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"Hit and run" in metagenomic era: high hopes

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Editorial

During three decades of my job-related life adventures, I was part of collective "search", trying to explain how nucleic acids structure and dynamics is affecting human health. Yet, losing the battle of fully understanding human retro-elements and retro-viruses might be imminent. Amazing technological shifts in understanding human genome organisation, from Southern blotting in 90s, to Next Generation Sequencing, today, will have strong impact on our future. In these early years, I was part of prominent Canadian research teams in the domain of DNA recombination, studding long interspersed nuclear elements (LINE), making up around 20% of the human genome (Dr Pierre Chartrand), and Alum elements, which are retrotransposons dependent on LINE retrotransposons for their replication (Dr Damian Labuda). Today, I feel sad and nostalgic, since I believe that - now- more than ever - we were walking in a good direction. Investment in studying nucleic acids played back to us as a species and as a society, especially in our increased capacity for fast medical diagnostics. As a Lab Co-Director of Molecular Microbiology at Jewish General Hospital in Montreal - I might be able to participate in clinical implementations of Next Generation Sequencing on the routine microbiology diagnostics and screening (having too high personal life-expectance). It would be hard to imagine that instability of human retro-elements will be on a daily repertoire of diagnostic laboratory tests, but introducing tools to routinely follow human genome stability - will be sort of "fair re- compensation" for our generation. Recombination and transfection of various endogenous and exogenous DNA segments, were (and are) intensively studied at biochemical level, all over the world. Each new discovery of human-related molecular factors involved in nucleic acid ligation, polymerisation and integration was adding pieces for mosaic called "human genome (in) stability". What roles are fulfilling endogenous (and exogenous) retro elements? From crystallographic analysis…toward cancer biology…yet, the answer was escaping. Retro-elements do not have pre-assigned "good or bad" ethical mission. They are considered as potential triggers of cancer development having cumulative effect without defined quantitative threshold. They are also "driving" evolution, but we don't have personal benefit, during our lives. Slowly, steadily and step by step, the concept of human genomic instability was interfering with the concept of recombination-driven "hit and run" ontogenesis. For some viruses this is dominant, but difficult to prove mechanism. Today, it becomes clear that persistent bacterial and fungal infections, too, becomes significant player in setting up the same "pre-cancer stage" within our cells. Now, we are entering the era of human-metagenomic instability…opening another level of complexity. "Hit and run" concept of pathogen-induced oncogenesis is not eternally closed within intellectual labyrinth, thanks to Harald zur Hausen (Nobel Prize in Physiology or Medicine 2008). Time correlation between events is not going to be rediscovered by Perpetual mobile type of mental experimental design, but by solving genomic puzzles. Synchronisation is not a proof. Although seminal work of Iwasakaa et al.,[1] and friends, back in 1982, was clearly showing that concept is correct, the simple instrumental tools to capture these events, leading toward cascade of genomic rearrangements, so typical for cancer cell - are not - in routine clinical setting. Some of us are pretending that we do not have "solid" proofs and that global genomic sequencing efforts will open doors for ethical issues. That is why, in Canada, we are sequencing beaver genomes and paying ethical committees to analyse Canada's new genetic privacy law …humans are too complicated. The medical version of Heisenberg's Uncertainty Principle, or Indeterminacy Principle, articulated in 1927, is re-borne. The evolutions of our knowledge and understanding the world around us, looks like spiral cycles of discoveries and rediscovers. Recently, world tragically lost Doctor Mark Wainberg, the legend of HIV molecular therapy and …. Much more. With him, the abstract human "knowledge spiral" get another twist toward better future. This text is not more than "advice" for the next generations of virologist/medical scientist /molecular biologist /geneticist /technologist and bioinformaticians:

a. Follow up dynamics of genomic change and define the noise of the system. If you are building "diagnostic mutation assay", define basal mutation noise in a "normal" population. When exactly our cells are out of this natural equilibrium and running too fast into the next mitosis? Make distinction between technological artefacts and real events.

b. Do not be obscured by small changes, follow events globally, including rearrangements of DNA blocks, not only single nucleotide mutations!

c. And keep searching - you never know who was wrong…and with which intentions.

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Conflicts of interest

None.

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