REVAMPING MOLECULAR BIOLOGY FOR THE TWENTIETH FIRST CENTURY, OR PUTTING BACK THE THEORETICAL HORSE AHEAD OF THE TECHNOLOGICAL CART

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Molecular biology (MB) is perhaps the branch of science that has shown the most impressive growth in the last fifty years and its results have an impact upon the whole range of the natural sciences from physics to biology. Yet this growth has been paralleled by an exponential increasement of empirical data coupled to a gradual erosion of the conceptual and theoretical aspects within the discipline. After decades of continuous success, MB now faces the challenge posed by several complex issues that clearly cannot be addressed by means of a traditional reductionistic approach. Among these challenges we can mention the problem of metazoan organismic development, the relationship genotype-phenotype in metazoans, understanding how molecular evolution can be related to organismic evolution and the understanding of both chronic-degenerative disease and ageing at the molecular level. Therefore, complexity is embedded within each major question for MB and this poses the need of new conceptual approaches far from reductionism and explanatory schemes based on simple, linear causality. Nevertheless, the current trend for solving these problems is to develop expensive technological platforms for massive experimental procedures, coupled to computer-aided analysis of data, where such an analysis most of the times is nothing but sheer data-crunching. The massive high-throughput technologies involved in the fashionable branching of MB into genomics, proteomics, metabolomics and as yet further unknown "omics", are a clear example of how technology has become the guiding light for MB, while the scientific part, understood as the rational search for explanation of natural phenomena, follows at the rearguard in the quest for biological knowledge, overwhelmed by those technological fads that are setting the scientific agenda in MB. The supposedly conceptual answer to the technological thunderstorm within

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MB has been to create a fuzzy entity by the name of systems biology [1], that lacking any well-defined theoretical foundation is just a catch-phrase for disguising conceptual poverty behind massive computing-power routinely applied to the analysis of huge molecular data resulting in no definite insights or conclusions. Yet, paradoxically, this massive high-throughput approach is producing empirical evidence that challenges some of the most entrenched reductionist concepts in MB that had set the particular scientific agenda several decades ago [2]. However, the current answer to this challenge has been to add further expensive technological complexity to experimental design coupled to more computing power, as if by some magic the iterated data-crunching may finally reveal simple solutions to the complex questions. No other field better exemplifies this situation than the molecular biology of cancer.

The almost forty year old paradigm suggesting that cancer is a genetic disease [3] resulting from specific mutations in particular sets of genes known as oncogenes and tumor suppressor genes (TSG), has been seriously put to test by the large-scale analysis of thousands of human-cancer samples in search of specific molecular signatures (specific sets of gene mutations or patterns of gene expression) that can be directly linked to specific types of cancer [4, 5]. For some time it has already been known that most sporadic, non-familiar, human cancers that represent more than 90 per cent of cancer incidence, cannot be explained as a result of mutations in a single gene or a very limited number of genes. This in contrast to the overexploited lab-rodent models for cancer in which expression of a single mutant protein coded by an oncogenic retrovirus leads to malignant transformation of almost any target cell infected by such virus [6]. Nevertheless, it was already known that such viruses are basically replication-defective and, thus, unable to naturally spread outside of the research laboratories, where such viruses are passed and maintained under rather contrived conditions using highly-inbreed laboratory animal-strains that are far from representing natural animal populations. Yet, there was hope that by analyzing the expression of thousands of genes in samples from patients affected by the same type of tumor, it could be worked out what was the minimum set of altered genes common to that kind of tumor. Moreover, it was thought that by massive analysis of samples corresponding to the different stages of development and progression of a given type of cancer, it would be possible to identify specific sets of gene-alterations that can be correlated with specific stages of cancer development, thus offering hard molecular guidance for assessing clinical staging, prognosis and therapeutic responses. Some ten years after these efforts began, the uncomfortable but unavoidable answer is that there are no specific molecular signatures for specific types of cancer, nor common molecular signatures for specific stages of cancer progression, nor fundamental sets of mutated

genes that are common to all types of cancer, nor specific sets of gene mutations that define a given type of cancer [7, 8]. Indeed, some of the most famous oncogenes identified in laboratory-models of cancer are very often inactive in the most common types of human cancer such as breast, colon and prostate, thus ruling out any causal role for such genes in the genesis of common human cancer [5]. Sadly, the current situation in this field is such that instead of a major conceptual review of the molecular paradigm for cancer, the scientific mainstream has decided to embark into further expensive high-throughput analysis, but now with the intention of characterizing each cancer at the individual level in hope that such an analysis will discover the key aberrant gene or molecule behind each individual cancer that may be the right target for a tailor-made therapy [9]. This rather naive and over-empirical approach reflects, on the one hand, a retreat from some of the most fundamental tenets of science that searches for common, general explanations and not for particular explanations that can only be applied to the particular case without any possible extrapolation. On the other hand, it shows a general lack of intellectual stamina among molecular biologists that do not dare to challenge an old explanatory paradigm that clearly has outlived its usefulness. Indeed, the massive data resulting from applying diverse high-throughput technologies to the molecular analysis of cancer indicate that there are actually no such things as oncogenes and TSG, and the lack of common molecular signatures linking specific sets of gene mutations and so patterns of gene expression to specific types of cancer suggests that the observed mutations in oncogenes and TSG are most likely just epiphenomena or side effects not causally linked to cancer [5,10,11]. The so-called oncogenes and TSG are basically regulatory genes that play important roles in the processes of growth and development, and become rather useless in aged organisms beyond their reproductive prime, which is the set of organisms where 90 per cent of cancer incidence occurs. Such genes are dispensable for cellular survival and so they may undergo random genetic drift (mutation), since they are not anymore under control of natural selection, inasmuch as any malfunction of such genes is of no consequence either for the individual's fitness nor the species survival [12]. Cancer is a complex phenomenon that affects not only cells but whole organisms, and it requires a complex explanation based on complex causal networks and manifolds, as there is going to be no single molecule or limited set of altered molecules that may explain the genesis and progression of such a complex phenomenon [13]. Indeed, many years ago it was wisely said that "cancer is no more a disease of cells than a traffic jam is a disease of cars." A lifetime study of the internal combustion engine would not help anyone to understand our traffic problems [14].

The complex questions that faces MB in the twentieth first century will only be solved by a massive conceptual paradigm shift that may redefine the causal way of thinking in the field, so that complex, emergent, non-linear phenomena may be understood in top-down and not in bottom-up terms [15-17], instead of being spuriously tackled by a combination of technological onslaught and linear, gene-centric thought. Analytical reductionism atomizes and blurs the true morphology of the complex phenomena under study, thus hindering the explanatory capabilities of the human intellect that as Aristotle clearly observed, firstly perceives and understands things as forms, no matter if such forms have an abstract (theoretical) or physical substrate [18]. Hence, for achieving true progress in the current century MB needs to put back again the theoretical horse ahead of the technological cart.

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