

SREBP-2 Responsive miR Operon Regulates Lipid Metabolism

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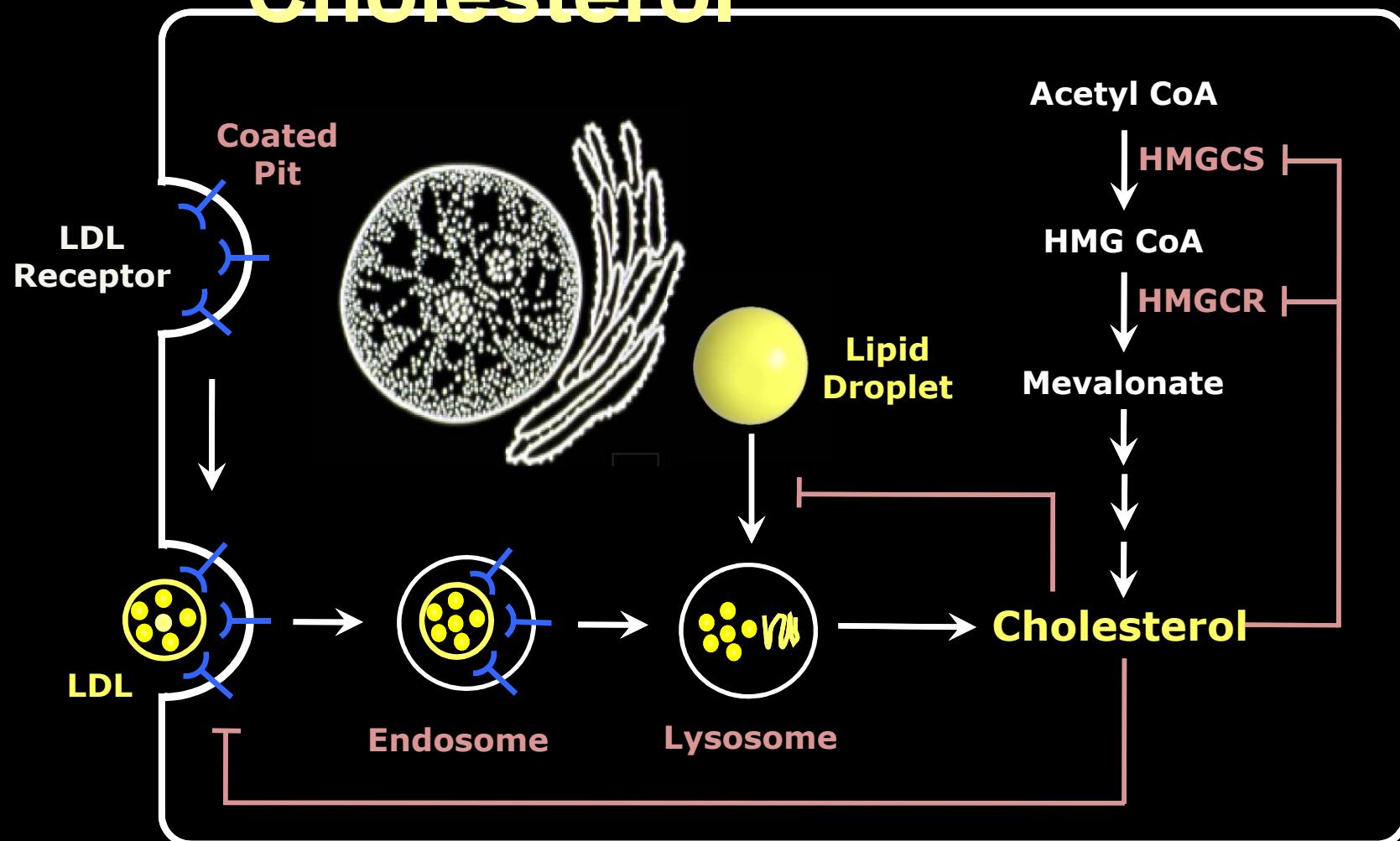
Cholesterol

The image features a detailed pencil sketch of the Vitruvian Man by Leonardo da Vinci, showing a man in a square frame with his arms and legs extended. A chemical structure of cholesterol is overlaid on his torso, with its hydroxyl group (HO) pointing towards his head.

