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Editorial

In the Spotlight

A 2023 Nobel Prize in Physiology or Medicine: Pathway for Next Generation of Vaccines

Nobelova nagrada 2023 za fiziologijo ali medicino: pot do naslednjega rodu cepiv

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This year's Nobel Prize in Physiology or Medicine has been awarded to Katalin Karikó and Drew Weissman for discoveries that enabled the development of messenger RNA (mRNA) vaccines against COVID-19. mRNA is a transient molecule in the cell that conveys the instructions for synthesis of a protein from the nucleus, where instructions are stored as a genetic code in the DNA, to the cell's protein making machinery (ribosomes) in the cytoplasm. It took several decades of research to uncover how mRNA could be used to deliver an antigen into cells and trigger the body's own immune response.

Traditional vaccine development, which used a weakened or dead virus to stimulate an immune response against the disease, is lengthy and costly. Progress in molecular biology enabled the development of vaccines based on individual viral components, where parts of the viral genetic code are used to make proteins that stimulate the formation of virus-blocking antibodies. The most recently developed mRNA vaccines contain viral mRNA that, when injected into the body, instructs the cells to produce parts of viral proteins that trigger the immune response. Since mRNA can be quickly synthesized and modified, the development of mRNA vaccines can be much faster than traditional vaccines. By discovering how to make mRNA stable and prevent immune activation by the mRNA itself, the seminal discoveries of his year's Nobel Prize laureates were essential to the development and implementation of mRNA vaccines.

Letošnja Nobelova nagrada za fiziologijo ali medicino je bila podeljena Katalin Karikó in Drewu Weissmanu za odkritja, ki so omogočila razvoj cepiv proti COVID-19 na osnovi sporočilne RNA (mRNA). mRNA je prehodna molekula v celici, ki posreduje navodila za sintezo proteinov iz jedra, kjer so navodila shranjena kot genetski kod v DNA, celičnemu sistemu za izdelovanje proteinov (ribosomov) v citoplazmi. Potrebnih je bilo več desetletij raziskav, da bi odkrili, kako uporabiti mRNA za prenos antigenov celicam in začetek telesu lastnega imunskega odziva.

Tradicionalni razvoj cepiv, ki je uporabljal oslabljene ali mrtve viruse za stimulacijo imunskega odziva proti boleznim, je drag in dolgotrajen. Napredek v molekularni biologiji je omogočil razvoj cepiv na osnovi posameznih virusnih delov. Pri tem so deli virusnega genetskega koda uporabljeni za proizvodnjo proteinov, ki stimulirajo tvorbo protiteles proti virusom. Najsodobnejša cepiva na osnovi mRNA vsebujejo del virusne mRNA, ki ob injiciranju v telo celicam posredujejo navodila za proizvodnjo delov virusnih proteinov, ki sprožijo imunski odziv. Ker je lahko mRNA hitro sintetizirana in nadgrajena, je lahko tudi proizvodnja cepiv na osnovi mRNA precej hitrejša kot proizvodnja tradicionalnih cepiv. Z odkritjem, kako molekulo mRNA napraviti stabilnejšo in kako preprečiti imunsko aktivacijo s samo molekulo mRNA, so bila temeljna odkritja letošnjih Nobelovih nagrajencev, ključna za razvoj in uporabo cepiv na osnovi mRNA.

Gene therapy produces a therapeutic effect by genetically modifying cells through introduction of a new gene or reconstruction of existing defective genetic material. In the case of mRNA vaccines, the genetic code for an antigen (i.e., a viral protein) triggers an immune response that ultimately leads to immune protection against the virus. Gene therapy has been gaining momentum in human medicine as a versatile therapeutic approach in the past decade, following the first gene therapy approvals in Europe in 2012 and 2016 for Glybera (to reverse lipoprotein lipase deficiency) and Strimvelis [to treat severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)], respectively (1, 2), and the first approval in the USA in 2017 for Kymriah (to treat acute lymphoblastic leukemia)(3). Besides offering hope for a cure to patients with rare diseases, certain types of cancer, and developmental genetic diseases, gene therapy also has enormous potential in preventing diseases via mRNA vaccines. In the post-genomic era, the development of technology and the availability of genomic data enables the rational and targeted design and clinical testing of various kinds of gene therapeutics.

Genes can be delivered to the cell of interest by DNA plasmids, viral vectors, mRNA, or other methods. Although gene transfer technology using mRNA was investigated for decades, several roadblocks, including a lack of mRNA stability and immune rejection of RNA molecules, hindered the efficiency of mRNA delivery. Through several decades of research, Katalin Karikó and Drew Weissman made vital discoveries that were instrumental in breaching these roadblocks. First, Karikó and Weissman discovered that the introduction of chemical modifications in mRNA nucleoside bases almost abolished inflammation when base-modified mRNA was delivered to dendritic cells (4). This discovery was a paradigm shift in our understanding of how cells recognize and respond to different forms of mRNA, as it showed that in vitro transcribed mRNA containing modified bases evades innate immune recognition. Additionally, they found that base modification of mRNA increased its stability and, consequently, protein production in cells (5, 6). These two discoveries, along with the unprecedented investment by the pharmaceutical industry, enabled the rapid development of the mRNA vaccine during recent pandemics and opened the flood doors for novel gene therapy opportunities, including vaccine development and cancer immunotherapy (7, 8).

