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RNA vaccines: a milestone toward a new era

RNK vakcine: prekretnica na putu ka novoj eri

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Introduction

In the beginning was ribonucleic acid (RNA), or, stated slightly less dramatically, the most likely course of events that led to the origin of life on Earth involved an "RNA world" – a prebiotic substrate based on the unique ability of ribonucleic acid to integrate within itself wide-scale catalytic properties (later relegated to proteins) and the coding of heritable information [subsequently taken over by deoxyribonucleic acid (DNA)] [1]. As a lasting legacy of such beginnings, present-day RNA has retained, as one of its main biological functions, the role of a messenger between these two realms – that of genetic information and the myriad structural or active macromolecular forms shaped by its translation into polypeptide sequences [2]. In addition, various types of non-coding RNA play crucial roles in the regulation of gene expression [3]. In the last few decades, mankind has gained immense knowledge about the key roles RNA assumes in biological systems (including RNA viruses, where it has retained, or perhaps regained, its primordial genetic function) [4]. The vast potential of this knowledge to transform the way we safeguard our health and combat disease, however, remained largely untapped until the most recent pandemic caused by an RNA virus (one among hundreds of thousands that inhabit the biosphere, prone to "exploit" any alteration of ecological conditions in order to obtain a new niche for growth, typically by crossing the species barrier [5]) triggered the first application of RNA-based vaccines the world has ever seen.

RNA vaccines in the coronavirus pandemic

High efficacy and safety achieved by both existing mRNA vaccines against coronavirus disease 2019 (COVID-19), BNT162b2 and mRNA-1273, as attested by clinical trials [6, 7], resulted in their emergency use approval by the Food and Drug Administration of the United States of America in 2020, followed by full approval in 2021 and 2022, respectively. Approval by regulatory agencies of most other countries swiftly followed. During the pandemic, these and other vaccines saved millions of lives and prevented serious complications in a great number of people [8]. Vaccination also presumably shortened the time needed to achieve the necessary conditions to ease restrictive epidemiological measures worldwide. The two mRNA vaccines proved capable of inducing both humoral and cellular immunity that was, on the whole, roughly comparable in strength to the immunity conferred by the infection itself (but with the obvious advantage of avoiding the serious risks that the infection entails) [9]. The vaccines also proved to be very safe; severe post-vaccination adverse events are apparently quite rare [10, 11], with partial exception of anaphylactic reactions (estimated frequency was 7.9 *per* million initial doses) [12] and myocarditis (overall incidence rate among men aged 18–25 years was 1.7 *per* 100,000 vaccines for BNT162b2 and 2.2 *per* 100,000 for mRNA-1273) [13]. Both of these adverse events are treatable, and their combined frequency and severity are no match for the dangers of COVID-19 itself. The often-voiced concerns that mRNA vaccines could substantially trigger autoimmunity in susceptible persons failed to materialize [14], which is in accordance with previous assessments that vaccine-induced autoimmunity is generally rare and exceptional [15, 16]. Speculations about the putative risks of mRNA vaccines in pregnancy or their alleged adverse impact on fertility also proved to be void [17], and the widespread myth that mRNA vaccines could interfere with the genetic material of the host had been baseless from the outset since mRNA cannot enter the cell nucleus nor does in any way interact with the host DNA. Finally, even though the actual duration of vaccine-induced humoral immunity (time of retention of

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neutralizing antibodies), in the long run, did not quite fulfill the initial expectations [18], particularly in view of the rapid evolution of new coronavirus variants in concern [19], both mRNA vaccines retained to date satisfactory effectiveness against the severe, life-threatening, or fatal disease [20]. Indeed, mRNA vaccines offer the additional advantage of being readily adaptable to newly emerging viral variants for the creation of booster vaccine preparations since the appropriate RNA sequence can be selected at will.

To the Nobel Prize and beyond

None of this success, however, would have come to pass without a series of key biotechnological breakthroughs that enabled the development of RNA-based platforms. The Nobel Prize for Physiology or Medicine awarded to Katalin Karikó (born 1955 in Szolnok, Hungary) and Drew Weissman (born 1959 in Lexington, Massachusetts, USA) for the discoveries related to nucleoside base modifications that eventually allowed the successful creation of the first mRNA vaccines [21] should, above all else, be regarded as a recognition of the importance of decades-long efforts in this direction by the laureates as well as many other scientists, including efforts in the development of RNA-based technology directed at the treatment of malignant disorders [22]. First and foremost, in order to make a vaccine, native viral RNA needed to be stabilized and protected against swift destruction *in vivo* by the resident ribonucleases, enzymes with hundreds of millions of years of experience in neutralizing any foreign RNA that found its way into the body. In addition, foreign RNA, in its native form, triggers a strong inflammatory reaction (and is destroyed in the process); as discovered by Karikó, Weissman, and their team, this can be avoided if such RNA is marked by the addition of pseudouridine residues, mimicking its physiological processing and tempering the inflammatory reaction without compromising the ability to activate innate immunity [23, 24]. Furthermore, in order to be used in a vaccine, mRNA needed to be delivered to the immune system, and this required the development of lipid nanoparticle technology [25] – another spectacular advancement that was, sadly, not reflected in this year's Nobel committee decision.

As a brief, but warranted digression, the advent of RNA vaccines will hopefully change the currently prevailing way of thinking: the more advanced or sophisticated a given technology is, the farther from nature it is perceived by the public. Here, we see exactly the opposite – by applying precise molecular modifications guided by deep knowledge of the system in question, we are able to intervene in a way much closer to the natural process itself. That will hopefully aid more people to think beyond the epistemologically dubious – or even spurious – dichotomy of "natural" vs. "artificial" [26].

Returning to RNA vaccines (and looking beyond COVID-19), their ability to efficiently initiate both humoral and cellular immune responses is clearly an immense asset, particularly in the protection against intracellular pathogens (or those with life cycles exhibiting a substantial intracellular phase). Importantly, the ability of RNA vaccines to trigger innate immunity *via* Toll-like receptors and other class-specificity receptors [27] effectively makes such vaccines their own adjuvants, eliminating the need for traditional adjuvants and allowing vaccine designers to control the elicited immune response with unprecedented precision in view of safety and effectiveness.

According to a recent review, twenty-seven RNA-based vaccines are already in clinical trials, while hundreds are undergoing preclinical investigations [28]. Among infectious diseases, the first candidates to be tackled by RNA vaccine technology include some of the greatest global challenges, such as malaria, tuberculosis, and human immunodeficiency virus-caused disease. Platforms based on RNA technology have also demonstrated a wide-scale potential to transform the treatment of many non-infectious disorders, notably autoimmune [29] and malignant disorders [30]. Admittedly (and unfortunately), the onset of this new era appears to be somewhat hampered by the widespread, complex, and highly detrimental psychosocial phenomenon of vaccine hesitancy or resentment [31–37]. Nevertheless, RNA vaccines (and possibly RNA therapeutics) are already promising to become a staple tool of personalized medicine of the future. In spite of some misguided calls to classify RNA vaccines as "gene therapies" (which they are not) and thus make them subject to overregulation [38], it is reasonably safe to say that this future has irrevocably begun.

Conclusion

All of the above testifies that we are indeed on the verge of a new era. In spite of various challenges and obstacles, including the widespread psychosocial phenomenon of vaccine hesitancy or resentment, RNA vaccines (and possibly RNA therapeutics) are likely to become one of the central tools of personalized medicine of the future.

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