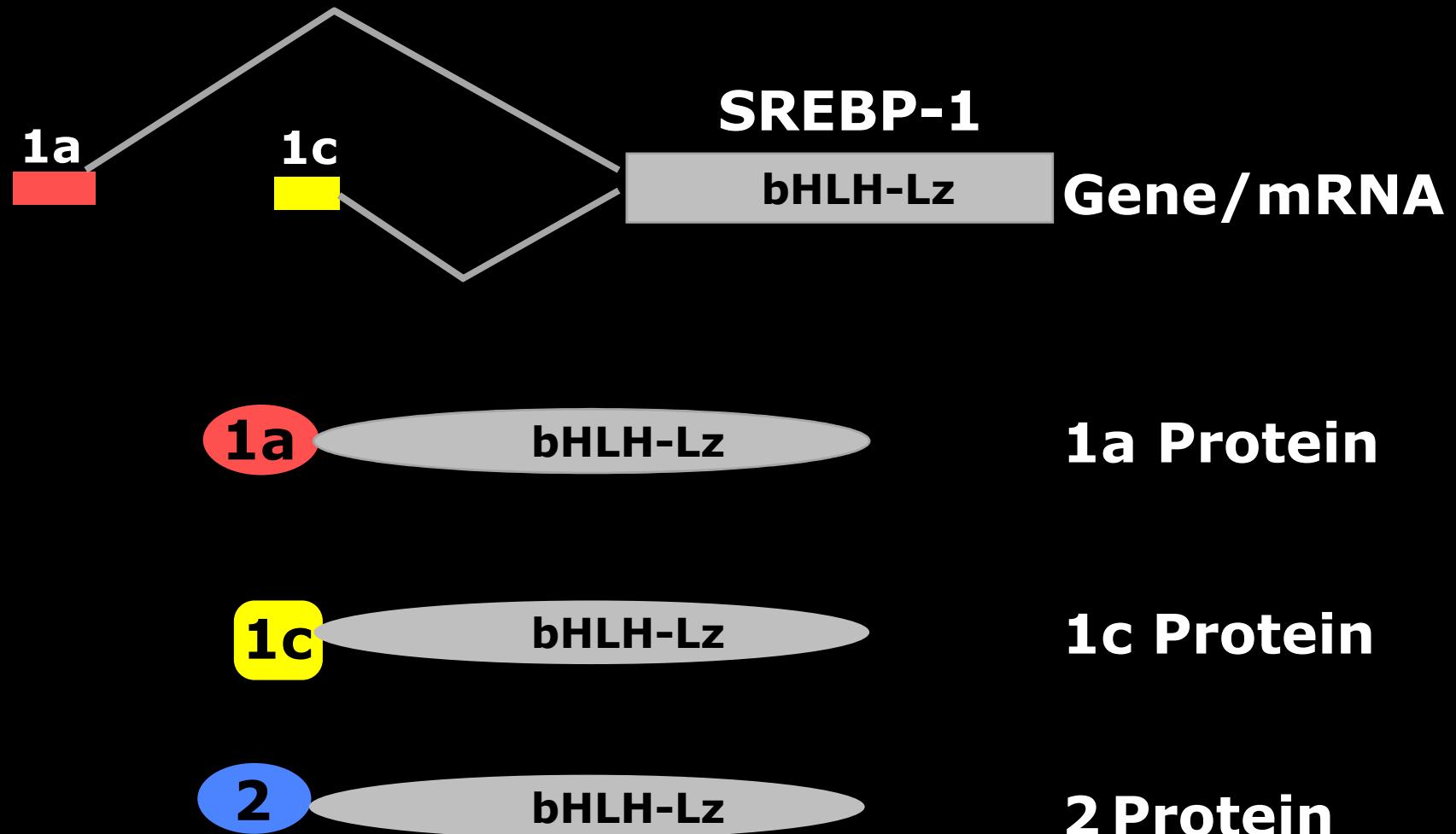
- Myelin – Brain
- Surfactant – Lung
- Lipoprotein & Bile acids – Liver
- Steroid hormone – Adrenal
- Barrier – Skin
- Vitamin D – Bone
- Sex hormone – Gonads
- Storage – Fat