Compared to the viral vectors currently used in most approved gene therapies, mRNA gene transfer is a safer alternative because mRNA is devoid of potentially toxic viral genes and regulatory elements present in the viral vectors. Furthermore, mRNA does not integrate into the genome, is non-replicative, and decays within a few days. This temporary therapeutic expression of the encoded protein is desirable in vaccine development and has been implemented in certain CAR-T therapy research applications (8, 9).

Genska terapija povzroči terapevtski učinek z genskim spreminjanjem celic z vnašanjem novih genov ali popravljanjem obstoječega, okvarjenega genetskega materiala. V primeru cepiv na osnovi mRNA genetski kod za antigen (npr. virusni protein) sproži imunski odziv, kar v končni fazi privede do imunske zaščite proti virusu. Genska terapija v zadnjem desetletju pridobiva na pomembnosti kot raznovrstni terapevtski pristop, po prvih odobritvah tovrstne terapije v Evropi leta 2012 in 2017 za Glybero (ki je zdravila pomanjkanje lipoproteinske lipaze) ter Strimvelis (ki zdravi hudo kombinirano imunsko pomanjkljivost zaradi pomanjkanja adenozinske deaminaze (ADA-SCID)) (1, 2) in po prvi odobritvi v ZDA za Kymriah (ki zdravi akutno limfoblastično levkemijo in ne-Hodgkinove limfome) (3). Poleg tega, da lahko ponudi upanje za ozdravitev bolnikom z redkimi boleznimi, nekaterimi oblikami raka in razvojnimi boleznimi, kaže genska terapija velikanski potencial pri preventivi bolezni s cepivi na osnovi mRNA. V po-genomski eri razvoj tehnologije in dostopnost genomskih podatkov omogočata racionalno in ciljno načrtovanje in klinično preizkušanje različnih oblik genske terapije.

Geni so lahko v ciljno celico dostavljeni s plazmidi DNA, z virusnimi vektorji, mRNA ter z drugimi metodami. Čeprav je bila tehnologija genskega prenosa z uporabo mRNA predmet raziskovanj že več desetletij, so številne ovire, vključno s pomanjkljivo stabilnostjo mRNA in imunskim zavračanjem molekul mRNA, zadrževale učinkovito dostavljanje mRNA v celico. Med večdesetletnimi raziskavami sta Katalin Karikó in Drew Weissman prišla do ključnih odkritij, nujnih za odpravo teh ovir. Najprej sta odkrila, da je uvajanje kemijskih sprememb v nukleozidne baze mRNA skoraj odpravilo vnetne procese, kadar je bila mRNA z modificiranimi bazami uvedena v dendritične celice (4). To odkritje je pomenilo premik v načinu razmišljanja, kako celice prepoznajo in odgovorijo na različne oblike mRNA. Ugotovila sta, da se in vitro prepisane mRNA, ki vsebujejo modificirane baze, izognejo prirojenemu imunskemu prepoznavanju. Poleg tega sta ugotovila tudi, da modifikacija baz pri mRNA poveča njeno stabilnost in posledično produkcijo proteinov v celici (5, 6). Ti dve odkritji sta, skupaj z do tedaj nepredstavljivimi investicijami v farmacevtski industriji, omogočili hiter razvoj cepiv na osnovi mRNA med nedavno pandemijo in na stežaj odprli vrata priložnostim novih genskih terapij, vključno z razvojem cepiv in imunoterapij raka (7, 8).

V primerjavi z virusnimi vektorji, ki so trenutno najpogosteje uporabljeni vektorji pri večini odobrenih genskih terapij, je genski prenos z mRNA varnejši pristop zato, ker mRNA ne vsebuje potencialno nevarnih virusnih genov in regulatornih elementov, ki se nahajajo v virusnih vektorjih. Poleg tega se mRNA ne vključuje v genom, se ne replicira in razpade v nekaj dneh. Tako začasno terapevtsko izražanje kodiranega proteina je zaželeno pri razvoju cepiv in je bilo uporabljeno tudi pri nekaterih oblikah razvoja terapij s CAR-T (8, 9).

