A Conversation with Alexander Tarakhovsky

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Alexander Tarakhovsky is the Irene Diamond Professor of Immunology at The Rockefeller University.

Guy Riddihough: I'd like to start our discussion with mimicry, because you have a specific interest in that with regard to the way pathogens try to take advantage of us and our cellular systems.

Dr. Tarakhovsky: Mimicry is a well-known way for pathogens to interfere with different host functions and, at the extreme edge, to take over host function. The natural response of the host to this effort is to change itself. The changes are remarkable because they enable the host to escape the virus or bacteria and live happily ever after. It's not quite as simple as that, because of the Red Queen hypothesis, which formalized the notion that we are in a constant adaptational fight against the viruses. More generally, when antagonizing forces shape each other, the impacts on multicellular organisms, including humans, can be both negative and positive. In terms of evolutionary progression, bad things aren't necessarily bad because, while the impact of viruses can be immense, the mechanisms of escape—the "Harry Houdinis" of the cell system—are also quite remarkable.

However, there is a place where changes are not very welcome. This place is the actual genome, as well as the epigenome. A core part of the epigenome is a set of proteins called histones. Histones are a founding unit of chromatin and there are multiple corpuses of histones, yet they are extremely well conserved. This kind of conservation implies that there's not much interest on the part of the cell to change them. We're working on the part of mimicry that gives viruses the ability to imitate histone sequences.

Viruses generally operate as molecular mimics. They work as perfect spies that acquire the language of a foreign state and they try to enter this new state and live a social life and become wives and husbands of the state. Like spies, they often are detrimental to the state. Yet going with the spy analogy, viruses are very frequently "Kim Philbys." They're double agents, so whatever is good for the state is good for the virus and vice versa.

Two major questions emerge. First, many of the viruses that use mimicry have never been a part of the eukaryotic system. Therefore, it is not clear how they manage to

build these histone-like sequences and use them successfully, although it's clear that there's a massive selection in favor of having sequences like this. Secondly, once they acquire the sequence, it generates a head-on conflict with the cell machinery. If the virus makes a histone-like sequence, and this histone is used to pressurize the system itself, it's natural to expect that the system will start to resist by changing the sequence. Except you can't change the sequence because if the sequence is changed, it will have detrimental consequences for the host. Detrimental not only within the immediate life span of the cell, but detrimental in the long term, because it changes the epigenetic setup of the cell.

Guy Riddihough: By mimicking histones, does the virus restrict the cell's "Red Queen" response because the histones are so restrained functionally?

Dr. Tarakhovsky: Maybe they can and maybe they cannot. There is no immediate experiment that can address this. Recent studies show that when histone imitations do take place, the effects are pretty dramatic. There's an actual transformation of the cell, rather than cell death. In children with brain tumors, a somatic mutation in one of the histones generates a potent toxic species of the histone that, being present in such stoichiometric amounts, is sufficient to annihilate the epigenetic state of the cell. Whatever causes this particular change in human tumors might actually happen frequently when viruses with these histone mimics enter the space and persist long enough to allow adaptation to take place. One of the mimicries we study comes from a virus that historically has been linked to human cancer, particularly glioblastomas. We know that many viruses are linked to cancer, yet viral oncogenes are not the driving cause of human cancer. The idea is that some mimics can create a precancerous epigenetic state. That's why I think the Red Queen model can only take us so far.

Guy Riddihough: Can you give us a specific example of a virus that uses histone mimicry and a hint about how the mechanism works?

Dr. Tarakhovsky: The most primitive kind of histone mimics are called competitors, which operate in a very simple way. There are a lot of histone-like sequences in certain viral proteins. They overwhelm the nuclear space, or even the nucleolar space, which is tiny compared to the rest of the nucleus, and these histone-like sequences are able to undergo the same type of posttranslational modification as histones. By being overabundant, they out-compete the histones for the regulators of transcription. Influenza has a protein called NS1 that has a histone H3-like sequence that allows it to suppress antiviral gene expression. The histone mimic alters the transcriptional program of the host cell such that the virus is more successful in its infection.

We've also known for a long time that many viruses—including hepatitis C, yellow fever, West Nile, encephalitis virus, to name a few—send a core protein into the nucleus and actually into the nucleolus, yet core proteins have nothing to do with the nucleus of the host. They're basically a coating, a capsule that covers the genetic portion of the virus. There's no theory to explain why this happens. I think the merit of studying histone mimicry is that it provides a mechanistic context for how interference with gene function take place, but it also creates a framework on which to build our understanding of what viruses actually do in the nucleus.

We also need to keep in mind that viruses have dual purposes. As much as they want to be successful, their success might be moderated by the necessity of keeping the host cells alive. They need to balance the cost to themselves against the cost to the host, and we've had some terrible epidemics like the 1918 influenza that reflect a system getting out of whack. Current influenza is "merely" a peaceful cohabitant. Of course, it's hard to think of it that way, because old people and the very young are still quite susceptible. But that's a very anthropocentric view of the system. In terms of the human race in general, viruses in the Red Queen model unfortunately work not only as agents that train the cells, they also test our genotypes. Many people, including my colleague Jean-Laurent Casanova at Rockefeller, have shown that our genetic makeup defines our susceptibility to viruses, so there's also a social element to these viruses.

