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The MSH3 Gene from a Neuropsychiatrist's Perspective

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Introduction

We read with great interest the article by Ambati BK, et al. "MSH3 Homology and Potential Recombination Link to SARS-CoV-2 Furin Cleavage Site" published on February 21st, 2022 in *Frontiers in Virology*. This perspective paper highlights a 19-nucleotide genetic sequence, a reverse complement of the human MSH3 gene, that contains the SARS-CoV-2 furin cleavage site (FCS). As this sequence (SEQ ID11652) was patented by Moderna in 2016 (US patent 9,587,003), some have suggested that the FCS may have been known prior to the COVID-19 pandemic [1].

Aside from its well-established role in averting tumor genesis, novel preclinical studies found that MSH3 is a key regulator of short tandem repeats (STRs), DNA sequences characteristic of monogenic neuropsychiatric disorders, such as Huntington's disease (HD) and fragile X syndrome (FXS) [2-4]. For example, FXS is caused by CGG repeats in the fragile X messenger ribonucleoprotein 1 (FMR1) gene [5]. Interestingly, the designers of COVID-19 mRNA vaccine chose to encode the 42 arginine residues (found in viral S protein) via a rare CGG codon, increasing the odds of STRs formation [6]. Many viruses,

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including SARS-CoV-2, human cytomegalovirus (HCV), and human immunodeficiency virus (HIV), were demonstrated to generate STRs, increasing the risk of tandem repeat disorders (TRDs) [7-12]. On the other hand, fragile X mental retardation protein (FMRP), the product of FMR1 gene, was demonstrated to target influenza and Zika viruses, while metabotropic glutamate 5 receptor (mGluR5) inhibitors, commonly utilized in FXS, often ameliorate SARS-CoV-2 symptoms, indicating a two-way street between viral infections and TRDs [13-15].

Recent studies have reported that STRs can increase the risk of schizophrenia and autism spectrum disorder (ASD), indicating that these sequences play a major role not only in monogenic but also in polygenic disorders [16,17]. Indeed, the findings of Ambati BK, et al. are in line with our own studies that connected FCS to pathological cell-cell fusion, neurodegeneration, and psychopathology [18,19]. As COVID-19 mRNA vaccines elicit the expression of full-length S antigen (including the FCS), these therapeutics may promote pathological syncytia [20]. Along this line, giant cell myocarditis and arteritis due to pathological cell-cell fusion were recorded in Vaccine Adverse Event Reporting System (VAERS) [21,22].

Pfizer and Moderna COVID-19 messenger RNA (mRNA) vaccines are heavily engineered to facilitate translation and improve stability, modifications that include codon optimization enriched with CG repeats [6]. However, as MSH3 regulates STRs, including the CG repetitions, vaccine efficacy is likely enhanced by the inhibition or attenuation of this protein. This may explain the reason Moderna was interested in patenting this molecule in 2016. In addition, as COVID-19 mRNA therapeutics encode the entire S antigen, MSH3 may be over expressed, a phenomenon associated with loss of function [23]. Indeed, MSH3 may be inactivated via promoter methylation or over expression [24].

From the neuropsychiatric perspective, the novel MSH3 findings are significant as this protein, encoded on chromosome 5 (q11-q13), shares a common promoter with dihydrofolate reductase (DHFR), a gene disrupted in many neuropsychiatric conditions, including ASDs, schizophrenia, depressive and bipolar disorder as well as immune dysfunction, diabetes, type I, and epilepsy [25-31]. Due to the common promoter, vaccine-induced MSH3 inhibition likely attenuates DHFR, predisposing to these pathologies. In favor of this statement, we bring the fact that treatment with methotrexate, a DHFR inhibitor, was associated with neuropsychiatric pathology, including anxiety, depression, suicidal behavior, and dementia [16], [32-36].

Taken together, the MSH3/DHFR locus may represent a hub where immunity, metabolism, and neuropsychiatric pathology intersect, therefore a better understanding of these genes would shed light on the etiopathogenesis of these conditions.