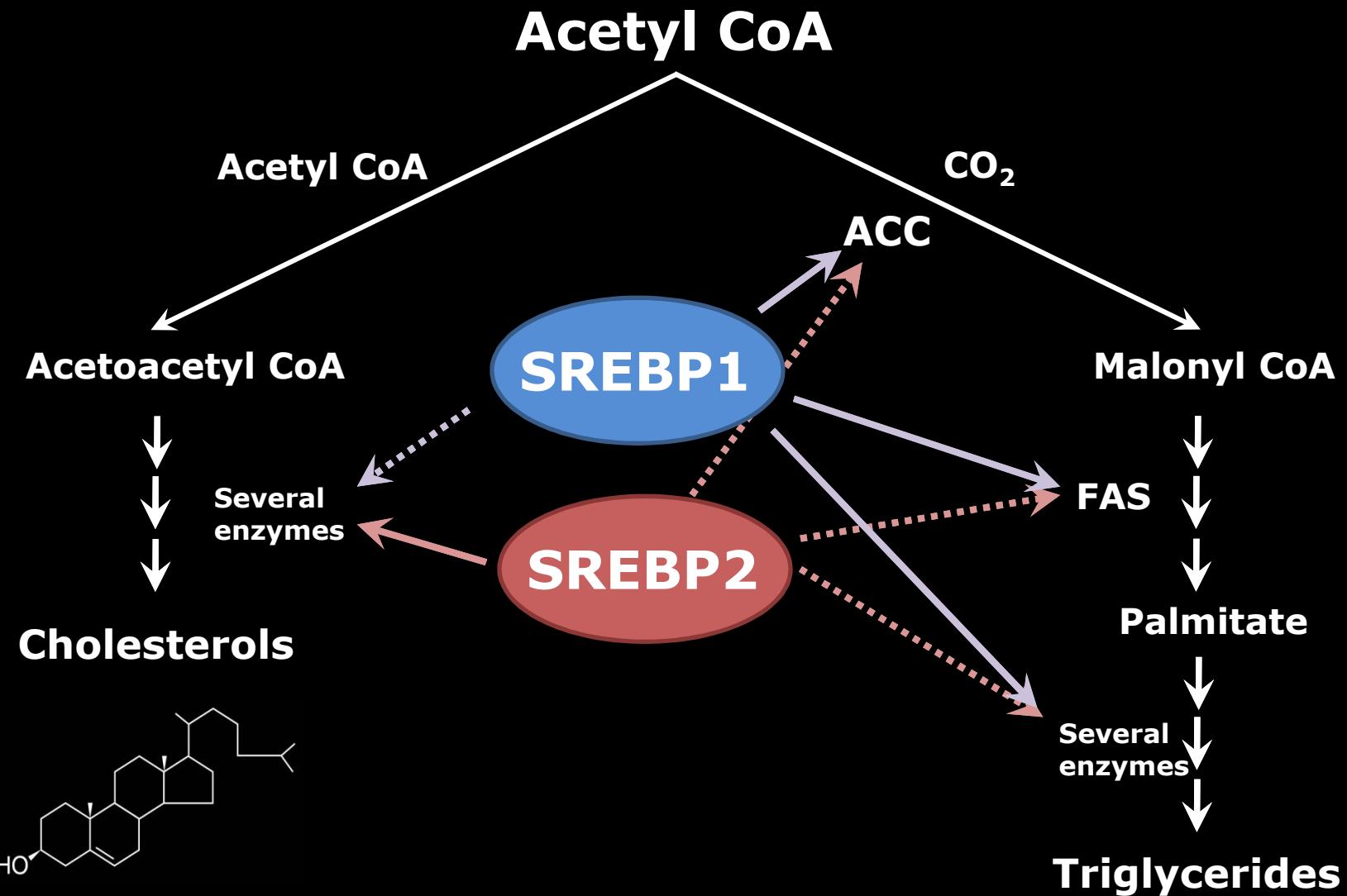
All Cell Membranes

Three Sources of Cholesterol

