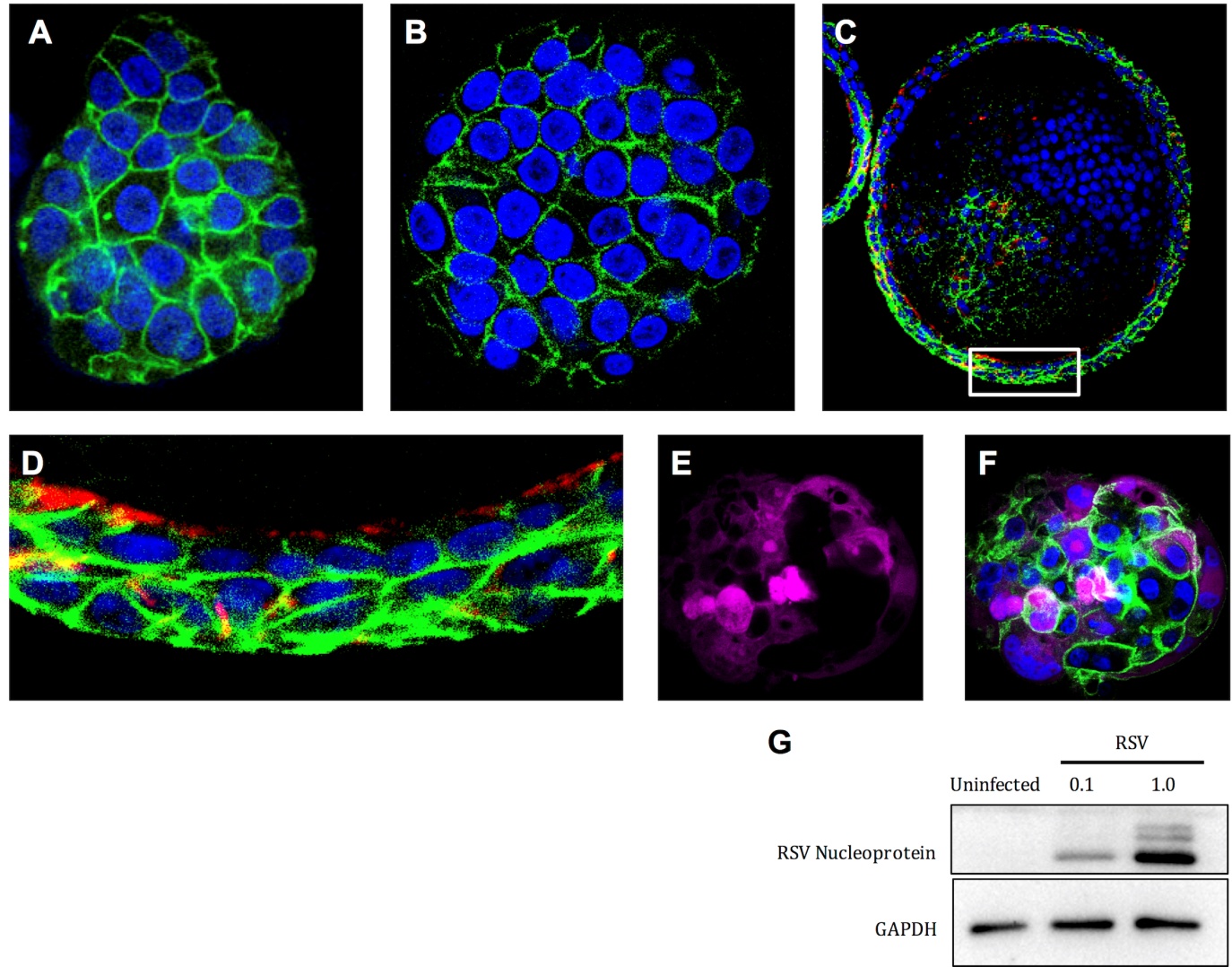
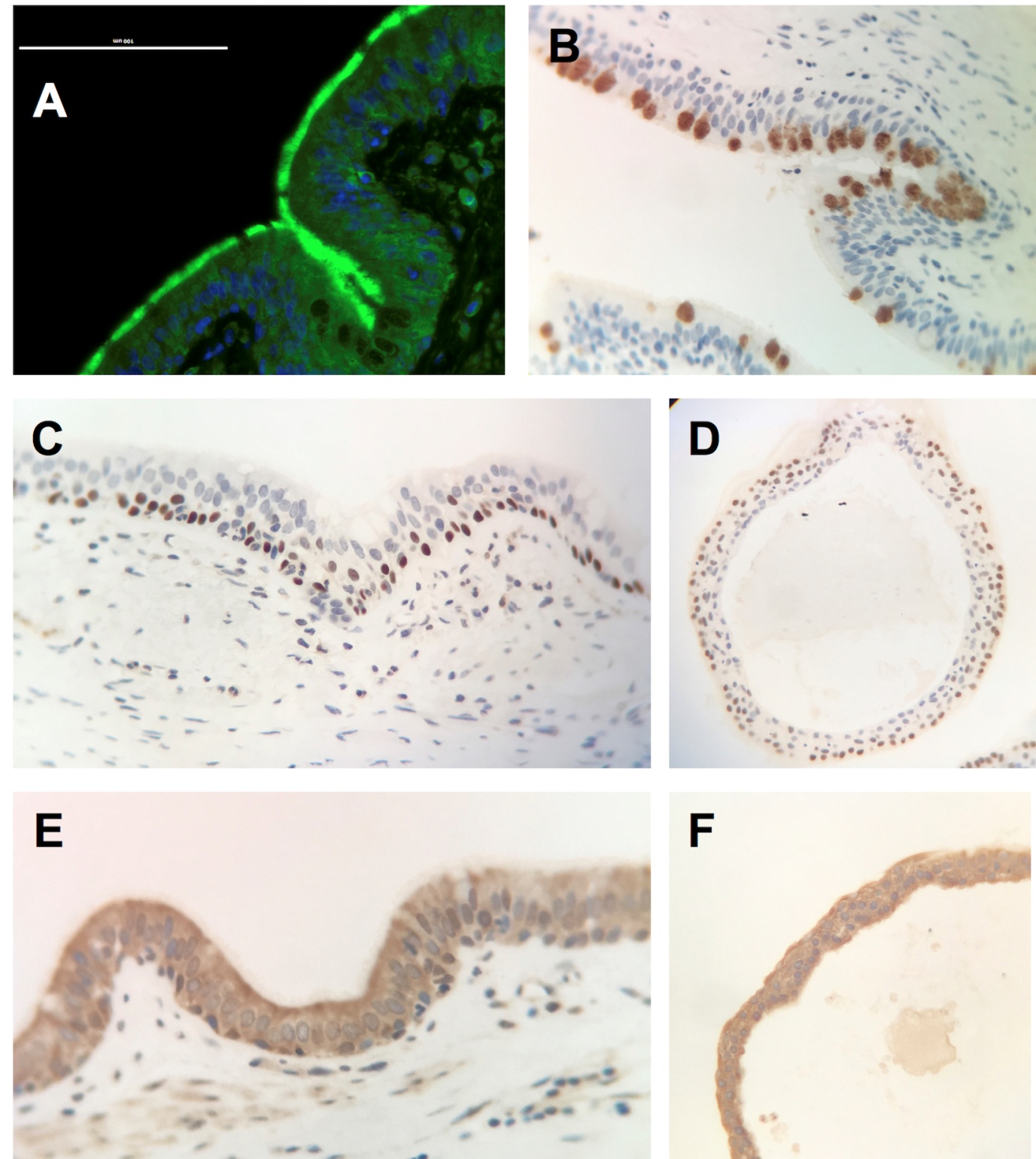
**Appendix**

|  |  |  |
| --- | --- | --- |
| **Rhinovirus genotype** | **2A Protease Recognition Site** | |
| **DNA Seq** | **Amino Acid Seq** |
| RV-A2 (minor) | ATTATCACTACAGCTGGCCCCAGT | IITTA\*GPS |
| RV-B14 (major) | GTGACATTAAATCCTATGGTTTAGGACCTA | DIKSY\*GLGP |
| RV-A16 (major) | AATCTAACAACTGTTGGGCCTAGTGACAT | NLTTV\*GPSD |

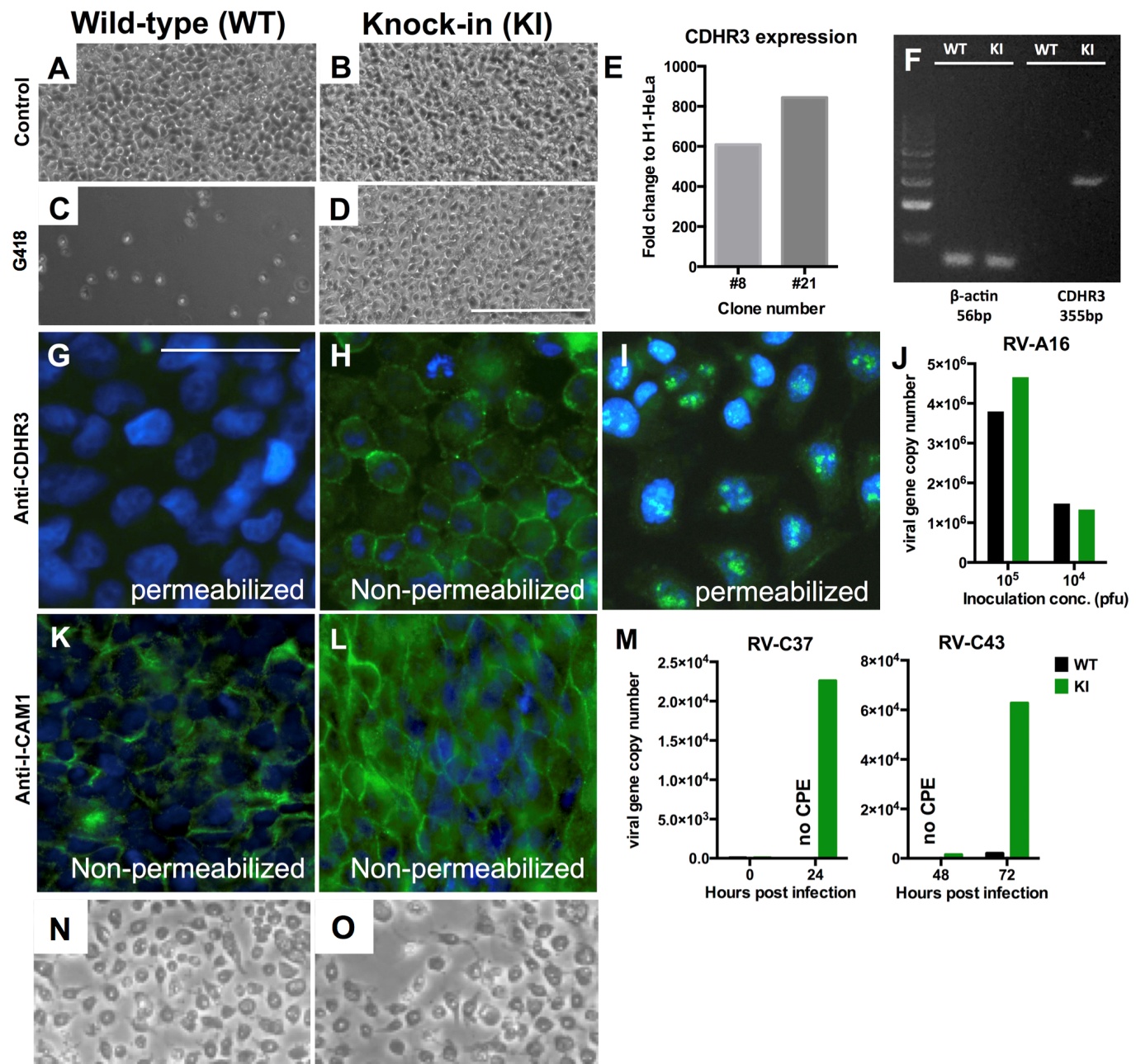
**Table 1. Rhinovirus 2A protease recognition site.** \* The asterisk means 2A Protease cut site



**Figure 1. The 3D human airway spheroid model system. (A, B)** Whole mount of 3D airway spheroids stained for membrane protein β-actenin in green and nucleus in blue.  **(C, D)** A cross-section of the 3D airway spheroids stained for ciliated cell marker acetylated tubulin in red. **(E, F)** A 3D airway spheroids were infected with red florescent protein (RFP)-RSV