Messenger RNA vaccines, a short overview

To elicit the generation of neutralizing antibodies, exogenously administered mRNA must be heavily engineered to avoid hydrolysis by the extracellular RNase [37,38]. Placing the nucleic acid backbone into lipid nano particles (LNPs), hides it from RNAase, while replacing Uridine with N1-methylpseudouridine (m1Ψ), renders the vaccine undetectable to sensors [39,40] [Figure 1]. Other

adjustments were made in the untranslated regions (UTRs) and polyadenylated (polyA) tail to protect and stabilize the vaccine [40,41]. Another alteration, addition of two proline residues, maintains the S antigen in prefusion conformation to enhance the exposure to host immune system [42]. Moreover, codon optimization includes increased CG content as well as G-quadruplex structures to promote quick translation [6]. Furthermore, MSH3 was also found to function as a sensor for G-quadruplexes, therefore opposing codon optimization [43,44].

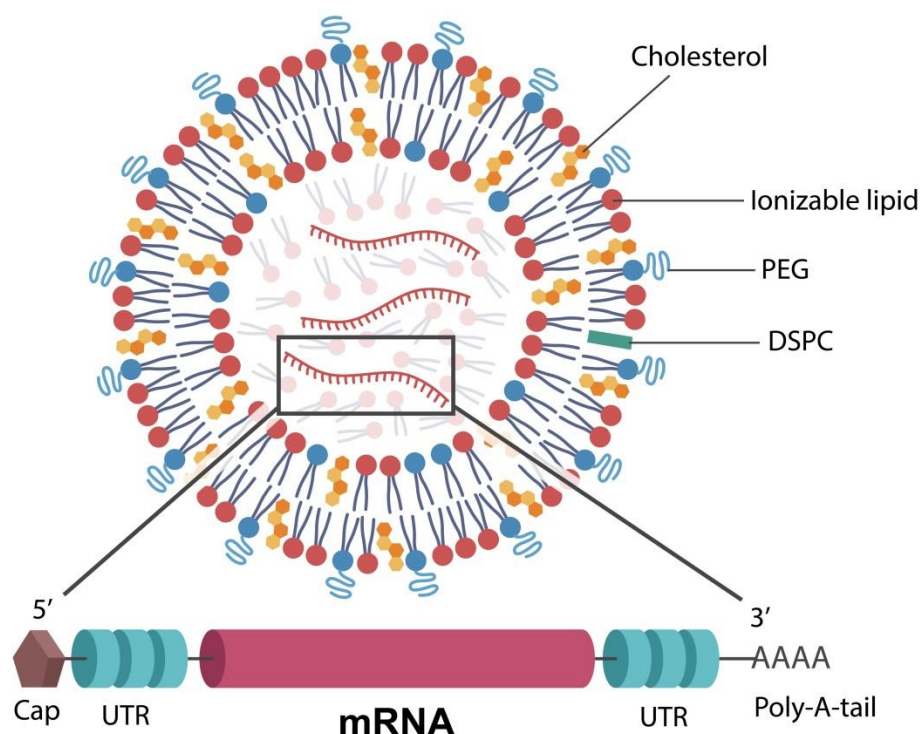


Figure 1: N1-methylpseudouridine (m1Ψ)-modified mRNA (in the rectangle) is surrounded by a lipid nano particle (LNP) comprised of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and an ionizable lipid. Polyethylene glycol (PEG) is conjugated with the lipid molecules to increase the mRNA duration of action. The mRNA encodes for the full-length S antigen and is flanked by two untranslated regions (UTRs) and a poly adenylated (poly) tail at the 3' end for stabilization. A cap at the 5' end offers further protection from exonuclease recognition.

LNPs, a future prospect

LNP-incorporated mRNA comprises an enormous technological success that goes beyond the vaccines, opening new avenues for developing “smart” therapeutics that can be delivered with pinpoint precision to specific sub cellular structures [45]. The development of such therapeutics is anticipated to redefine clinical pathways, including for non-communicable diseases. However, are these therapies ready for

worldwide application in their present molecular form? This question has been asked before, often in relation to the potential toxicity of lipid formulations used in the past, especially as part of cancer therapeutics delivery [46,47].

We anticipate that LNPs will be rapidly adopted into neuropsychiatry, especially as polyethylene glycol (PEG), an LNP component, can temporarily increase the permeability of blood-brain barrier (BBB), allowing direct nano particle access to neuronal networks [48]. Indeed, we envision a near future when micro or nano grams of LNP-attached psychotropic drugs could be delivered to intra neuronal targets, averting systemic adverse effects. However, for that to happen, the LNP may need to be redesigned as some of the currently utilized lipids may interfere with the psychotropic drugs as we recently documented [49].

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