-Michel Rossignol

« *One moment does not lead to another. The door opens and the tiger leaps.* »²

« *But cells are matter that dances.* »³

Fifty years ago, molecular biology began to delve into issues that were considered to belong to other disciplines, often venturing beyond the realm of biology¹. It was a tsunami. This lecture examines the impact of this tsunami on the fields of developmental biology, evolutionary biology, and the problem of cancer. Has molecular biology changed these disciplines over the past fifty years? What results can be attributed to it, and have these results affected their concepts?

¹ Introduction to: "Biology and the Molecular Revolution: Selected Narratives" by Jean-François Nicolas and Jean-Michel Rossignol, to be published in 2023 in "History of Contemporary Research," CNRS editions.

² Virginia Woolf, *The Waves*.

³ Uri Alon, *An Introduction to Systems Biology Design Principles of Biological Circuits*, 2020.

In 1970, molecular biology^{2,3} was empowered by its "central dogma,"⁴ which classified and ranked molecules, introduced new concepts to understand life, and produced molecular analysis tools through "genetic engineering"⁵ (restriction enzymes, PCR, sequencing, hybridization, transfection, viral vectors, genomic libraries, transgenesis, etc.). Among its concepts, in addition to the central dogma, those of genetic regulation (DNA level, genes) and allostery (protein level) would prove to be fundamental. They demonstrate how molecules and genes interact to create essential information flows for life.

Molecular Biology and Cancer. In 1970, cancer was on the list of problems considered to be within the grasp of molecular biology. It was generally understood as the occurrence of cells multiplying uncontrollably, for themselves, following a simple event, in an organism considered permissive and neutral (the cancer cell being part of the immunological "self"). Three hypotheses about the origin of the simple event prevailed, each supported by some experimental results: cancer as a disease of cell differentiation (changes in the properties of cancer cells mimic changes in cells during development), cancer as a viral disease (some viruses cause cancer), and cancer as a somatic genetic disease (carcinogens are often mutagens) and sometimes as a somatic evolutionary process⁴.

Fifty years later, the first two hypotheses of the 1970s have been rejected in favor of the theory of cancer due to somatic mutations accompanying an evolutionary process. However, it has become clear that cancer is not simply the generation of cells multiplying uncontrollably in a neutral organism. We now have a solid synthesis⁵ that organizes research, with a plausible theory of cancer^{6,7,8}, which had been clearly glimpsed since the 1970s^{4,9}. Still, there are areas that remain unclear. As we will see, the birth of new scientific and medical fields is evident, as evidenced by the titles of some general works on these topics^{10,11,12,13,14}.

Perhaps the most unexpected discovery is how little the complexity of the phenomenon was initially appreciated. We now know that the "simple event" corresponds to, on average, mutations in about ten key genes, selected from over a hundred possible ones (which have been identified), for the cancer cell to acquire the properties that make it so impressive. The process of tumor initiation and progression takes several decades. We also know that the multi-mutated cell is not the sole element of cancer. In addition to internal mutations, external modifications come into play. Cancer cells co-opt normal cells from about ten

different types to construct microenvironments (or pseudo-organs). From the network of interactions involving all microenvironment cells, through signaling pathways and their ligands, properties emerge that account for angiogenesis (the construction of blood vessels in the tumor) and metastasis.

A word about these ten key mutations and why ten rather than one or two. The answer is that tumor cells progress through successive clonal expansions⁶ in an organism that is both hostile and aiding. The ten key mutations represent adaptations to selection pressures coming from both the cell and the organism's properties (and treatments!). The progression of cancer only makes sense in an evolutionary explanation. Let's briefly look at it.

The first mutation activates signaling pathways in a cell involved in normal proliferation control (various ways are possible). Uncontrolled proliferation - the first clonal expansion - follows. However, it eventually leads the mutated cells toward senescence⁷ the destiny of any somatic cell that divides, and most of them die.

The tumor can only progress if a new key mutation appears that neutralizes senescence. Again, various ways are possible. These mutations often affect p53, a transcription factor, which, in normal cells, responds to DNA damage or stress signals by either initiating damage repair or self-destruction through what is called "programmed cell death."⁸ The now mutated cancer cell in two key genes escapes this programmed death and initiates a new clonal expansion. But with mutated p53, these clone cells can no longer repair their DNA. They become genetically unstable and accumulate other, so-called "passenger" mutations. These mutations are not essential for tumor progression, and most of these cells will disappear after a fixed number of divisions because, like normal somatic cells, their division limit is determined by the length of their chromosome telomeres⁹. They are not immortal.

The next step involves the appearance of a third mutation in a new key gene that makes the cancer cell immortal, for example, a mutation that activates an

⁴ **Central Dogma** of Molecular Biology: A dogma stating that the flow of information can move from DNA to RNA and from RNA to proteins, but not from proteins to RNA or DNA.

