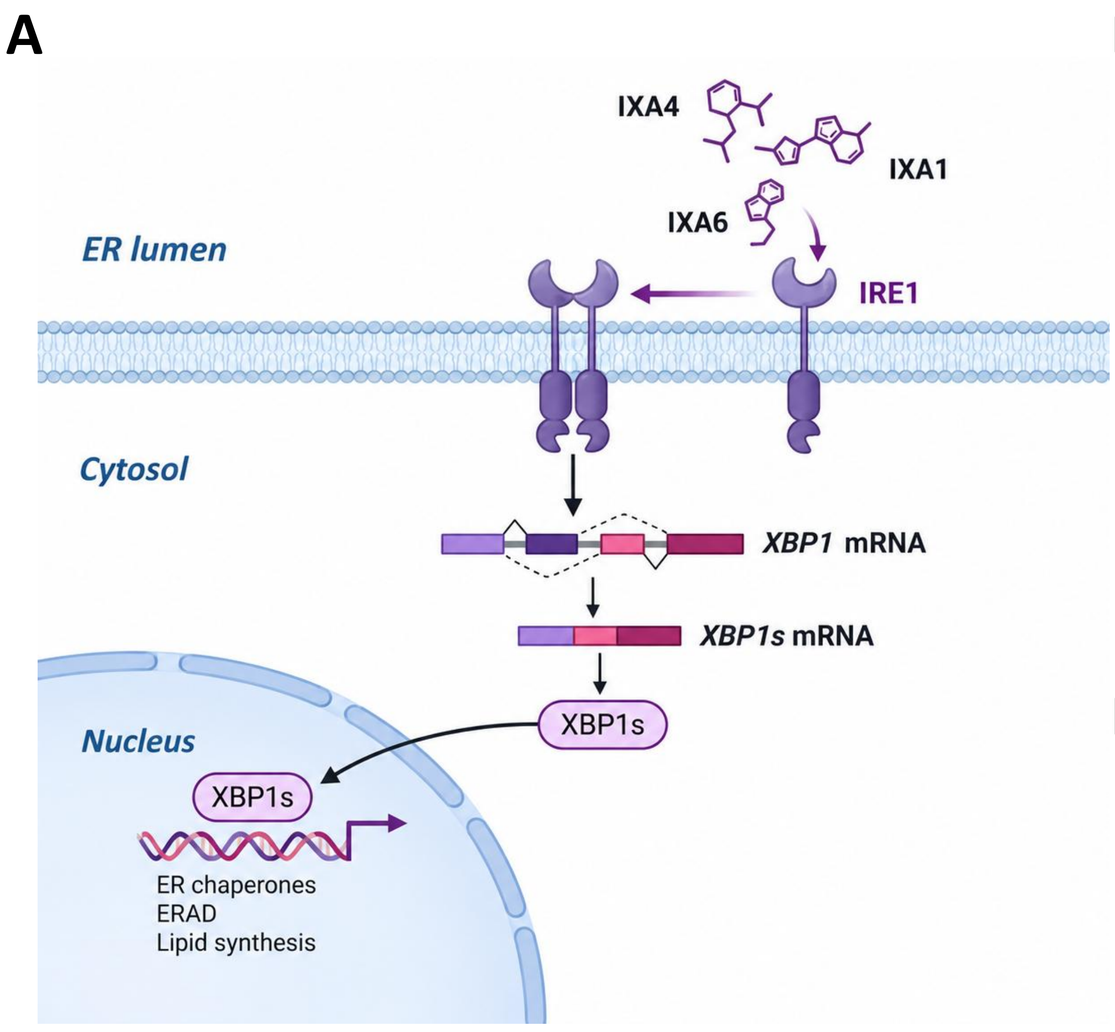
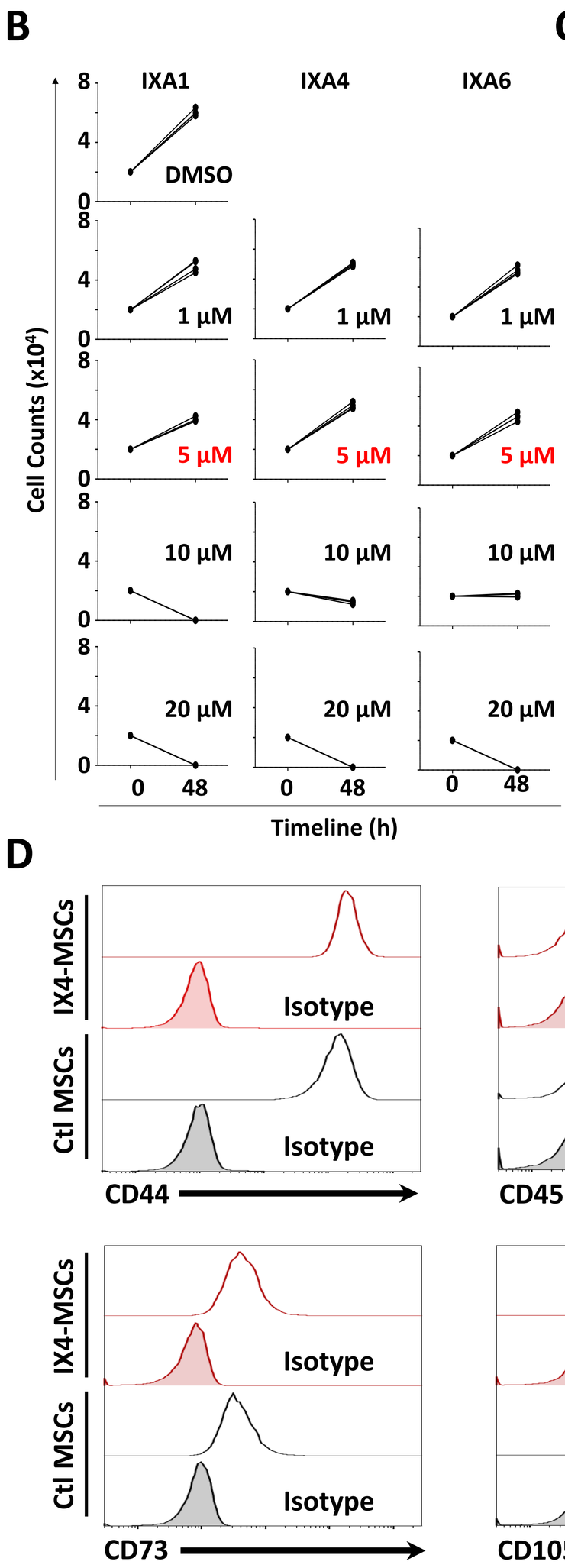
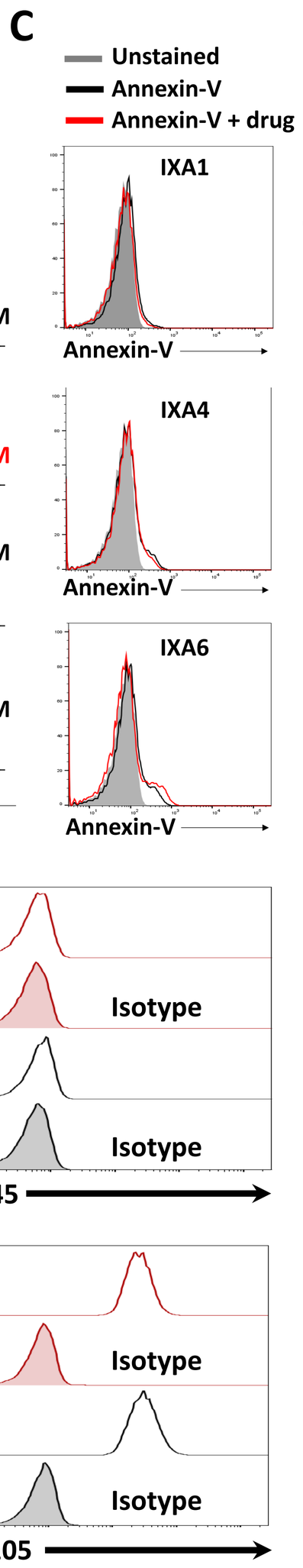
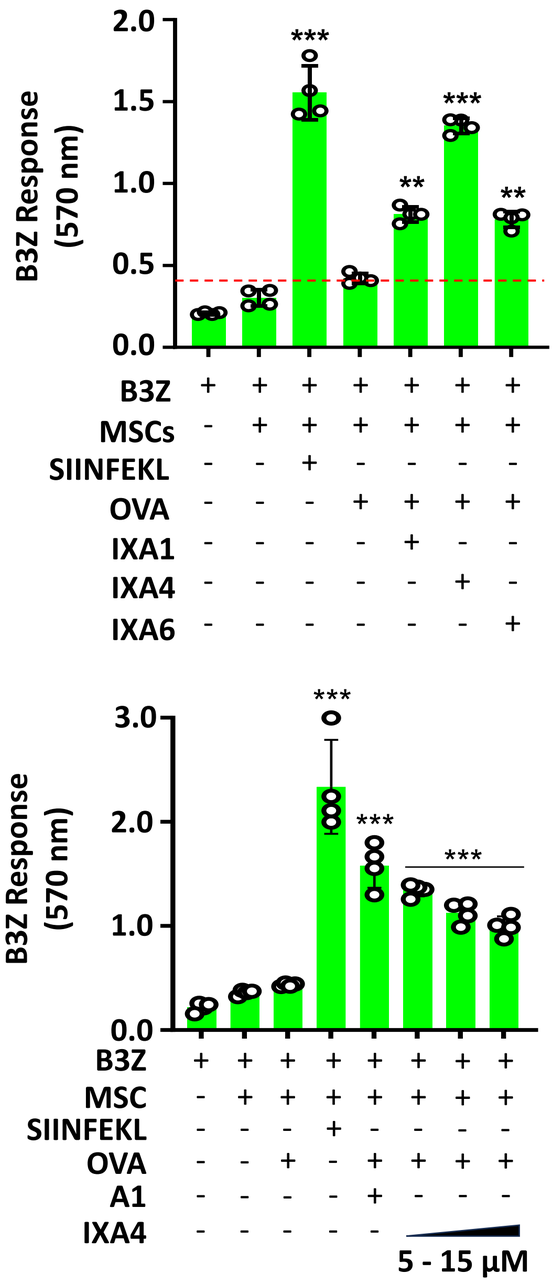