V veterinarski medicini, tudi zaradi manj stroge zakonodaje v primerjavi s humano medicino, genska terapija ni nič

Due to the less stringent regulations in veterinary medicine compared to human medicine, gene therapy is not new in veterinary medicine. Rather, comparative medicine is leading the way in the development of novel approaches, such as combining gene therapy with electrochemotherapy in cancer treatment to improve the therapeutic outcome, a technique pioneered by and also mastered through the collaborative efforts of Slovenian veterinarians, medical doctors, and comparative researchers (10-13). In horses and dogs, interleukin (IL)-12 based gene therapy improved the electrochemotherapy antitumor effects on spontaneously occurring tumors in large and companion animals (10-13) and has potential in translating to human medicine. Furthermore, mRNA vaccines hold great promise in veterinary medicine. In past years, several mRNA vaccines have entered clinical trials. Due to their low risk of insertional mutagenesis, high potency, and potential for low-cost manufacturing, mRNA vaccines promise solutions to combat emerging and re-emerging infectious diseases, such as rabies, Zika, and influenza (14, 15)

The exciting discoveries leading to this year's Nobel Prize in Physiology or Medicine will impact future human and veterinary medicine and may be critical to help combat current and future zoonotic diseases.

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novega. Primerjalna medicina nas vodi v razvoju novih pristopov, kot je kombinacija genske terapije z elektrokemoterapijo raka za izboljšanje terapevtskega učinka, tehnik, ki so jih s skupnimi napori vzpostavili in vodili slovenski veterinarji, zdravniki in primerjalni raziskovalci (10–13). Pri konjih in psih je genska terapija z interlevkinom (IL)-12 izboljšala protitumorske učinke elektrokemoterapije pri spontanih tumorjih velikih živali in hišnih ljubljenčkov (10–13) in ima tudi potencial translacije v humano medicino. Poleg tega v veterinarski medicini veliko obljubljajo tudi cepiva na osnovi mRNA. Številna cepiva se v zadnjih letih že klinično preizkušajo. Zaradi nizkega tveganja za insercijsko mutagenezo, visokih zmogljivosti in potencialno nizkih stroškov proizvodnje cepiva na osnovi mRNA obetajo rešitve za boj proti novim in obstoječim kužnim boleznim, kot so steklina, zika in gripa (14, 15).

Vznemirljiva odkritja, ki so privedla do letošnje Nobelove nagrade za fiziologijo ali medicino, bodo vplivala na humano in veterinarsko medicino in bodo lahko tudi ključno pripomogla k boju z zoonozami danes in v prihodnosti.

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References

1. Glybera. Amsterdam: European medicines agency, 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/glybera (15. 11. 2023)
2. Strimvelis. Amsterdam: European medicines agency, 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/strimvelis (15. 11. 2023)
3. FDA approval brings first gene therapy to the United States. Silver Spring: Food and Drug Administration, 2023. https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states (15. 11. 2023)
4. Karikó K, Buckstein M, Ni H, Weissman D. Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. Immunity 2005; 23: 165–75.
5. Karikó K, Muramatsu H, Welsh FA, et al. Incorporation of pseudouridine into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability. Mol Ther 2008; 16: 1833–40.
6. Anderson BR, Muramatsu H, Nallagatla SR, et al. Incorporation of pseudouridine into mRNA enhances translation by diminishing PKR activation. Nucleic Acids Res 2010; 38: 5884–92.
7. The Nobel prize in physiology or medicine 2023. Stocholm: Nobel Prize Outreach, 2023. https://www.nobelprize.org/prizes/medicine/2023/press-release/ (15. 11. 2023)
8. Maus MV, Haas AR, Beatty GL, et al. T cells expressing chimeric antigen receptors can cause anaphylaxis in humans. Cancer Immunol Res 2013; 1: 26–31.
9. Rajcevic U, Smole A. Preclinical mouse models for adoptive cell therapies. Slo Vet Res 2022; 59: 173–84.
10. Pavlin D, Čemažar M, Serša G, Tozon N. IL-12 based gene therapy in veterinary medicine. J Transl Med 2012; 10: 234. doi: 10.1186/1479-5876-10-234
11. Kulbacka J,Paczuska J, Rembiałkowska N, et al. Electrochemotherapy combined with standard and CO2 laser surgeries in canine oral melanoma. Slo Vet Res 2017; 54: 181–6.
12. Milevoj N, Lampreht Tratar U, Nemec A et al. A combination of electrochemotherapy, gene electrotransfer of plasmid encoding canine IL-12 and cytoreductive surgery in the treatment of canine oral malignant melanoma. Res Vet Sci 2019; 122: 40–9.

13. Lampreht Tratar U, Milevoj N, Cemazar M et al. Treatment of spontaneous canine mast cell tumors by electrochemotherapy combined with IL-12 gene electrotransfer: comparison of intratumoral and peritumoral application of IL-12. Int Immunopharmacol 2023; 120: 110274. doi: 10.1016/j.intimp.2023.110274

14. Le T, Sun C, Chang J, Zhang G, Yin X. mRNA vaccine development for emerging animal and zoonotic diseases. Viruses 2022; 14: 1–19. doi: 10.3390/v14020401

15. Aida V, Pliasas VC, Neasham PJ et al. Novel vaccine technologies in veterinary medicine: a herald to human medicine vaccines. Front Vet Sci 2021; 8: 654289. doi: 10.3389/fvets.2021.654289