at a MOI of 1, the whole spheroid was fixed at 3 days post-infection and RSV-infected cells was in magenta. **(G)** 3D airway spheroids were left uninfected or infected with RSV at multiplicity of infection of 0.1 and 1.0. Whole spheroid extracts were prepared at 48 hours post-infection and analyzed by western blotting. RSV infection was confirmed by the presence of RSV nucleoprotein. GAPDH was used as loading control.



**Figure 2. The human respiratory epithelial models. (A)** Human bronchial explant culture expresses ciliated cell stained in green by β-tubulin antibody and **(B)** goblet cell stained in reddish brown by MUC5AC antibody. **(C,E)** Human bronchial explant culture and **(D,F)** the 3D airway spheroid stained with **(C,D)** basal cell using p63 antibody and  **(E,F)** the distribution of rhinovirus C receptorusingCDHR3 antibody in reddish brown.



**Figure 3. Construction of CDHR3529Y expressing H1-HeLa cells. (A)** H1-HeLa (ATCC, CRL-1958) was purchased directly from ATCC. **(B)** Plasmid expressing human CDHR3 was purchased (Origene, RC218636) and mutated CDHR3529Y was engineered by point mutation using Q5® site directed mutagenesis Kit (E0554S, New England Biolabs) and validated by sanger sequencing. Lipofectamine 2000 was used to transfect into H1-HeLa cell and CDHR3529Y expressing cell was selected using G418. **(C)** Wild-type H1-HeLa was killed by G418 while **(D)** the survived cells were seeded onto a 96-well plate for clonal expansion. (Scale bar, 200μm) **(E)** Several clones were selected and the expression of CDHR3 of each clone was determined by qPCR. With the highest CDHR3 expression, clone #21 was selected for subsequent experiments. **(F)** Electrophoresis was performed to confirm the expression is at specific size. **(G-I)** The successful knock in of the CDHR3 protein was examined for their cellular localization by immunofluorescence assay using anti-CDHR3 antibody (HPA011218, Sigma) and counterstained with DAPI.(Scale bar, 50μm) **(G)** WT H1-HeLa expressed no CDHR3 as indicated, while KI H1-HeLa expressed CDHR3 **(H)** on the surface and **(I)** at the nucleoli. **(J)** WT (black) and KI (green) both supports the replication of control RV-A16 strain to replicate with two different dilution of virus inoculations. **(K-L)** The normal expression of ICAM-1 was maintained in **(L)** WT and **(K)** KI H1-HeLa cell by using anti-ICAM-1 antibody (HPA002126, Sigma) and counterstained with DAPI. **(M)** An experiment using nasopharyngeal aspirate specimen of RV-C37 and RV-C43 genotypes indicated that a significant increase in viral gene copy number in the supernatant of the inoculated KI H1-HeLa (green bars) with **(N-O)** cytopathic effect but not in that of the WT H1-HeLa culture (black bar).