A
IXA4
IXA1
IXA6
ER lumen
IRE1
Cytosol
XBP1 mRNA
XBP1s mRNA
XBP1s
Nucleus
XBP1s
ER chaperones
ERAD
Lipid synthesis

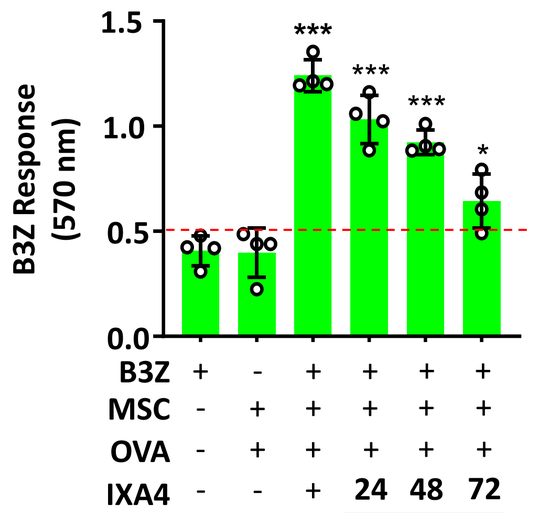

B
IXA1
IXA4
IXA6
DMSO
1 µM
5 µM
10 µM
20 µM
Cell Counts (x10⁴)
Timeline (h)
0
48

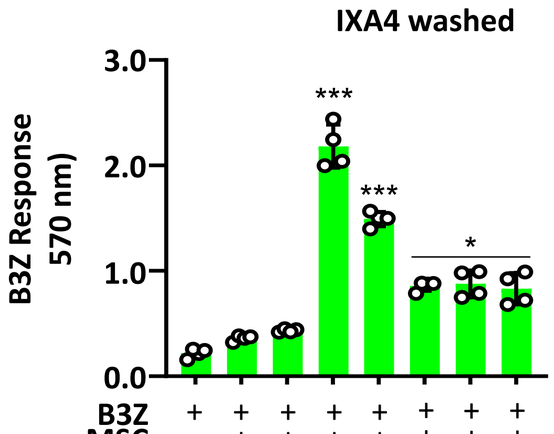

C
Unstained
Annexin-V
Annexin-V + drug
IXA1
IXA4
IXA6
Annexin-V

D
IX4-MSCs
Ctl MSCs
Isotype
CD44
CD45
CD73
CD105


E
B3Z Response (570 nm)
B3Z
MSCs
SIINFEKL
OVA
IXA1