⁵ **Genetic Engineering:** A technology for modifying the DNA of a cell or organism.

⁶ **Clonal Expansion:** Generation of a large population of cells, all derived from a single founder cell that has acquired a more favorable phenotype than its neighbors and can eventually displace them.

⁷ **Senescence:** Irreversible cessation of the proliferation of viable cells.

⁸ **Programmed Cell Death or Apoptosis:** Cellular process of self-destruction by fragmentation, without the release of cytoplasm. Apoptotic cells are eliminated by phagocytosis.

⁹ **Telomere:** Nucleoprotein structure (containing repeated DNA sequences) at the end of chromosomes, which protects them from degradation and prevents fusion with other chromosomes. Telomeres shorten with each division.

enzyme, telomerase¹⁰ capable of maintaining telomere integrity. A new clonal expansion of the cell mutated in three key genes and many others (due to genetic instability) follows, and it continues to accumulate more mutations. However, the modifications resulting from all these mutations have alerted the organism's immune system, which now recognizes these cells as foreign (not part of the immunological "self") and eliminates them. Many will disappear. The tumor must now face selection pressure coming from the organism.

More mutations in other key genes and new clonal expansions are required for quadruple-mutated, genetically unstable cells to evade host attacks.

Note that many of the key mutations involve control genes that either block or allow access to these cellular processes (which involve dozens of other genes). The transcription factor p53 is a good example. These mutations always have a permissive action, never an instructive one. Also, genetic instability, a characteristic of all cancer cells, facilitates the emergence of both key mutations and many passenger mutations. This is what makes the study of cancer so challenging: identifying the key mutations among a multitude of neutral passenger mutations! Big data methods are of great help.

These are five of the ten elements of the current model of tumor progression. It took several decades to establish this model. Among the other elements of the current synthesis, the establishment of microenvironments by cancer cells, their dissemination, and the formation of metastases are still not fully understood.

The impact on medicine is significant and has brought molecular biology into the daily lives of oncologists. It plays a role in diagnosis and treatment. For example, molecular classification based on partial or complete sequencing of the genomes of cancer cells has been added to tumor histopathology. Furthermore, each individual's tumor is always different from another's because each tumor results from a unique combination of mutations in ten key genes (selected from over a hundred possibilities). The choice of treatments often stems from identifying these genes. With targeted drugs, increasingly derived from genetic engineering, the results can be spectacular!

The techniques that have enabled these advances primarily come from molecular biology, molecular developmental biology (since the 1980s), such as the use of transgenic mice to test oncogene function or the involvement of the immune system, and post-sequencing of the human genome (the "omics" and

¹⁰ **Telomerase:** Ribonucleoprotein reverse transcriptase that elongates the repeated sequences of telomeres.

big data, after 2000). Among the concepts borrowed from this new field, those from the synthetic theory of evolution (random genetic or epigenetic variation, selection, clonal expansion, genetic drift, and even punctuated equilibria) are particularly structuring and constitute a plausible theory of cancer. Other concepts are borrowed from development (reactivation of embryonic operations, stem cell concept, epithelial-mesenchymal transition). From 2015 onwards, the use of systems biology has become essential (understanding signaling pathways, comparing the sequences of thousands of cancer cell genomes, for example, to distinguish key mutations from passenger mutations).

Molecular Biology and Development. The history of the relationship between molecular biology and development is quite different. By 1970, embryology had long been at an impasse. Experimental embryology had produced decisive results, but Chemical Embryology had failed to identify the actors in the mechanisms at play. Concepts like morphogenetic fields¹¹ or even induction¹² were depreciated. Furthermore, how could one imagine that proteins, catalysts of chemical reactions, could build an organism? Many biologists considered the problem of development to be beyond human comprehension¹³. Some believed that hundreds of thousands of genes might be involved (the size of animal genomes suggested it). Many molecular biologists thought it was necessary to start from scratch with new animal models. What happened?

The solution came from an unexpected source, with an organism foreign to embryology, and very few thought it could one day guide the understanding of vertebrate development: the fruit fly, *Drosophila*. In 1980, Christiane Nüsslein-Volhard and Eric Wieschaus, using classical saturation mutagenesis techniques applied to larval segment formation genes, showed to everyone's surprise that only a tiny number of genes are involved. Furthermore, by late 1982, thanks to the "chromosome walk" (a painstaking task) by molecular biologist David Hogness, the first two development genes were cloned. They were the thread of Ariadne. Indeed, in

¹¹ **Morphogenetic fields:** A concept of experimental embryology borrowed from physics (as was the concept of induction), aimed at explaining regulation and equipotence of its cells (the field is a harmonic-equipotential system: the whole is contained in each part, as per Driesch), induction (in Spemann's case, induction is a "field action"), and determination. The field is seen as independent (A. Gurwitsch) or associated (P. Weiss) with the material embryo. For Spemann, the field includes not only physical but also chemical factors.

