

Copper(II) outcompetes other metal ions in spike fragment complexation, driving ROS-dependent oxidation

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Streszczenie

The SARS-CoV-2 spike protein plays a central role in viral entry into lung cells and has been implicated in promoting reactive oxygen species (ROS) formation in COVID-19 patients. Despite extensive research, the molecular factors contributing to spike-associated redox activity remain insufficiently understood, particularly the influence of metal ions. Here, we investigate the coordination properties of biologically essential metal ions (Cu^{2+} , Fe^{2+} , Fe^{3+} , Mn^{2+} , Co^{2+} , Zn^{2+}) and the potentially essential (Ni^{2+}) with modified spike protein fragments (Ac-ADGKAHFPRE-NH₂, **S4**, and Ac-HDGKAAFPRE-NH₂, **S5**). Our studies showed that Cu^{2+} ions form the most stable complexes at pH 6.7 (lung conditions). Potentiometric and spectroscopic analysis revealed distinct coordination modes, with a predominant $3\text{N}\{\text{N}_{\text{im}}, 2\text{N}^-\}$ for **S4** and $1\text{N}\{\text{N}_{\text{im}}\}$ for **S5**. Electrochemical and EPR studies demonstrated that Cu^{2+} -peptide complexes undergo redox cycling, including their reduction to Cu^+ . This redox activity drives ROS production, confirmed by ascorbate consumption, rhodamine 6G degradation and gel electrophoresis, which identified $\cdot\text{OH}$, $^1\text{O}_2$ and $\text{O}_2^{\cdot-}$. The generated ROS induce DNA double-strand breaks, with the Cu(II) -Ac-ADGKAHFPRE-NH₂ complex (**CuS4**) exhibiting higher oxidative potential than Cu(II) -Ac-HDGKAAFPRE-NH₂ (**CuS5**). Peptide oxidation in $\text{Cu(II)}/\text{H}_2\text{O}_2$ systems further showed that ROS produced by these complexes directly oxidize specific amino acid residues. In the presence of ascorbic acid, oxidation occurs mainly at the histidyl residue, whereas in its absence, selective lysyl oxidation yields α -aminoadipic acid, demonstrating redox-dependent, residue-specific oxidative pathways.

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