IXA4
IXA6

F
B3Z Response (570 nm)
B3Z
MSC
SIINFEKL
OVA
A1
IXA4
5 - 15 µM


G
B3Z Response (570 nm)
B3Z
MSC
OVA
IXA4
24
48
72
IXA4 washed


H
B3Z Response (570 nm)
B3Z
MSC
SIINFEKL
OVA
A1
MK-28
50 - 150 µM

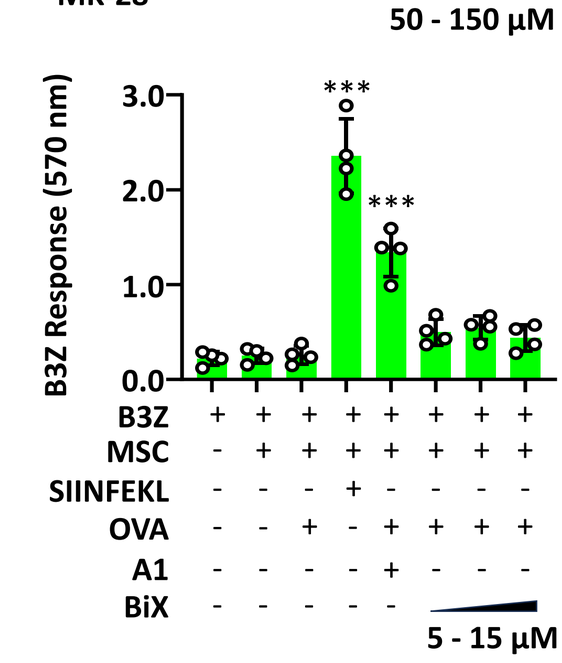

I
B3Z Response (570 nm)
B3Z
MSC
SIINFEKL
OVA
A1
BiX
5 - 15 µM

FIGURE 1

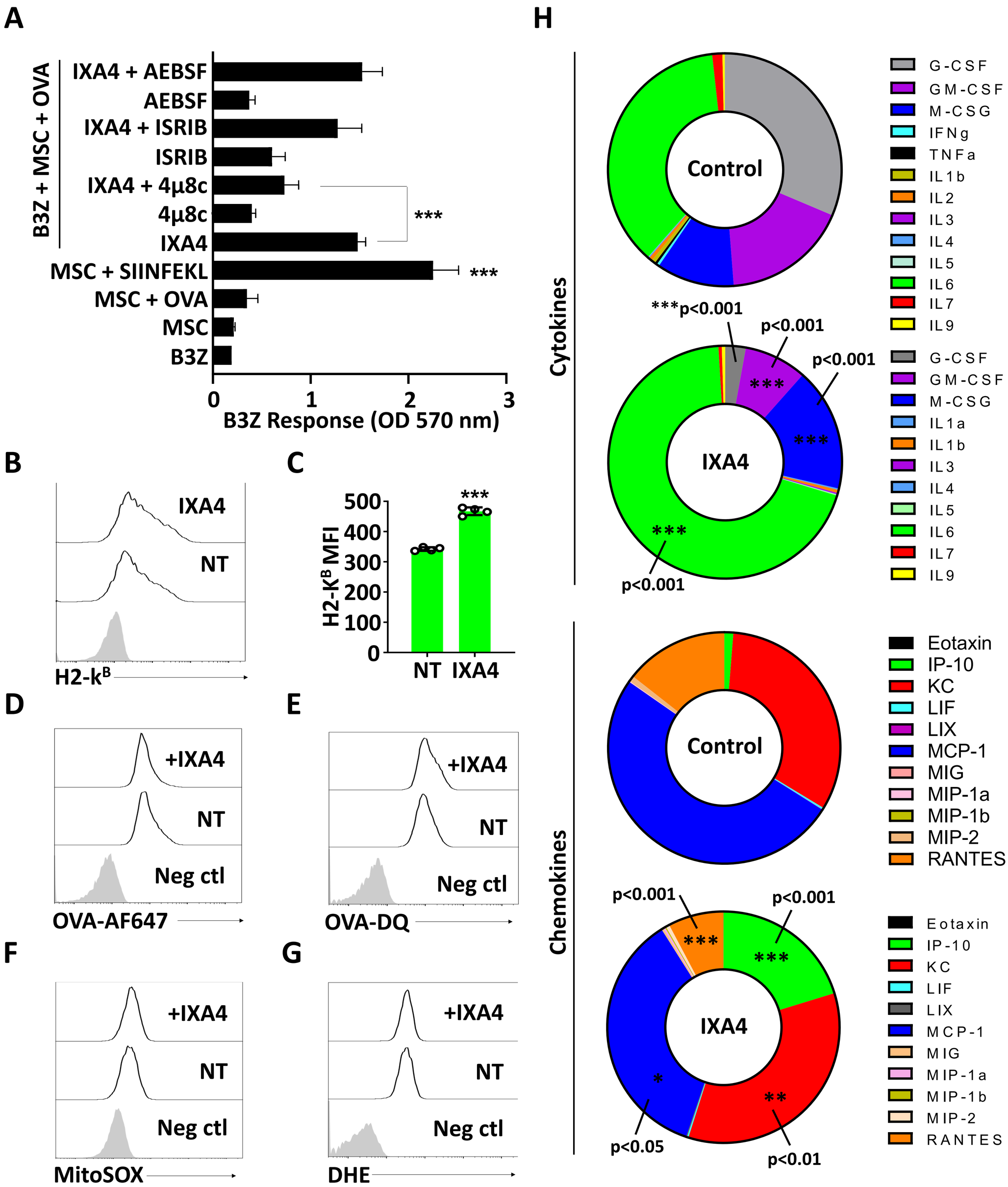
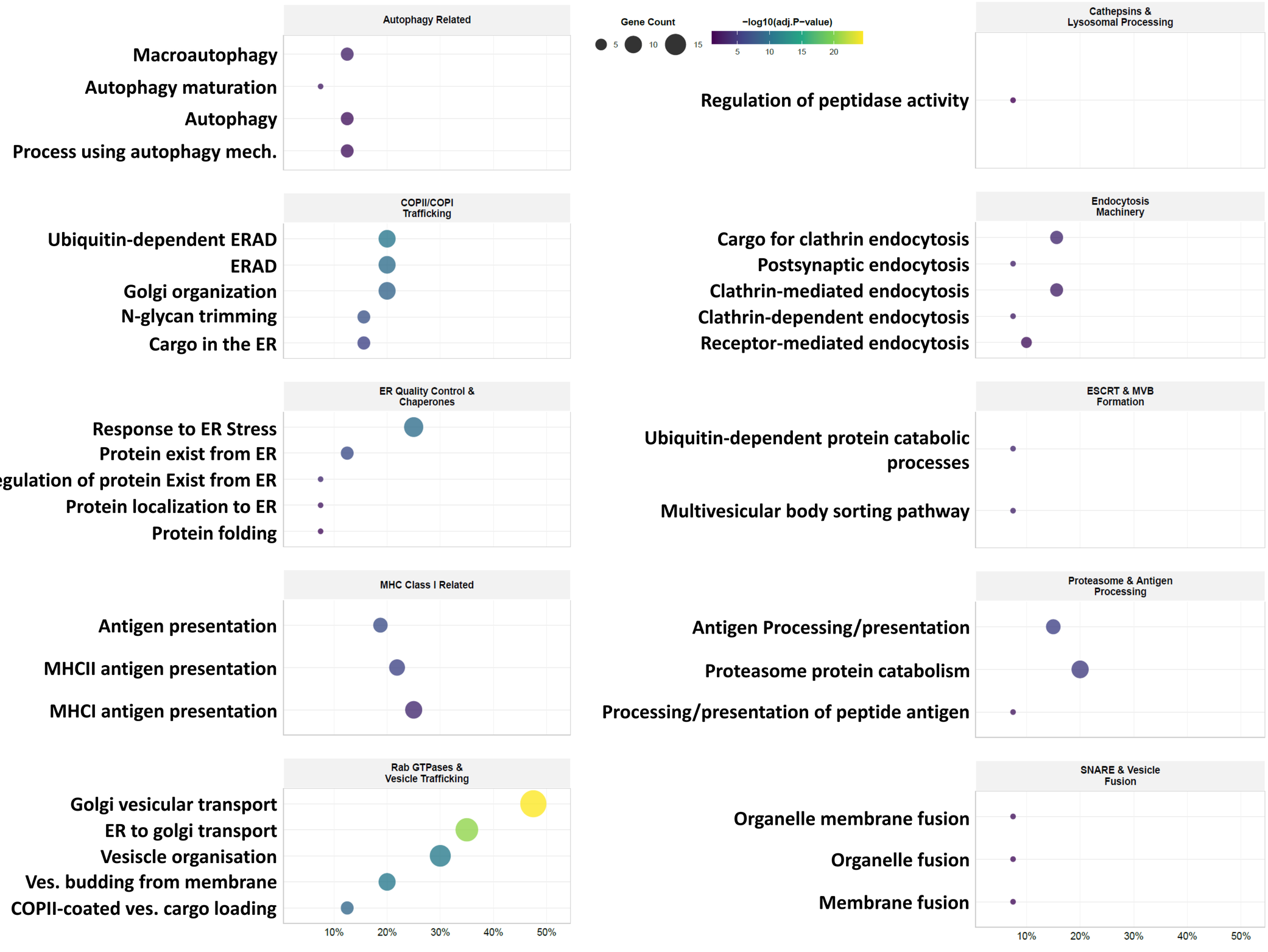
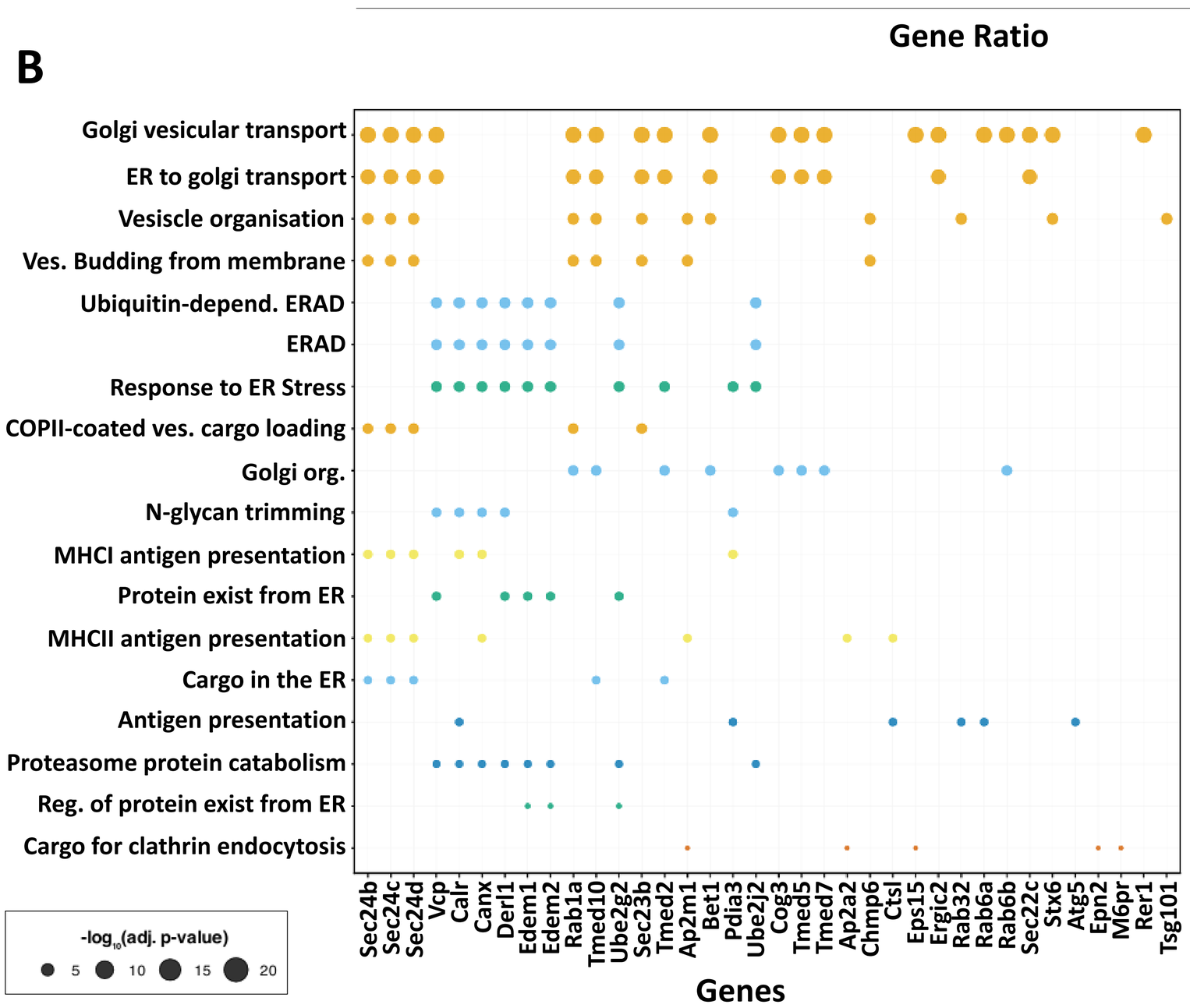