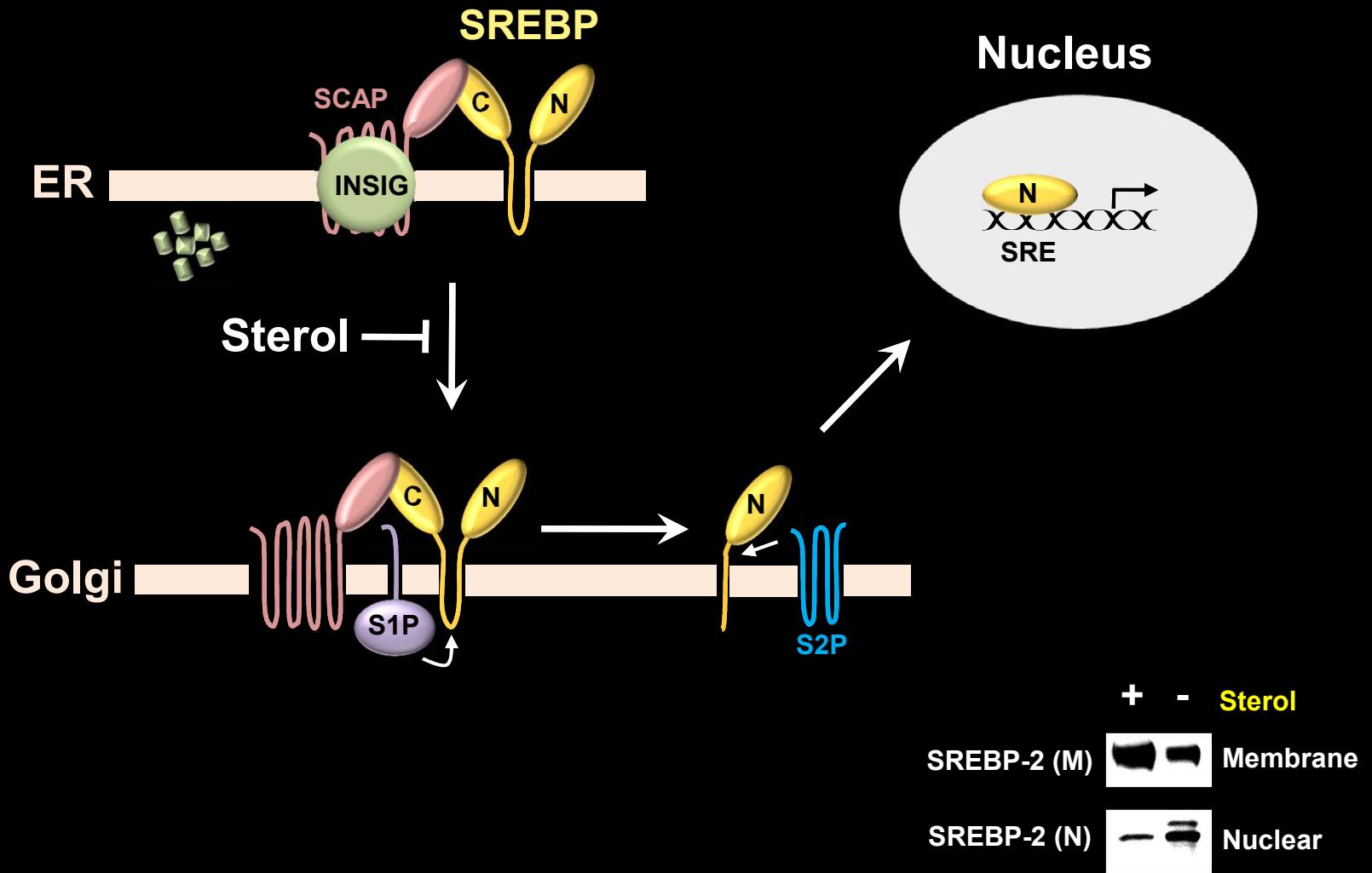


Sterol Regulatory Element Binding Proteins (SREBPs)

