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THE ROLE OF ZINC IN IMMUNE MECHANISMS

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Zinc deficiency has serious consequences for human health, as zinc is essential for many physiological functions. Zinc deficiency significantly suppresses the immune response, making the human body more vulnerable to virus infections.

Complexes of Zn^{2+} are effective against many viruses, including the influenza virus, herpes simplex virus, coronavirus, smallpox virus, human adenovirus, vesicular stomatitis virus, human immunodeficiency virus (HIV), and SARS-CoV-2 [1]. Scientific research indicates that the cations Cu^{2+} and Zn^{2+} are capable of preventing influenza virus growth in mammalian cells, and on surfaces containing these metals, the viral titre is significantly reduced [2]. The mechanism of the antiviral action of Cu^{2+} and Zn^{2+} involves DNA destruction by free radicals, modulation of viral proteases, and morphological changes in virus particles [1].

In 2025, a study was conducted on the effect of Zn^{2+} on the influenza A virus (IAV). A research group led by Ahn Young Jeong published a scientific article stating that zinc ions inhibit IAV hemagglutination in a concentration- and temperature-dependent manner for at least 24 h.

The influenza A virus uses the hemagglutinin (HA) protein to bind to sialic acid. Sialic acid is the terminal carbohydrate residue on the glycoproteins or glycolipids of the cell membrane, specifically the endosomal membrane to which influenza A hemagglutinin binds. That is why the study used a hemagglutination

assay to assess the virus's ability to bind to receptors on the membrane [2]. In the process of scientific research, the researchers incubated 100 μL of the IAV strain with 100 μL of working solutions of zinc chloride and copper chloride at concentrations of 0, 1, 2, 5, or 10 mM, prepared in DMEM medium. After incubating the samples, the zinc ions were chelated by adding equimolar ethylenediaminetetraacetic acid (EDTA). Turkey erythrocytes were used to analyze the ability of ions to affect hemagglutinin. Maximum results were achieved within 1 h and persisted for at least 24 h, with the effect being concentration-dependent [2]. Inhibition was also temperature-dependent and was optimal at temperatures above room temperature [2]. Importantly, serial passage of the virus in the presence of zinc ions did not lead to the development of resistance [2].

The mechanism underlying this effect was directly investigated in a structural study by Jong Hyeon Seok and colleagues (2020), published in the journal *Scientific Reports* [3]. Using X-ray crystallography, researchers determined the three-dimensional structure of influenza A virus hemagglutinin (HA) in complex with a zinc ion [3]. An unexpected finding was that the Zn^{2+} ion binds to the amino acid residues Glu68 and His137. The binding of Zn^{2+} to Glu68 and His137 induces structural changes in the hemagglutinin protein [3].

Under normal conditions, the conformation of HA occurs in the acidic environment of the endosome at a pH of approximately 5.0. The acidic medium acts as an indicator to the virus that it is already inside the cell. However, in the presence of Zn^{2+} , this change occurs even at neutral pH (7.4) [3]. Importantly, this change is irreversible: treatment with the chelator EDTA does not restore the native structure of HA [3]. Moreover, the conformations induced by Zn^{2+} or acidic pH are not recognized by the neutralizing antibody CR9114, confirming that they correspond to the post-fusion (inactive) state of the protein [3].

There are also scientific research studies on the effect of Zn^{2+} on other viruses. For example, research on the effect of zinc pyrithione against SARS-CoV-2. In 2022, researchers published a article in the *Journal of Enzyme Inhibition and Medicinal Chemistry*, in which they studied the effect of zinc pyrithione on the SARS-CoV-2

coronavirus. Zinc pyrithione is a coordination complex in which the Zn^{2+} ion is bound to two pyrithione molecules (1-hydroxy-2(1H)-pyridinethiol).

Zinc in the form of a free ion (Zn^{2+}) does not readily penetrate the cell membrane due to its lipid nature. To transport zinc into the cell, special carrier molecules-ionophores-are required. One of these is pyrithione. Zinc ionophores bind Zn^{2+} ions and transport them across the membrane, creating high intracellular concentrations of the metal. This approach has proven to be an effective antiviral agent, as increasing zinc levels inside the cell disrupts the life cycle of many viruses [4].

The researchers synthesized several compounds and analyzed them in an acetate buffer solution (pH = 5.5) to simulate conditions in the endosome, and in a HEPES buffer (pH = 7.4). Attention was focused on two enzymes involved in the SARS-CoV-2 life cycle: cathepsin L (responsible for viral entry into the cell via endocytosis) and PLPro (papain-like protease) (responsible for viral replication).

At the biochemical level, the mechanism of action is as follows: Zn^{2+} ions, delivered into the cell via pyrithione, bind to the active sites of enzymes. In the case of PLPro, which is a zinc-dependent metalloprotease, additional Zn^{2+} ions disrupt its catalytic activity [5]. In the case of cathepsin L-a lysosomal cysteine protease-zinc blocks its ability to cleave viral proteins necessary for the virus to exit from the endosome [5]. The most significant finding of this study was the evaluation of the effectiveness of zinc pyrithione in an ex vivo model of primary human lung tissue [4]. It is important to note that zinc pyrithione is already a commercially available substance (used as an antifungal agent in anti-dandruff hair shampoos), making it a potential candidate for repositioning (repurposing) as an antiviral drug against COVID-19 [5].

Another scientific research in 2009 confirmed the effectiveness of the same zinc ionophores (pyrithione and quinocitol) against picornaviruses-a group that includes rhinoviruses (the common flu) and enteroviruses [4]. Scientists found that these compounds effectively inhibit viral replication by disrupting the processing of viral polyproteins [4]. This means that masks and filters can be impregnated with zinc

to disinfect the air. The virus cannot develop resistance to zinc because it acts on the protein's basic structure rather than on a single vulnerable site.

Conclusions: Zinc not only supports the immune system “from the inside”, but also acts as a direct chemical inhibitor of virus activity. This makes it one of the most promising agents for the development of both new drugs and innovative means of passive protection.

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