A
B3Z + MSC + OVA
IXA4 + AEBSF
AEBSF
IXA4 + ISRIB
ISRIB
IXA4 + 4μ8c
4μ8c
IXA4
MSC + SIINFEKL
MSC + OVA
MSC
B3Z
***
***
0
1
2
3
B3Z Response (OD 570 nm)
B
IXA4
NT
H2-k^B
C
***
500
400
300
200
100
0
H2-K^B MFI
NT
IXA4
D
+IXA4
NT
Neg ctl
OVA-AF647
E
+IXA4
NT
Neg ctl
OVA-DQ
F
+IXA4
NT
Neg ctl
MitoSOX
G
+IXA4
NT
Neg ctl
DHE
H
Cytokines
Control
***p<0.001
p<0.001
p<0.001
***
***
***
IXA4
p<0.001
G-CSF
GM-CSF
M-CSG
IFNg
TNFa
IL1b
IL2
IL3
IL4
IL5
IL6
IL7
IL9
G-CSF
GM-CSF
M-CSG
IL1a
IL1b
IL3
IL4
IL5
IL6
IL7
IL9
Chemokines
Control
IXA4
p<0.001
p<0.001
***
***
*
**
p<0.05
p<0.01
Eotaxin
IP-10
KC
LIF
LIX
MCP-1
MIG
MIP-1a
MIP-1b
MIP-2
RANTES
Eotaxin
IP-10
KC
LIF
LIX
MCP-1
MIG
MIP-1a
MIP-1b
MIP-2
RANTES

FIGURE 2

A


Autophagy Related
Macroautophagy
Autophagy maturation
Autophagy
Process using autophagy mech.
Gene Count
5
10
15
−log10(adj.P−value)
5
10
15
20
Cathepsins & Lysosomal Processing
Regulation of peptidase activity
COPII/COPI Trafficking
Ubiquitin-dependent ERAD
ERAD
Golgi organization
N-glycan trimming
Cargo in the ER
Endocytosis Machinery
Cargo for clathrin endocytosis
Postsynaptic endocytosis
Clathrin-mediated endocytosis
Clathrin-dependent endocytosis
Receptor-mediated endocytosis
ER Quality Control & Chaperones
Response to ER Stress
Protein exist from ER
Regulation of protein Exist from ER
Protein localization to ER
Protein folding
ESCRT & MVB Formation
Ubiquitin-dependent protein catabolic processes
Multivesicular body sorting pathway
MHC Class I Related
Antigen presentation
MHCII antigen presentation
MHCI antigen presentation
Proteasome & Antigen Processing
Antigen Processing/presentation
Proteasome protein catabolism
Processing/presentation of peptide antigen
Rab GTPases & Vesicle Trafficking
Golgi vesicular transport
ER to golgi transport
Vesiscle organisation
Ves. budding from membrane
COPII-coated ves. cargo loading
SNARE & Vesicle Fusion
Organelle membrane fusion
Organelle fusion
Membrane fusion
10%
20%
30%
40%
50%