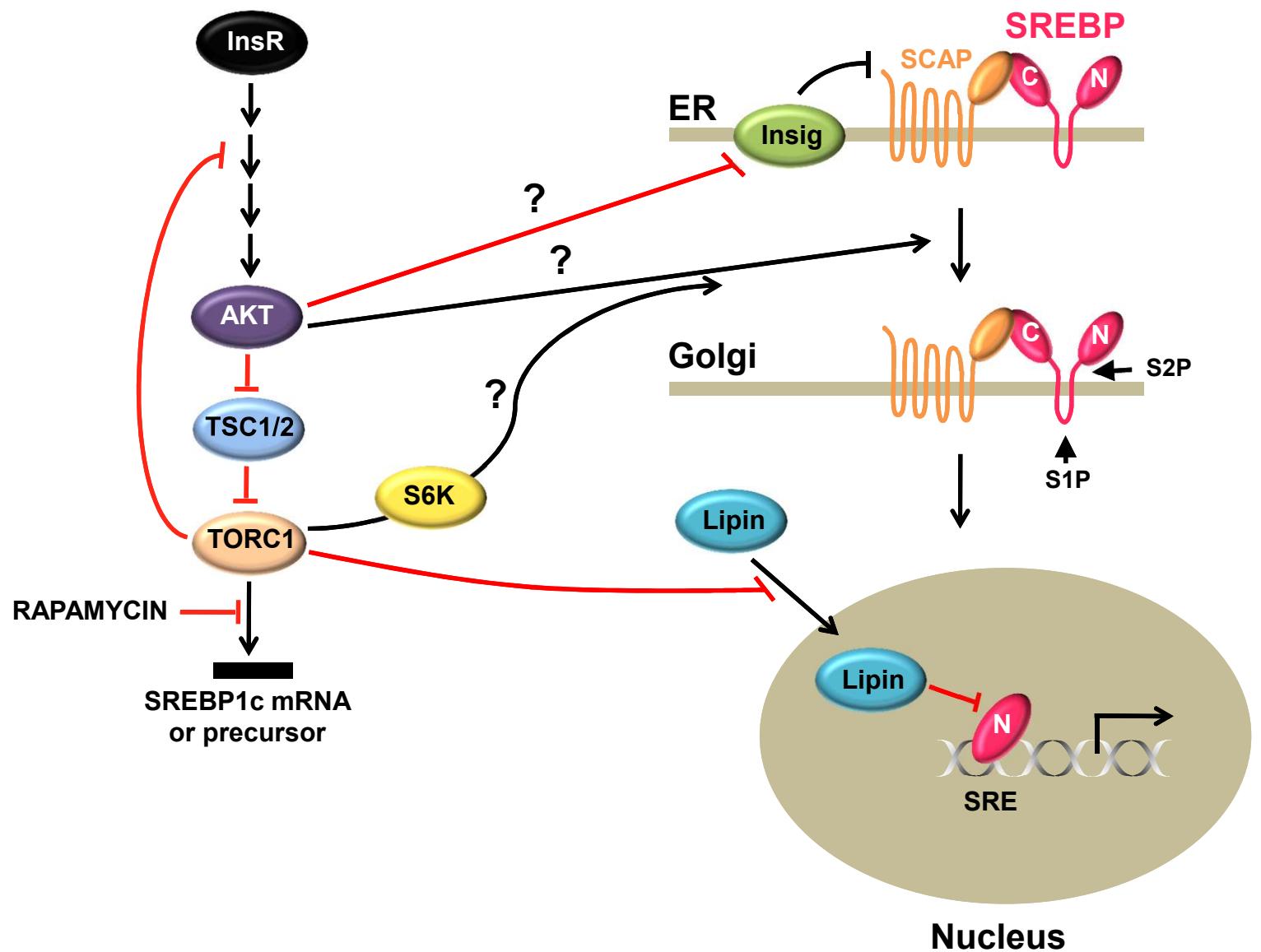




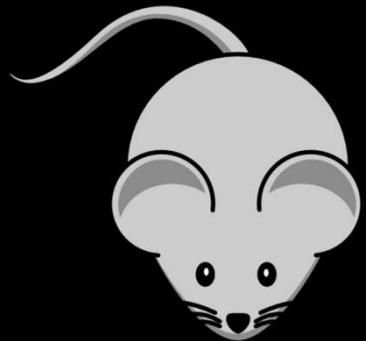
SREBPs Processing



SREBPs Maturation



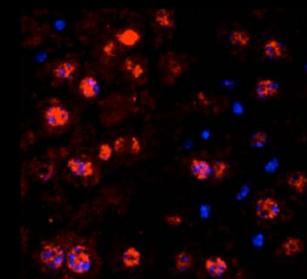
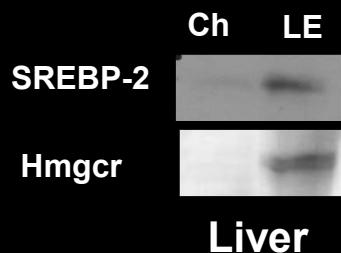
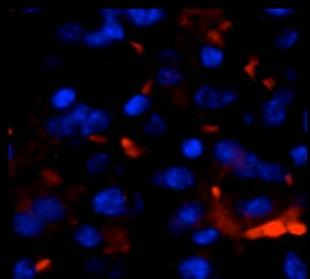