¹² **Induction:** A process by which a group of cells influences the development of another group of cells (through signaling pathways). Induction can be instructive or permissive.

¹³ For instance Evelyn Fox Keller wrote: "I see nothing counterintuitive in the possibility that there are phenomena in the natural world extending beyond the grasp of human comprehension-if only by virtue of their complexity. Embryonic development might very well be one of those". Making sense of life, 2002, page 296.

1984, homologous genes were found in vertebrates, and they served the same function! Another big surprise followed, and more would come. These results laid the foundation for molecular genetics of development and gave rise to a new discipline, evolutionary developmental biology (evo-devo).

Fifty years later, the problem of development seems to be largely resolved in its mechanisms. It turns out that the principles had already been enunciated in 1970. New concepts, the advancement of knowledge about development mechanisms rehabilitated several concepts from experimental embryology while discarding others. New concepts borrowed from systems biology have been incorporated. But the most unexpected development was the emergence of evolutionary developmental biology: by deciphering the mechanisms of development, the mechanisms of evolution also began to be unveiled.

The techniques that have allowed these advances primarily come from classical genetics (genetic screens) and molecular biology (genetic engineering, gene cloning and sequencing, genomic and cDNA libraries, hybridization, genome sequencing, etc.).

Molecular Biology and Evolution. What about the science of Evolution? In 1970, it was not on the agenda of molecular biology. In its modern synthesis theory (MS, or "modern synthesis" or neo-Darwinism), it had incorporated the genetics of Thomas Hunt Morgan into the three pillars of Darwinism: phenotypic variation, differential fitness adaptation, and heritable adaptation¹⁵. It deduced from them the predominance of gene dynamics in populations, described by population genetics mathematics. Its laws were those of natural selection. As they showed that a sum of small variations can explain macroevolution, saltationism¹⁴ had been ruled out in favor of genetic gradualism¹⁵. And, of course, any form of Lamarckism was excluded. Finally, and perhaps most importantly (for our discussion), as adaptation takes into account phenotype, novelty¹⁶, and innovation¹⁷, no recourse to the mechanisms that generate them was necessary. It is perhaps this right to ignore the infinite complexities of phenotype and novelty generation that gives strength to this theory, its attraction, its beauty. The central dogma of molecular biology had only strengthened the foundations of the modern synthesis. The genotype-phenotype relationship had found its molecular basis

¹⁴ **Saltationism:** Theory of evolution in which significant adaptive leaps can occur in one or a few generations.

¹⁵ **Gradualism:** Theory of evolution in which species evolve gradually and continuously through natural selection.

¹⁶ **Novelty:** The appearance of a morphological character that did not preexist (without homology to any other character) in common ancestors. Requires a change in the body plan (see innovation).

¹⁷ **Innovation:** Radical modification of a preexisting morphological character to which it is homologous. Does not require a change in the body plan (see novelty).

(DNA, RNA-protein), and the impossibility of reversing phenotype to genotype fully justified its exclusion (and hence development) from the theory. In fact, in 1986, Bruce Wallace, a student and later a collaborator of Theodosius Dobzhansky, could write, "*The issue for this symposium is whether developmental biology requires a rethinking of the Modern Synthesis. I shall argue that it does not*"¹⁶. Did the triumph of natural selection and genetics over biology mark the end of the story for this science?

Fifty years later, the enormous progress in understanding the molecular structure of the genome, the construction of the phenotype and its adaptability, variation, novelty, innovation, and genotype-phenotype relationships (each of these elements has turned out to be so much more complex than imagined!), systematic genome sequencing, have they questioned the MS or even the theory of evolution? First and foremost, it must be emphasized that the latter remains unchanged: the three pillars of Darwinism are the unshakable foundation of this science. However, judging by the titles of these few books^{16,17,18,19,20,21,22,23,24}, the MS is being questioned, a subject of intense debate, and the problems are difficult to resolve! And therefore impossible to summarize here. Let's settle for a deliberately somewhat caricatured explanation and some comments that will introduce this book.

The explanation: for the MS to be challenged, it would need to be proven (a) that something other than genes matters in transmission, adaptation, or phenotype, (b) or that these entities are not autonomous, (c) or that modes of variation do not fit into gradualism. This would affect its axioms as well as the framework for its mathematical treatment. What is the situation?

Regarding gradualism, the situation is as follows. The molecular understanding of variation, innovation, novelty, and morphological or molecular homology by evolutionary developmental biology is a challenge that, according to some, could justify the return of saltationism. Mutations that affect selector genes, master genes, those underlying the co-option of gene groups (one of the elements of facilitated variation²⁵) or even those involving gene expression control elements can cause qualitative leaps of different magnitudes. Moreover, the contribution of genes through horizontal transfer (massive in the case of endosymbiotic fusions, etc.) or massive genome duplications also does not fit very simply into the framework of gradualism.

