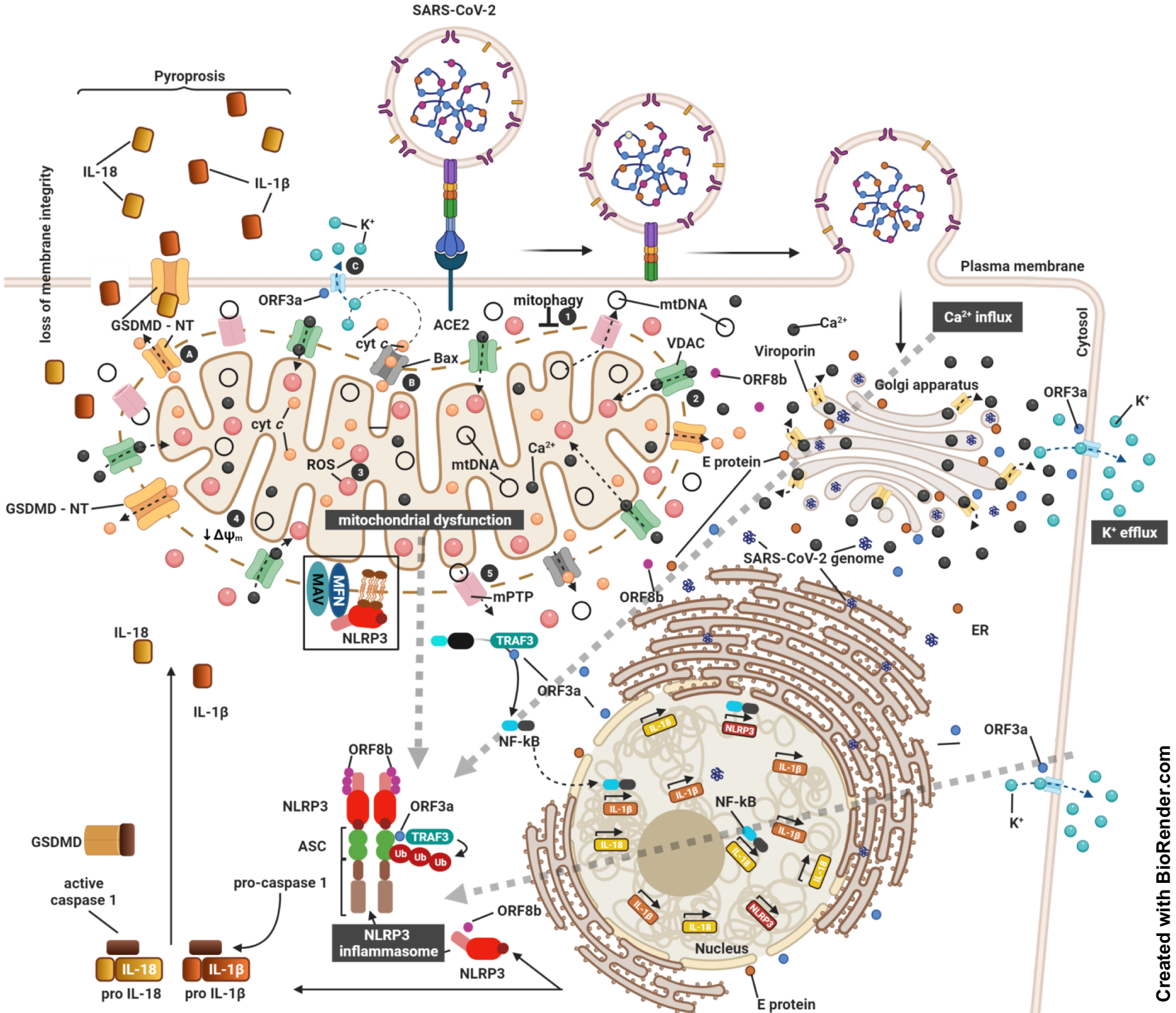
SARS-CoV-2
Pyroprosis
IL-18
IL-1β
loss of membrane integrity
K+
C
ORF3a
GSDMD - NT
A
ACE2
cyt c
Bax
B
mitophagy
1
mtDNA
VDAC
2
Ca2+
Viroporin
ORF8b
Golgi apparatus
ORF3a
K+
Plasma membrane
Ca2+ influx
Cytosol
cyt c
ROS
3
mtDNA
Ca2+
E protein
GSDMD - NT
4
↓Δψm
mitochondrial dysfunction
MAV
MFN
NLRP3
5
mPTP
ORF8b
SARS-CoV-2 genome
ER
K+ efflux
IL-18
IL-1β
TRAF3
ORF3a
NF-kB
ORF8b
NLRP3
ORF3a
ASC
TRAF3
Ub
GSDMD
active caspase 1
pro-caspase 1
NLRP3 inflammasome
ORF8b
NLRP3
IL-18
IL-1β
pro IL-18
pro IL-1β
NF-kB
Nucleus
E protein
ORF3a
K+
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Activation of the NLRP3 inflammasome by SARS-CoV-2 via mitochondrial dysfucntion.

The three SARS-CoV proteins (E, ORF3a and ORF8b) induce the activation of inflammasome.

E protein (**orange**) induces Ca^{2+} efflux from Golgi apparatus, where it storages, to the cytosol. This induces its into the mitochondria via VDAC (**2**) to Generate mtROS (**3**). ORF3a (**blu**) induces K^{+} efflux to the extracellular space and promotes inflammasome assembly through TRAF3-mediated ubiquitination of ASC. On the other hand, TFRA3-ORF3a interaction is required for NF-kβ activation, resulting in transcription of the pro–IL-1β/IL-18 and NLRP3 genes. ORF8b (**violet**) is able to interact directly with NLRP3 stimulating its activation. Consequently to inflammasome activation, the formation of GSDMD pores on the plasma and mitochondrial (**A**) membranes occur causing IL-1β/IL-18 secretion, the cellular swelling associated to pyroptosis and the induction of mitochondrial apoptotic pathway via Bax-dependent release of cyt c in the cytosol (**B**)**.** In addition, activation of BAX can trigger NLRP3 activation via apoptotic caspases (**dotted line**) in a K+ efflux-dependent manner (**C**).

Thus, SARS-CoV-2 triggers NLRP3 inflammasome assembly and activation by damaging the mitochondria and inducing the production of mtROS (**3**) and the lost of mitochondrial membrane potential ($\Delta\Psi_m$) (**4**) to release damaged mitochondrial DNA (mtDNA) in the cytosol through the mitochondrial pore transition (mPT) (**5**) . Therefore, mitophagy (**1**) plays an important regulator of NLRP3.

Cardiolipin, MAVS and MFNs can tether NLRP3 to the mitochondria for its activation in a mtROS-dependent manner (**black box**).