SPNS2 found to be directly exporting S1P for signaling, can be inhibited

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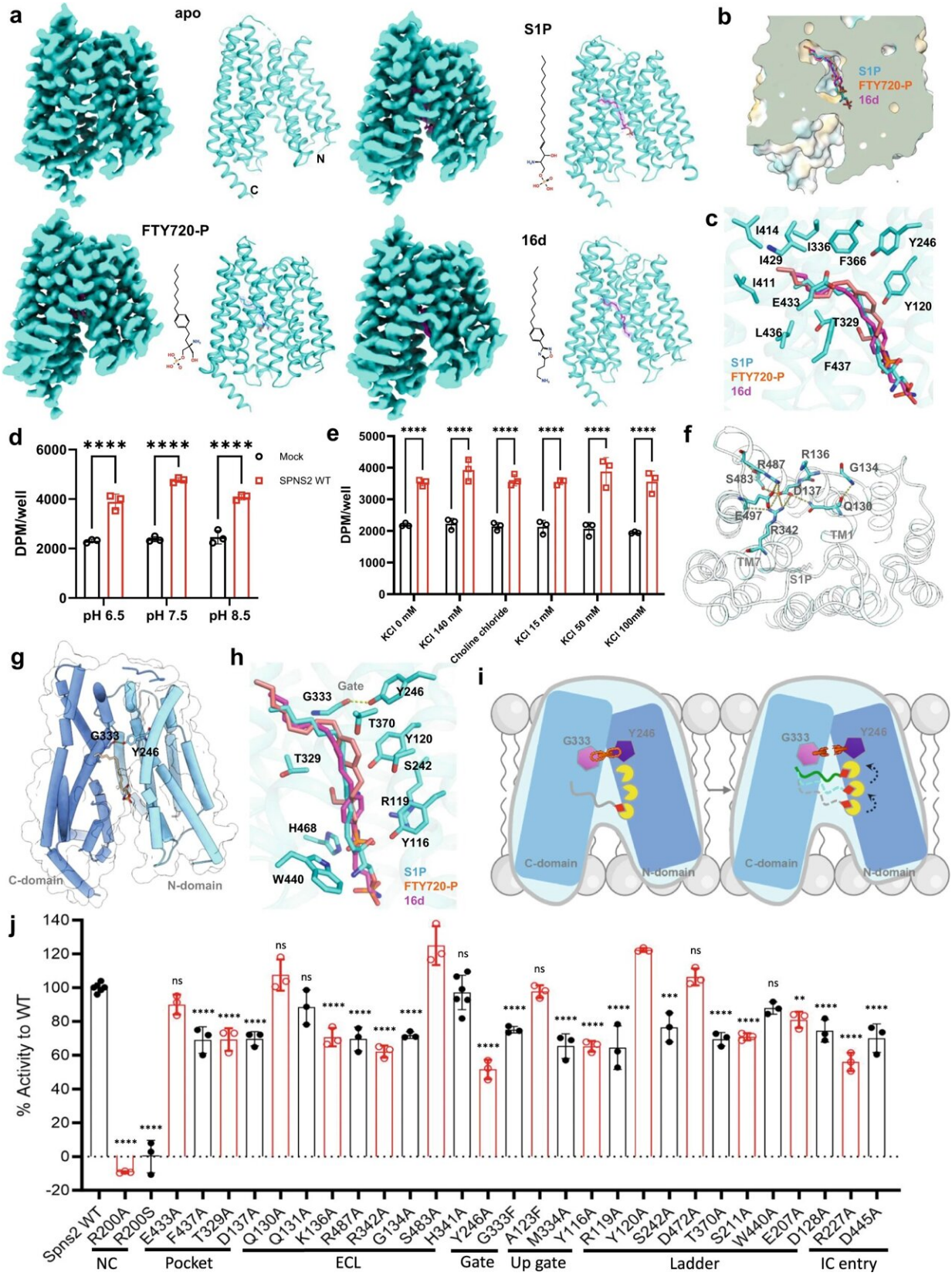
a
apo
S1P
FTY720-P
16d
N
C
b
S1P
FTY720-P
16d
c
I414
I336
Y246
I429
F366
I411
E433
Y120
T329
L436
F437
S1P
FTY720-P
16d
d
DPM/well
Mock
SPNS2 WT
pH 6.5
pH 7.5
pH 8.5
e
DPM/well
KCl 0 mM
KCl 140 mM
Choline chloride
KCl 15 mM
KCl 50 mM
KCl 100mM
f
R136
R487
G134
S483
D137
Q130
E497
R342
TM1
TM7
S1P
g
G333
Y246
C-domain
N-domain
h
Gate
G333
Y246
T370
Y120
T329
S242
R119
H468
Y116
W440
S1P
FTY720-P
16d
i
G333
Y246
C-domain
N-domain
j
% Activity to WT
Spns2 WT
R200A
R200S
E433A
F437A
T329A
D137A
Q130A
Q131A
K136A
R487A
R342A
G134A
S483A
H341A
Y246A
G333F
A123F
M334A
Y116A
R119A
Y120A
S242A
D472A
T370A
S211A
W440A
E207A
D128A
R227A
D445A
NC
Pocket
ECL
Gate
Up gate
Ladder
IC entry

Structural basis of S1P transport via human SPNS2. **a** Overall structures of SPNS2 in apo, S1P-bound, FTY720-P-bound and 16d-bound states. Left panel, orthogonal views of the cryo-EM density map; right panel, a model of the complex in the same view. **b** The hydrophobic pocket for the lipophilic tail of S1P and FTY720-P. The yellow surface color indicates a hydrophobic region, and the blue color indicates a hydrophilic region. **c** The detail of the hydrophobic pocket for substrate binding. **d** The effect of changing extracellular pH on the transport activity of SPNS2. **e** The effect of changing extracellular potassium and sodium concentration on the transport activity of SPNS2. **f** A polar interaction network on the extracellular side of SPNS2. **g** A gate formed by the hydrogen bond interaction between Y246 and G333 to lock SPNS2 in an inward-facing state. **h** A hydrophilic tunnel filled with polar residues below the G333/Y246 gate. **i** A proposed “ladder” mechanism for S1P transport via SPNS2. **j** The transport activities of SPNS2 mutants. Data are presented as mean ± SD; $n = 3$ independent samples; n.s., no significance; $*P$