Two concrete examples of these situations. 1) The selector gene *Apterous* controls the identity of the dorsal compartment of the wings of insects. In beetles and only in them, *Apterous* has added, all at once, by co-option, to the identity of the anterior wing, all the exoskeleton development genes. The

emergence of the elytra is partly due to this co-option of the "exoskeleton" genetic module into the "compartment" genetic module by Apterosus²⁶. Note that this co-option is facilitated by these modularities: from the embryo (compartments), the genetic network, and the gene regulatory regions. This is also a case of "divergence by dissociation": the hind wings are not affected. 2) In mammals, some of the characteristics of the placenta are due to the exaptation¹⁸ of retrovirus elements! These two examples show that the tree of evolution is determined, at least in part, by the nature of mutations. This is indeed a return to saltationism.

Propositions (a) and (b) also give rise to debates. A typical example is the plasticity of development, the origin of phenotypic plasticity. This plasticity is well-documented and can allow immediate adaptation to environmental changes. This is recognized by all. But if the new phenotype induced by the environment persists for a sufficiently long time, it is likely to be genetically assimilated¹⁹. For Stuart A. Newman, the same applies to the organization induced by the physical properties of cells and tissues^{27, 28}. If there is genetic assimilation, then adaptation, phenotype, and transmission become interdependent; (b) seems to be refuted. Furthermore, adaptation is no longer random; it is biased by the ability of organisms to produce it, and it precedes transmission; (a) also seems to be refuted. The importance given to plasticity and genetic assimilation in evolution is significant for some. Mary Jane West-Eberhard writes: "*Environmental induction is probably more important than mutation for the origin of adaptive novelties*"¹⁹.

Many other points of contention on propositions (a) and (b) exist: non-genetic modes of transmission, the importance of developmental constraints, adaptability, and natural selection^{16,24,22,17,25,21 18,20,23,19}.

These debates, sometimes started as early as the 1930s, show no signs of ending. Denis M. Walsh and Philippe Huneman wrote in 2017: "*It is an important theoretical, historical, and philosophical exercise to hold early 21st-century biology up against 20th-century evolutionary theory and to ask how much the former challenges the latter, and how well, if at all, the latter can accommodate the former*"²². What a contrast to what Jacques Monod wrote in 1970¹: «*Essentially, however, the problem (of evolution) has been resolved and evolution now lies well to this side of the*

¹⁸ **Exaptation:** The redirection of the function of an organ to establish a new function. For example, reptile scales evolved into feathers, initially for thermoregulation in some dinosaurs, and later became an essential structure for flight in certain dinosaurs and their descendants, the birds.

¹⁹ **Genetic Assimilation:** A process described by Conrad H. Waddington in which a phenotype induced by a particular environmental condition becomes genetically determined after several generations of selection. The phenotype will be visible even in the absence of the triggering environmental factor. Genetic assimilation could result from new mutations or the revelation of preexisting cryptic mutations.

frontier of knowledge. » *Chance and necessity*, (page 198), translated from the French by Austryn Wainboase.

It feels like what is probably lacking is a theory of development that includes the results of the evolutionary developmental biology and perhaps even "eco-evo-devo." The premises of this can be seen^{29,30,31}. In our view, it would provide the keys for a synthesis with the MS.

In any case, when development could finally start to take an interest in evolution from the 1980s, a considerable step forward was taken in understanding the mechanisms of novelty and innovation (see notes 15 and 16). And when it could begin to experimentally test evolutionary scenarios after the 2000s, a second equally important step was taken.

This ultimately vindicates the evolutionists of the late 19th century who thought with Wilhelm Roux, "*In consequence of the intimate causal connections existing between ontogeny and phylogeny, many of the conclusions drawn from the study of ontogeny will throw light on phylogenetic processes.*"

Conclusion

There was indeed a molecular tsunami. It affected all of biology and even the science of evolution.

So, there was a molecular tsunami, but was there also a conceptual tsunami? Less certain!

For development, most concepts were just waiting to be reformulated to shine once again. For the new science of cancer, it borrowed them from other sciences. For the science of biological systems, it owes them to complex systems. As for evolutionary science, the return of saltationism is... a return, and the issue of phenotypic plasticity remains a problem. Perhaps the most visible conceptual changes have occurred in the young science of evolutionary development. The concepts of modularity and molecular parsimony, key to understanding what in variation is novelty or innovation (see notes 15 and 16), should help create a developmental theory as a prelude to a synthesis with the MS.

So, many more innovations than novelties.

However, as this lecture demonstrates, our understanding of phenomena in all fields is incomparable to what it was fifty years ago, and there were many unexpected surprises.

How many tigers still lurk behind the doors?

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