B


Gene Ratio
Golgi vesicular transport
ER to golgi transport
Vesiscle organisation
Ves. Budding from membrane
Ubiquitin-depend. ERAD
ERAD
Response to ER Stress
COPII-coated ves. cargo loading
Golgi org.
N-glycan trimming
MHCI antigen presentation
Protein exist from ER
MHCII antigen presentation
Cargo in the ER
Antigen presentation
Proteasome protein catabolism
Reg. of protein exist from ER
Cargo for clathrin endocytosis
Sec24b
Sec24c
Sec24d
Vcp
Calr
Canx
Derl1
Edem1
Edem2
Rab1a
Tmed10
Ube2g2
Sec23b
Tmed2
Ap2m1
Bet1
Pdia3
Ube2j2
Cog3
Tmed5
Tmed7
Ap2a2
Chmp6
Ctsl
Eps15
Ergic2
Rab32
Rab6a
Rab6b
Sec22c
Stx6
Atg5
Epn2
M6pr
Rer1
Tsg101
Genes
-log10(adj. p-value)
5
10
15
20
COPII/COPI trafficking
ER quality control and chaperones
Proteasome and antigen processing
Endocytosis machinery
MHCI Related
Rab GTPase and vesicle trafficking

C

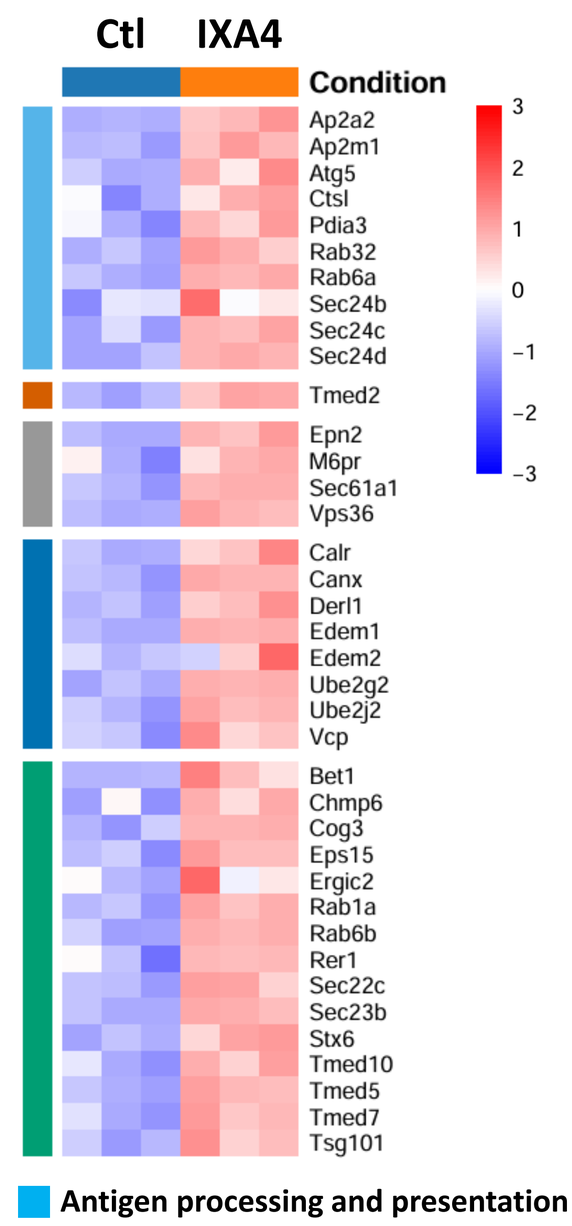
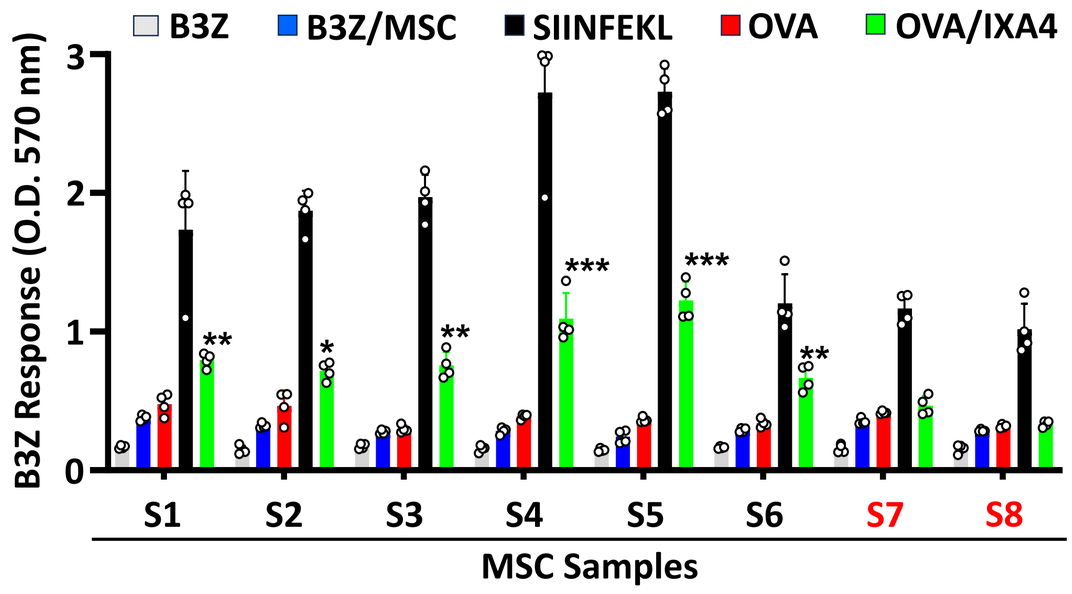

Ctl
IXA4
Condition
Ap2a2
Ap2m1
Atg5
Ctsl
Pdia3
Rab32
Rab6a
Sec24b
Sec24c
Sec24d
Tmed2
Epn2
M6pr
Sec61a1
Vps36
Calr
Canx
Derl1
Edem1
Edem2
Ube2g2
Ube2j2
Vcp
Bet1
Chmp6
Cog3
Eps15
Ergic2
Rab1a
Rab6b
Rer1
Sec22c
Sec23b
Stx6
Tmed10
Tmed5
Tmed7
Tsg101
3
2
1
0
−1
−2
−3
Antigen processing and presentation
ER stress
Protein transport
Protein degradation
Vesicle transport and organization

