# M1237I Mutation in Taiwan SARS-CoV-2: Hypothesis and Possible Treatments

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Mutation in M1237I has been present in 20 patients of COVID-19 infection with alpha variants of SARS-CoV-2 in Taiwan (May 13 to June 24, 2021; GISAID website). There have been 2048 cases reported to have M1237I mutation worldwide so far (July 25, 2021). It has been shown that D614G and M1237I together caused the decrease of sensitivity to convalescent sera, suggesting that M1237I mutation may increase viral virulence. (Li et al., 2020).

This mutation is located at the cysteine-rich domain of cytoplasmic tail of SARS-CoV-2 spike protein (Figure 1). The double cysteine residues near M1237 in this cysteine-rich domain (**CC**-MTS-**CC**) of SARS-CoV-1 have been previously shown essentially for protein palmitoylation, plasma membrane anchoring and spike protein-mediated cell-cell fusion (Petit et al. 2007).

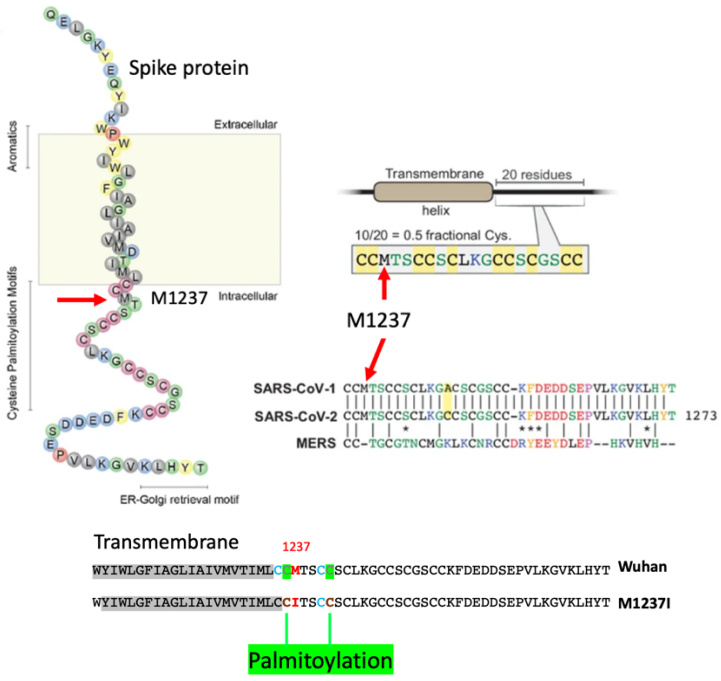



Figure 1. The location of M1237 in cysteine rich domain at cytoplasmic tail of SARS-CoV-2 spike protein. (figure was adapted from Sanders et al., Elife (2021) e65962. ; Buonvino & Melino Cell Death Discovery (2020) 6: 134 ).

Based on computational (GPS-lipid) prediction, palmitoylation possibility of cysteine 1236 and cysteine 1241 reduces due to M1237I mutation. The first palmitoylation site may be destroyed, while the second palmitoylation site could be attenuated (Figure 2).

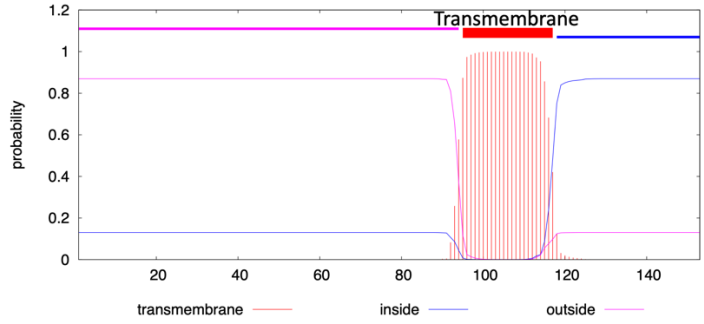



Figure 2. M1237I may change palmitoylation of SARS-CoV-2 spike protein. Transmembrane motif was predicted by TMHMM version 2.0 and shifted in M1237I mutations, which may lead to change of palmitoylation of viral spike protein.

SARS-CoV-2-induced cell-cell fusion (syncytia formation) has been also confirmed by several studies *in vitro* or in patients (Buchrieser et al., 2020; Giacca M et al., 2020). SARS-CoV-2 spike protein is sufficient to induce a rapid (~45.1 nm/s) membrane fusion to produce syncytium, which could readily internalize multiple lines of lymphocytes to form typical cell-in-cell structures, remarkably leading to the death of internalized cells (Zhang et al., 2021, Lin et al, 2021).