Guy Riddihough: Another aspect of your research is an interest in epigenetic effects, specifically, what happens when a cell divides and must maintain all of the genes required to form its lineage.

Dr. Tarakhovsky: Our lab has a unique angle on this type of research. Many years ago we found that one of the key epigenetic regulators, a Polycomb protein called EZH2 (enhancer of zeste homolog 2), plays an important role in the regulation of cell surface receptor-mediated signals, particularly in T cells. EZH2 is present not only in the nucleus, but also in the cytosol, where it makes a complex that looks very much like the complex in the nucleus. Well, proteins like to multitask, but I think that multitasking is not really the explanation. I think that there is a reason that many of the transcription regulators are present in the cytoplasm. Bob Roeder's lab identified

OCA-B, which is a critical transcription factor for B-cell development, as being a membrane-associated protein. One of the OCA-B isoforms has a myristoylation site that hooks it to the plasma membrane, and the presence of this protein has an impact on signaling.

I think that when the population of cells in an organism is highly heterogeneous, they actually compete with each other. Competition between cells is relevant for every system, healthy or diseased. Fitness is not an absolute term. It's defined relative to its neighbor, and it's a big part of our understanding of how competition is regulated. Many factors that have a major role in proliferation (e.g., MYC) contribute tremendously to competitiveness. Many studies in tumor biology are geared toward understanding how competitiveness feeds into tumor growth, or how tumors are kept in check because they're not competitive enough in the first place.

Guy Riddihough: How does this relate to the Polycomb protein being in the cytoplasm?

Dr. Tarakhovsky: When T cells develop they produce billions of cells, and the Polycomb proteins are distributed asymmetrically among cells. We'd predict that if you have suboptimal amounts of Polycomb, you are likely to make mistakes. There should be a way to eliminate cells that don't have enough Polycomb, but how does a cell know that it doesn't have enough Polycomb? If there's a signaling function related to Polycomb, it's pretty obvious. There simply would not be enough signal coming into that cell, and that cell will lose the competition against those that do have enough. It has nothing to do with the histone methylation or epigenome functions. Signaling, being more digital, allows a sort of pruning to happen before bad things happen to the rest of the cell. That's important as one thinks about these sorts of epigenetic factors.

Guy Riddihough: That would be a way of ensuring less heterogeneity in populations that don't need to be heterogeneous.

Dr. Tarakhovsky: The population has to be heterogeneous, but it has to be within constraints that don't push it beyond lineage specifications. It has to stay within what we can vaguely define as homeostatic limits.

Guy Riddihough: I'd like to finish with two questions. First, what do you think is the role of science?

Dr. Tarakhovsky: For me, science functions the same way as art. I don't think science has a greater role than being a way for humans to exercise their creativity. I oppose the idea of science being "applied."

Guy Riddihough: Would you distinguish technology or biotechnology from pure science?

Dr. Tarakhovsky: I am very much in favor of invention, but I'm against labels. They're a dangerous way of pigeonholing things. Science is a way of exercising abstract thinking. Learning how life is organized around molecules is fantastic. If whatever is learned can be used to

invent, to design new drugs, to create new materials, I think that's wonderful. I do, however, think that science should stay "science": one word. One doesn't need to say, "I'm doing applied science" or "I'm doing translation science." This is bogus. If you study human diseases, you are still doing science. You're exercising your abstract power. You don't need to empower yourself or give yourself special value by saying, "I'm doing translation science." That, I am completely against.

Guy Riddihough: Given that answer, I'll ask the last question, which is what's the purpose of art?

Dr. Tarakhovsky: I had the privilege to talk about this at *documenta*, which is one of the biggest contemporary art exhibitions in the world. I built my talking around the Red Queen model, because I think the antagonism between a system that is well-adapted to something and something new coming in and shaking it up is essential for fitness, for evolution, for development. The purpose of art is not to be pleasing, but to be disturbing, like viruses. It can be detrimental, or painful, or terrible, but so are viruses. Like

viruses, art can be commensal, surrounding us, and we look at it, and it feeds into our pattern recognition and doesn't stir us at all. But it also can suddenly shake us and send us off course because we don't quite understand what it is.

For example, Malevich drew the famous "Black Square" at the beginning of the last century. It was the perfect art "virus," because after all the figures being drawn, the representational art, even Impressionism, it was a complete shock, a smack in the face. It supports my feeling that art should stimulate our recognition, our imagination, and that's how it feeds into science. Not in the sense that the images of art are similar to the images of science. That's boring. The interesting part is that it transforms us. It generates new patterns, and because many of us live daily lives by basically browsing through habitual patterns, it shakes us. That's why I feel that any art that goes outside in a genuine way because it reflects someone's intuition is wonderful, but so is science, as long as it's done for a good reason with good intentions and a lack of self-promotion.

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