FIGURE 3

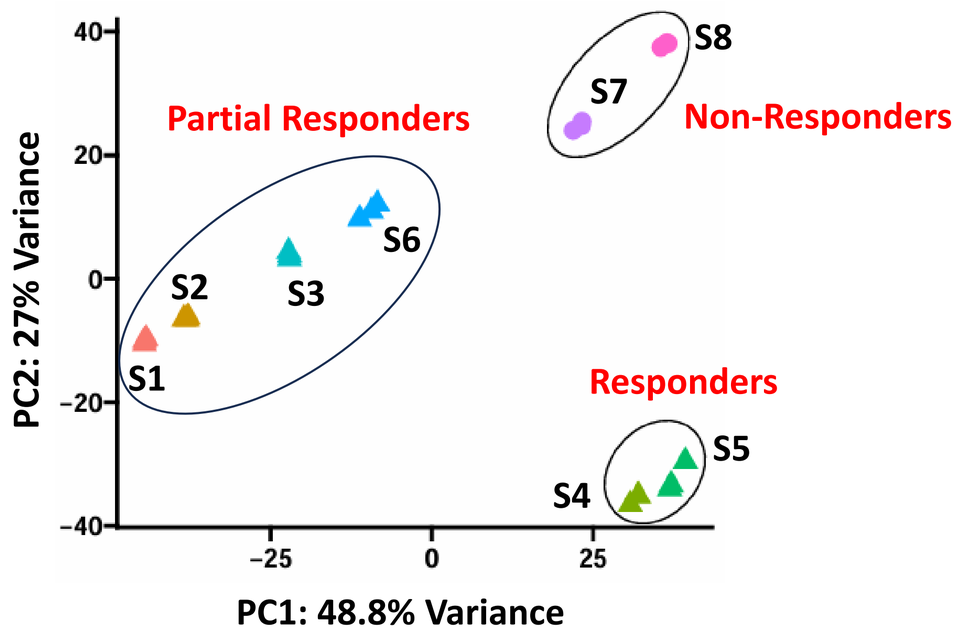
A
C57BL/6
Mice
5 x 10^5 B16F0
Melanoma (SC)
5 x 10^5
IRM-4 cells
(SC)
Anti-PD-1
(200 ug/dose IP)
Survival
B
Females
0.05mg/ml
Tumor volume (mm^3)
Timeline (Days)
C
Probability of Survival
Timeline (Days)
**
*
D
Females
0.5mg/ml
Tumor volume (mm^3)
Timeline (Days)
E
Probability of Survival
Timeline (Days)
***
*
F
Males
0.5mg/ml
Tumor volume (mm^3)
Timeline (Days)
G
Probability of Survival
Timeline (Days)
**
**