Normal chow diet
+
1% Cholesterol (Ch)



Normal chow diet
+
Lovastatin/Ezetimibe (LE)

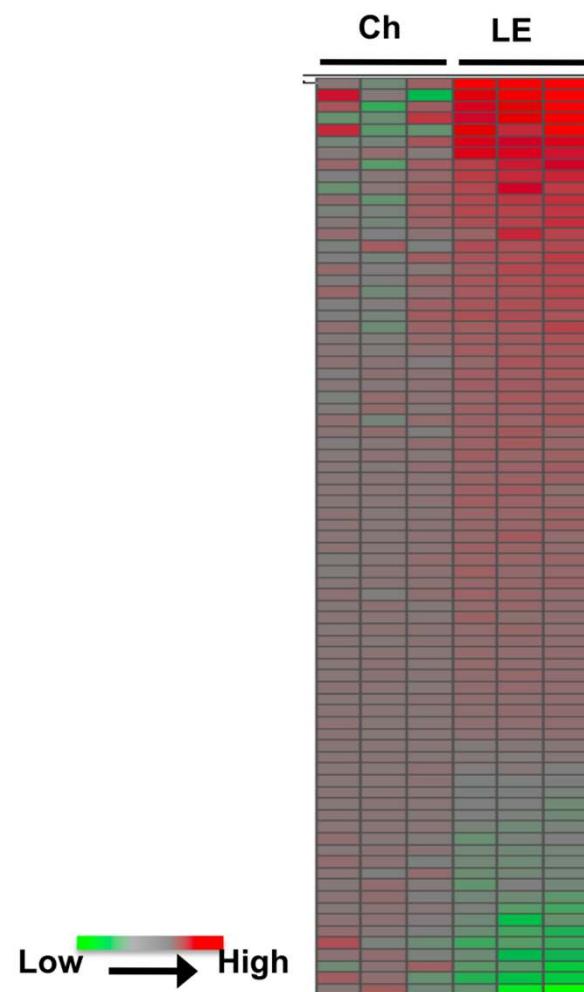


Lovastatin inhibits cholesterol synthesis
Ezetimibe inhibits cholesterol uptake
SREBP-2 and target genes ↑

