Abstract

The currently available COVID-19 vaccine is thought to be sufficient in protecting against SARS-CoV-2 infection, whilst the constant mutations of SARS-CoV-2 and the failure of the vaccine to evoke protective mucosal immunity have remained problems. This condition has brought forward the idea of targeting nucleocapsid (N) protein as a more conserved region of SARS-CoV-2, in addition to the spike-1 protein (S1), using a multivalent concept. Additionally, employing the oral delivery system, which remains the safest route to induce mucosal immunity, can prevent the initial SARS-CoV-2 infection. Using immunoinformatics approaches, the S1 and dual S1-N vaccine were built from conserved antigenic and immunogenic epitopes, which showed no toxicity, allergenicity, and autoimmunity potential detected within the complete vaccine construct. While the unstable N-only vaccine construct candidate was eliminated. Accordingly, the vaccine is suitable for the European population with favorable binding to the Toll-like receptor-2 (TLR-2) and Toll-like receptor-4 (TLR-4) to trigger innate immunity. Similarly, the vaccine has been shown to induce both IgA and IgG irrespective of their immune classes. *Lactococcus lactis,* a food-grade bacterium with Generally Recognized as Safe (GRAS) status, is selected as the host for vaccine delivery due to its intrinsically resistance to the extreme gastrointestinal (GI) tract environment. Subsequently, the vaccine construct demonstrated perfect *in silico* codon adaptability to *L. lactis*, providing a promising effective vaccine delivery.

Keywords

COVID-19, SARS-CoV-2, Nucleocapsid (N), Spike-1 Protein (S1), Dual Spike-1-Nucleocapsid Protein (S1-N), Multivalent, Multi-epitope, Mucosal Immunity