FIGURE 4

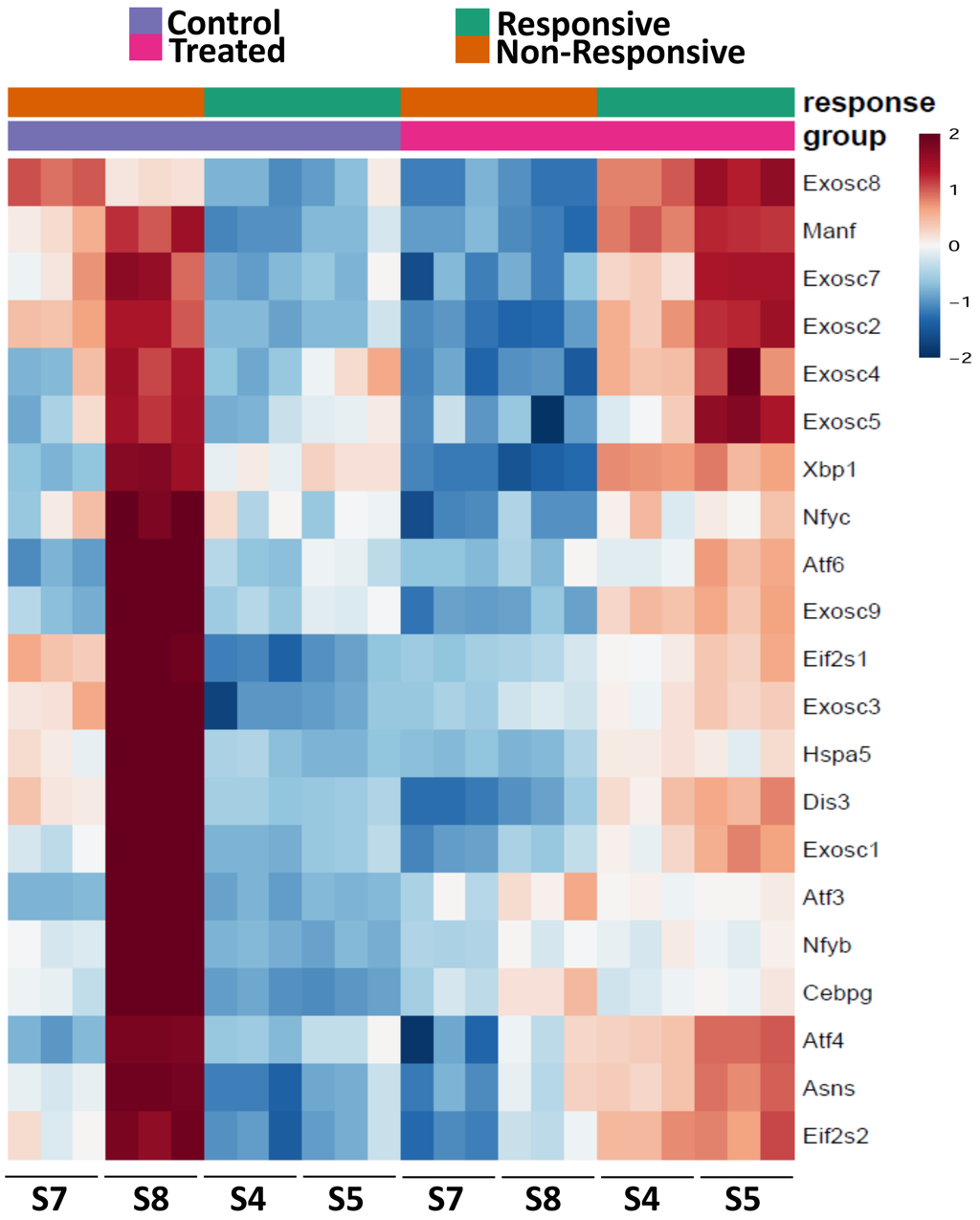
A



B



D



C

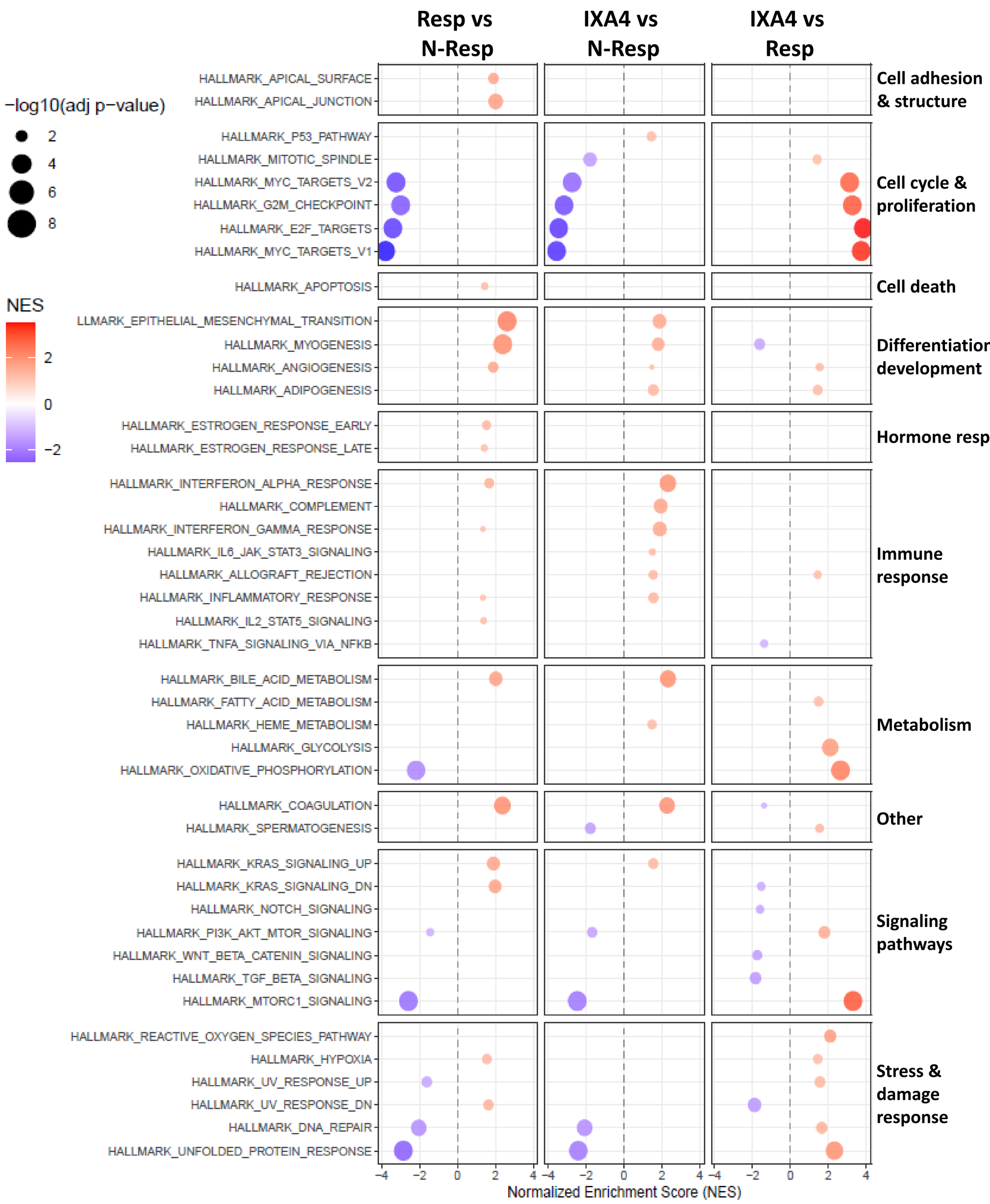


FIGURE 5

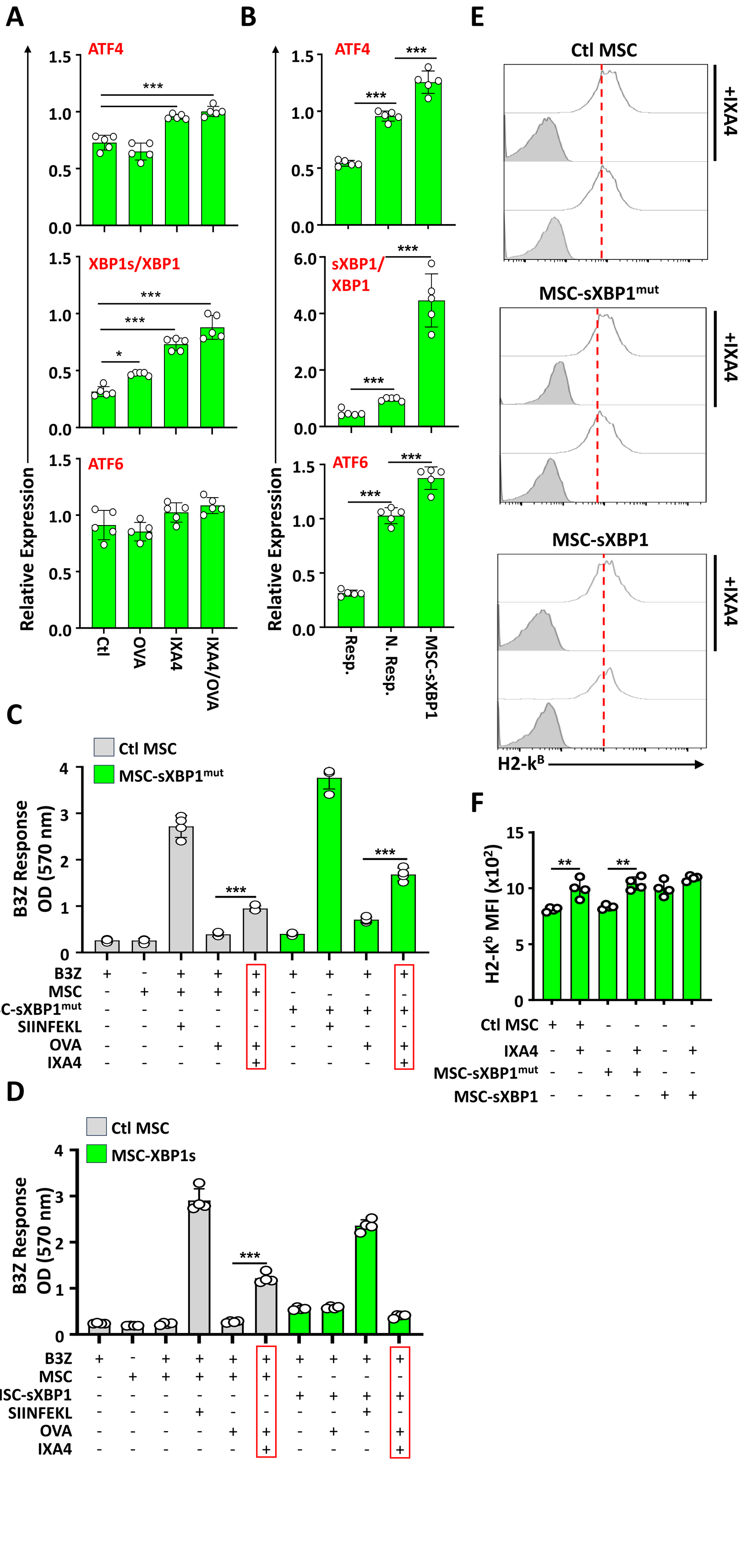

A
ATF4
XBP1s/XBP1
ATF6
Relative Expression
Ctl
OVA
IXA4
IXA4/OVA
B
ATF4
sXBP1/ XBP1
ATF6
Resp.
N. Resp.
MSC-sXBP1
E
Ctl MSC
+IXA4
MSC-sXBP1mut
MSC-sXBP1
H2-kB
C
Ctl MSC
MSC-sXBP1mut
B3Z Response OD (570 nm)
B3Z
MSC
MSC-sXBP1mut
SIINFEKL
OVA
IXA4
F
H2-Kb MFI (x10²)
Ctl MSC
IXA4
MSC-sXBP1mut
MSC-sXBP1
D
Ctl MSC
MSC-XBP1s
B3Z Response OD (570 nm)
B3Z
MSC
MSC-sXBP1
SIINFEKL
OVA
IXA4