Infection of many enveloped viruses generates fusogenic viral protein present on the host cell plasma membrane, which leads to neighboring cells fusing into multinucleated 'syncytia' (Ciechonska and Duncan, 2014; Compton and Schwartz, 2017; Duelli and Lazebnik, 2007). Such cases like respiratory syncytial virus (RSV), human immunodeficiency virus (HIV), and others suggest that cell-cell fusion could play critical roles in pathogenicity, including viral replication, or evasion of the host immune response (Frankel et al., 1996; Johnson et al., 2007; Maudgal and Missotten, 1978). Studies on SARS-CoV-1 (Li et al., 2003) and SARS-CoV-2 identified similar syncytia (Buchrieser et al., 2020; Cattin-Ortolá et al., 2020; Hoffmann et al., 2020a; Ou et al., 2020; Papa et al., 2020; Xia et al., 2020; Zang et al., 2020b), which may be relevant to patient pathology (Bryce et al., 2020; Giacca et al., 2020; Rockx et al., 2020; Tian et al., 2020) (Figure 3).

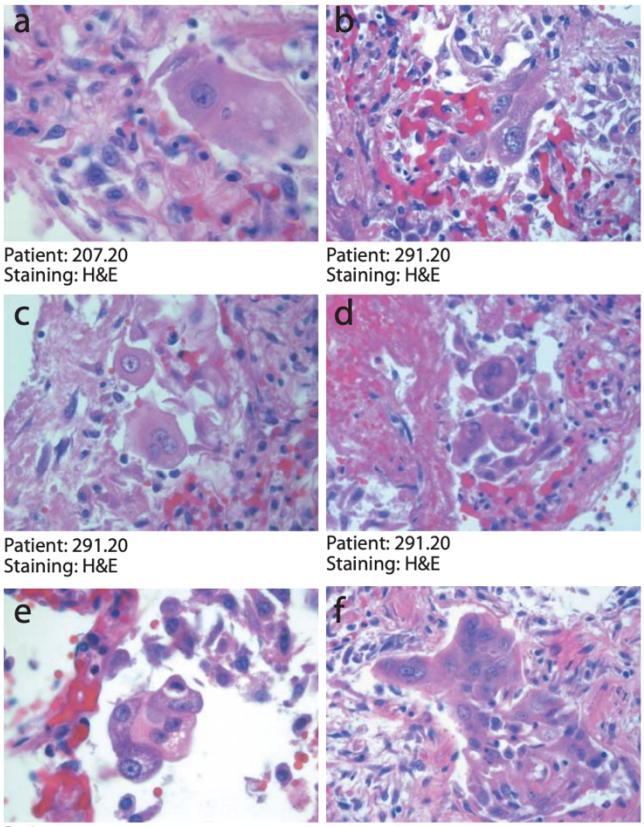
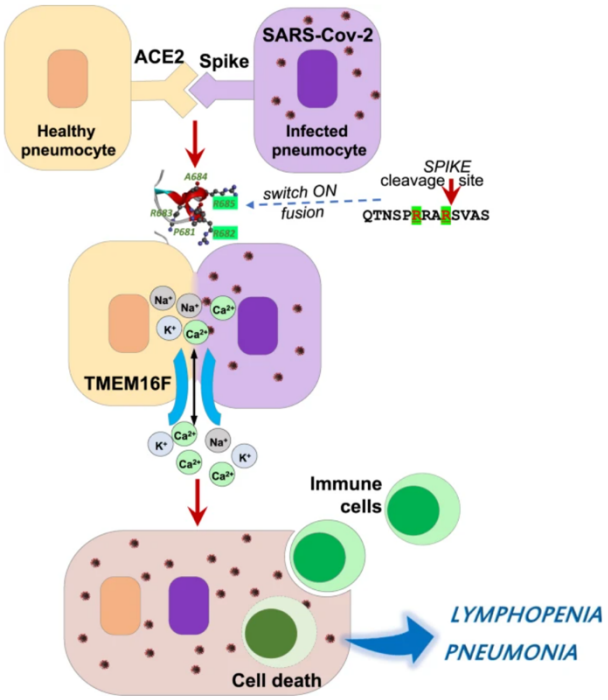



Figure 3. Unique cytological features of SARS-CoV-2. A consistent and typical feature in COVID-19 lungs was the appearance of major cytological abnormalities, including the presence of giant cells (a, x63; b, x40), with a large cytoplasm, which often became bi- or multi-nucleated (c-f, x40). (Figure from Giacca M et al., 2020)

Since blocking membrane fusion suppresses SARS-CoV-2 replication (Zang et al, 2021), M1237I mutation may enhance membrane fusion that causes faster viral replication, cell death, and lymphopedia and pneumonia (Figure 4). It remains an open question if syncytia are related to viral and host cell membrane composition, and whether their formation provides mechanistic insights into cholesterol-targeting therapeutics repurposed for COVID-19 treatment (Daniels et al., 2020; Zhang et al., 2020). Cholesterol-targeting therapeutics, such as the use of **statins**, is associated with a reduced risk of mortality among Individuals with COVID-19 (Zhang et al.,

2020). Other study has suggested that **niclosamide** (antihelminthic drug) could be repurposing for COVID-19 therapy (Braga et al., 2021).




***I highly recommend that the researchers should test whether (1) M1237I variant replicates faster (2) causes more cell-cell fusion (3) the effects of these drugs on M1237I variant in viral replication assays.***

Figure 4. The SARS-CoV-2 spike protein and cellular TMEM16 ion channel collaboratively mediated the formation of syncytia in COVID-19 infections. (figure is adapted from Lin et al., 2021)

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