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MnFe2O4 nanoparticles invasion in nose-associated lymphoid tissue

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Motivation and Aim: Over the past decades, nanomaterials have become widespread in medicine. For example, at the moment, magnetic nanoparticles (MNPs) are already used as contrast agents in magnetic resonance imaging (MRI), magnetic indicators in magnetic particle imaging (MPI) and alternating current biosuceptometry (ACB), as well as in magnetic hyperthermia therapy [1]. In addition, MNPs are actively used as a platform for targeted delivery of therapeutic agents, including in the development of vaccines [2]. At the same time, recent data show that MNPs in vaccines can act as adjuvants with immunostimulatory properties. One of the most promising approaches to inducing the production of specific antibodies to various pathogens that affect the upper and lower respiratory tract are intranasal vaccines that stimulate local lymphoid tissue, which, both in humans and in other terrestrial mammalian species, including rodents, is located in nasal passages (nasal associated lymphoid tissue (NALT)). In this connection, the study of the factors causing the capture of nanosized objects by cells of nasal epithelium, including NALT, is of fundamental importance for understanding the mechanisms of interaction of the local immunity system with viral and bacterial pathogens, and practical, for increasing the effectiveness of vaccination.

Methods and Algorithms: Using transmission electron microscopy (TEM) and magnetic resonance imaging (MRI), we studied the capture of intranasally administered MnFe2O4 nanoparticles (MnFe2O4-NPs) by nasal epithelial cells, including NALT cells. TEM and MRI contrast MnFe2O4 NPs were administered to Balb/c mice (age: 12 weeks, Th2 immune response). An hour after the particle injection, the nasal epithelium was isolated and fixed for subsequent TEM.

Results: Using both MRI and TEM, we confirmed the accumulation of intranasally injected MnFe2O4-NPs in mouse NALT. In addition, we discovered, for the first time, that inorganic nanoparticles are able to penetrate the cilia membrane of epithelial cells and be transported to the cytoplasm via intraflagellar retrograde transport. Previously, such transport was described only for viral particles. We also demonstrated the endocytosis-independent nature of the uptake of MnFe2O4-NPs from the nasal cavity using MRI in experiments with preliminary administration of specific and nonspecific inhibitors of macropinocytosis, clathrin-, calveolin-, and dynamin-dependent types of endocytosis. Successive stages of NP invasion are described. In the cytoplasm, NPs accumulate inside the membrane vacuole.

Conclusion: The results obtained, on the one hand, demonstrate the possibility of using MNPs to increase the efficiency of antigen delivery to local immunity cells, and, on the

other hand, expand the understanding of the mechanisms of interaction between epithelial cells and nanosized objects.

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