FIGURE 6

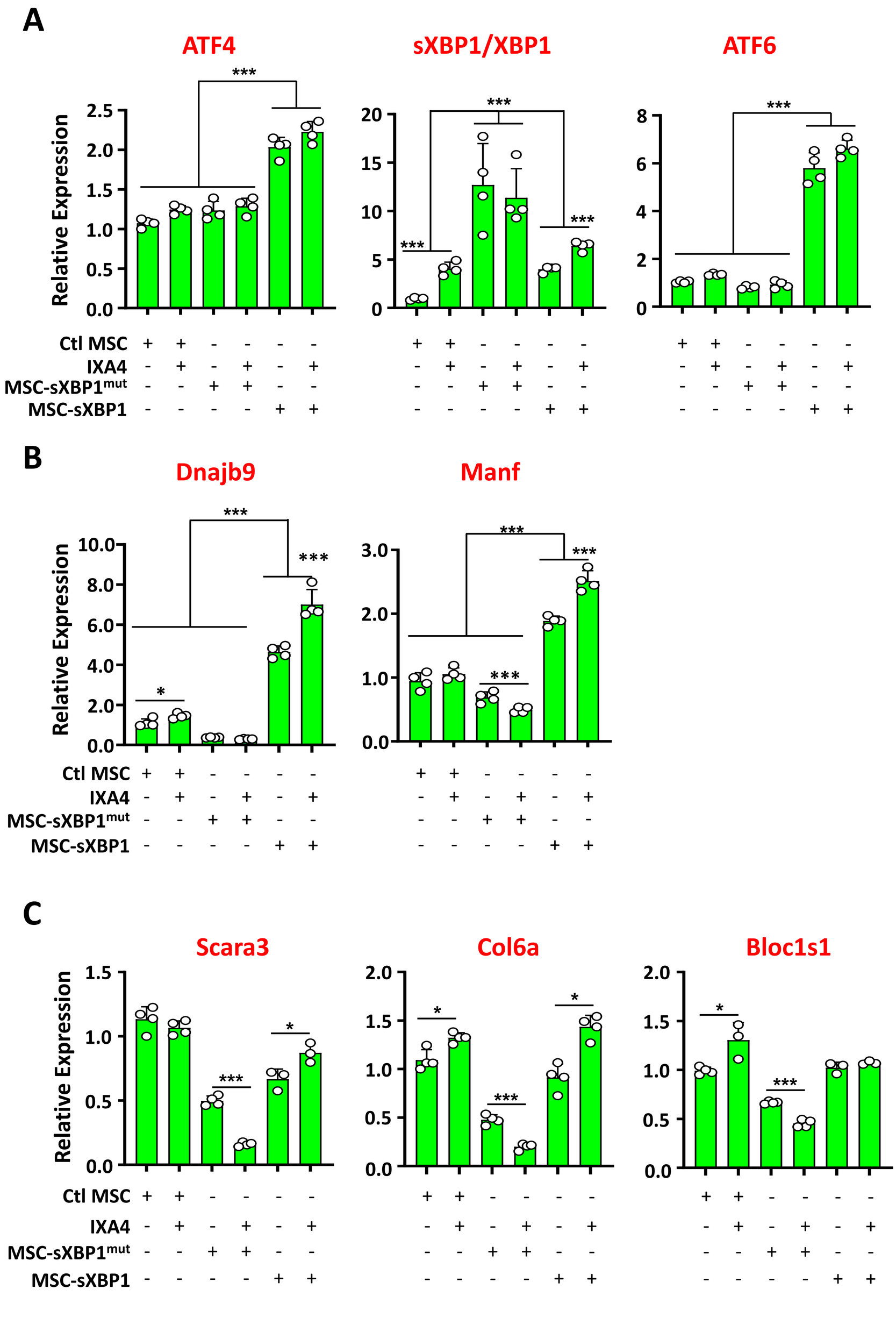
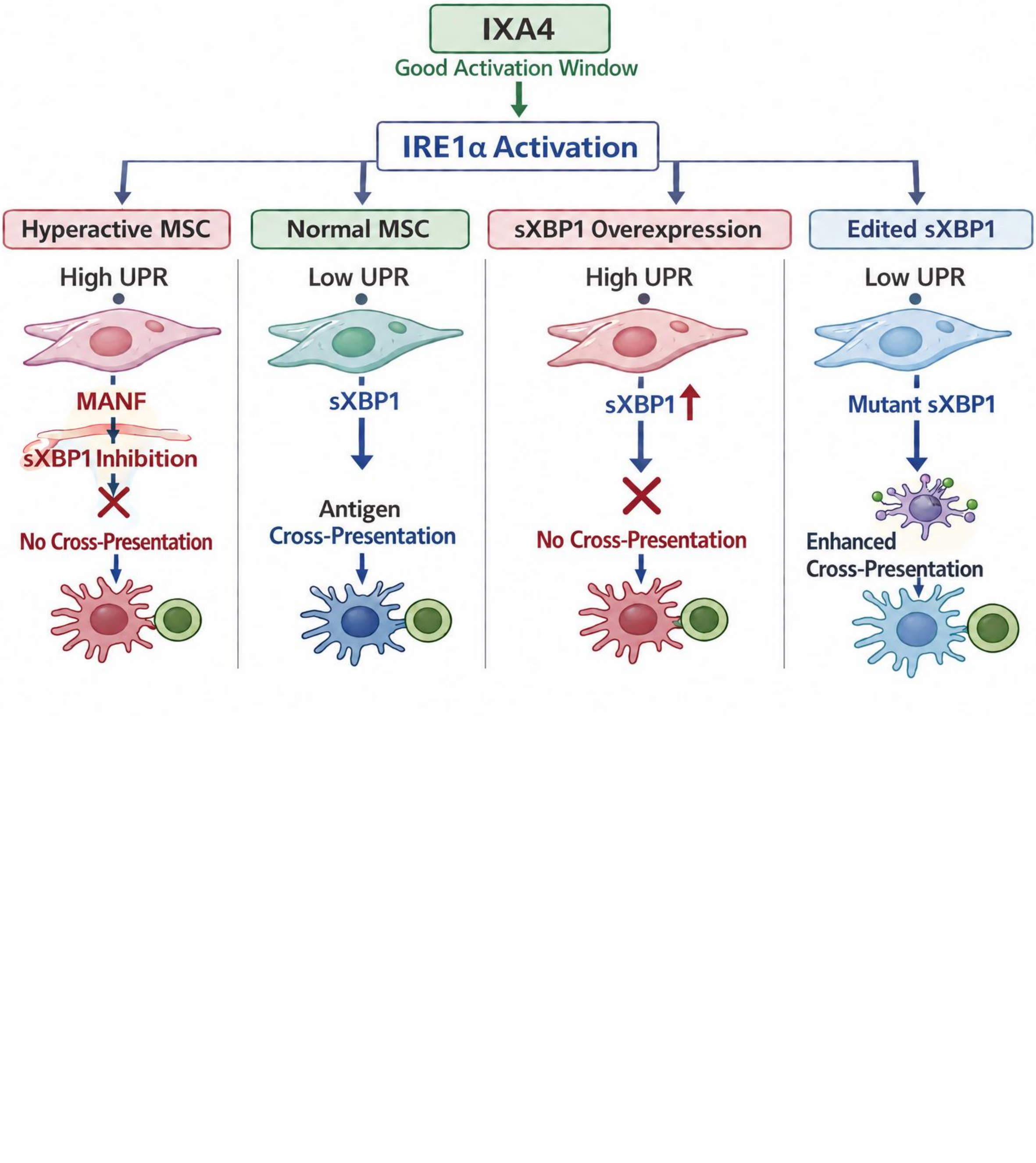

A
ATF4
sXBP1/XBP1
ATF6
Relative Expression
***
Ctl MSC
IXA4
MSC-sXBP1mut
MSC-sXBP1
B
Dnajb9
Manf
*
C
Scara3
Col6a
Bloc1s1

FIGURE 7


IXA4
Good Activation Window
IRE1α Activation
Hyperactive MSC
Normal MSC
sXBP1 Overexpression
Edited sXBP1
High UPR
Low UPR
High UPR
Low UPR
MANF
sXBP1 Inhibition
No Cross-Presentation
sXBP1
Antigen
Cross-Presentation
sXBP1
No Cross-Presentation
Mutant sXBP1
Enhanced
Cross-Presentation