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共同研究報告　（年次終了）

In recent years, outbreaks of infectious diseases have seriously impacted the world. The emerging infectious diseases require urgent development of reliable and safe vaccines. Compared with conventional vaccines, such as live attenuated and inactivated vaccines, messenger RNA (mRNA) vaccines have emerged as a promising platform. mRNA vaccines can be developed rapidly by obtaining gene sequences for pathogen-derived proteins, enabling a rapid response to emergencies such as pandemics. mRNA vaccines developed by Pfizer/BioNTech and Moderna played a critical role in controlling the COVID-19 pandemic caused by SARS-CoV-2 in 2019. In addition, mRNA vaccines have been used for a variety of infectious diseases; these include an mRNA vaccine approved for the respiratory syncytial virus and another for influenza virus, which is in development.

mRNA vaccines induce robust antigen-specific antibody production and T cell responses that prevent infection and severe diseases. However, the mRNA vaccines often cause systemic adverse reactions, including fever and fatigue, and localized adverse reactions, such as pain and swelling, at the vaccination site. The frequency and severity of these adverse reactions increase with repeated vaccinations, although multiple vaccinations enhance antigen-specific immune responses. The occurrence of adverse reactions has led to vaccine hesitancy and fear, and this aversion can prevent the application of mRNA vaccines against future human threats. Therefore, addressing these adverse reactions is crucial for improving public acceptance. In humans, blood levels of inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, are increased after mRNA vaccine administration. Furthermore, blood levels of cytokines such as IL-6 correlate with the severity of adverse reactions following mRNA vaccination, suggesting the importance of inflammatory cytokines in inducing adverse reactions. Antigen-specific immune responses induced by mRNA vaccines are also part of the mechanism underlying the increased frequency and severity of adverse reactions after boost vaccination in humans. For example, the rate of increase in the abundance of type 1 T helper (Th1) cells in the blood after boost vaccination correlates with a high frequency of adverse reactions, and the concentration of interferon (IFN)-γ and the titer of neutralizing antibodies in the blood strongly correlate with the frequency and severity of adverse reactions. The inflammatory properties of mRNA vaccines have also been studied in mice; levels of inflammatory cytokines such as IL-6 are increased in the blood of mice after administration of mRNA vaccines. However, previous reports on humans and mice have been limited to studies reporting the correlation between the frequency and severity of adverse reactions, the cytokine levels, and the specific cell number, and only a few studies have directly examined the factors that cause adverse reactions. In addition, most studies in mice have focused on inflammatory reactions after the prime vaccination, leaving the reason for the increased rate of adverse reactions after boost vaccination unexplored. Therefore, understanding the precise mechanisms of adverse reactions after prime and boost vaccinations is critical for designing mRNA vaccines with fewer adverse reactions. Here, we attempted to elucidate the mechanisms underlying adverse reactions after mRNA vaccination in mice. We identified some cytokines and specific cells that play crucial roles in the induction of adverse reactions after prime and boost vaccinations. Our findings provide a basis for developing next-generation mRNA vaccines with reduced adverse reactions and overcoming vaccine hesitancy.