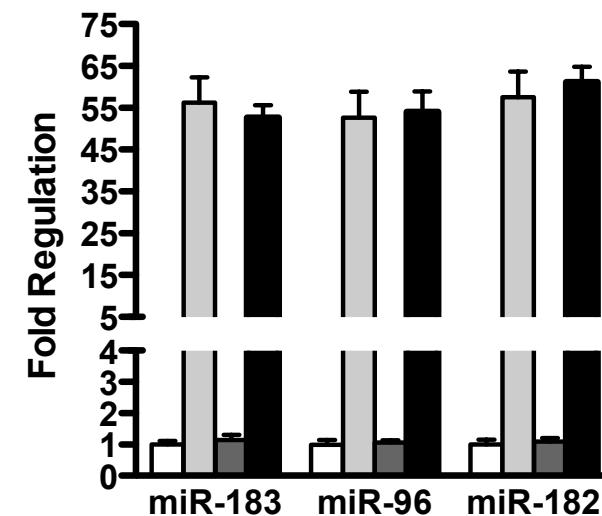
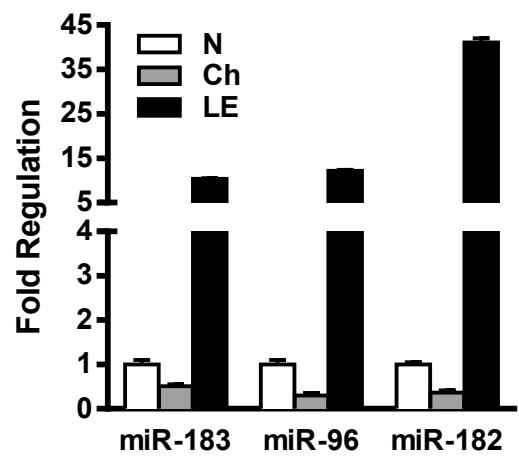


miRNA profiles LE vs Ch

| miRNA | Fold change |
|--------------------|-------------|
| mmu-miR-182 | 81.6 |
| mmu-miR-470* | 28.3 |
| mmu-miR-34b-3p | 17.7 |
| mmu-miR-741 | 12.5 |
| mmu-miR-877 | 7.2 |
| mmu-miR-20b | 6.2 |
| mmu-miR-297a* | 5.7 |
| mmu-miR-19a | 4.3 |
| mmu-miR-875-5p | 3.6 |
| mmu-miR-33* | 3.2 |
| mmu-miR-188-5p | 3.2 |
| mmu-miR-467a* | 3.0 |
| mmu-miR-195 | 2.9 |
| mmu-miR-877* | 2.9 |
| mmu-miR-126-5p | 2.8 |
| mmu-miR-130b | 2.7 |
| mmu-miR-101a | 2.3 |
| mmu-miR-339-3p | 2.1 |
| mmu-miR-301b | 2.1 |
| mmu-miR-331-3p | 2.1 |
| mmu-miR-135a* | 2.1 |
| mmu-miR-185 | 2.1 |
| mmu-miR-676 | .50 |
| mmu-miR-15a | .28 |
| mmu-miR-339-5p | .26 |
| mmu-miR-425 | .23 |
| mmu-miR-221 | .20 |
| mmu-miR-215 | .19 |
| mmu-miR-210 | .10 |
| mmu-miR-455 | .04 |



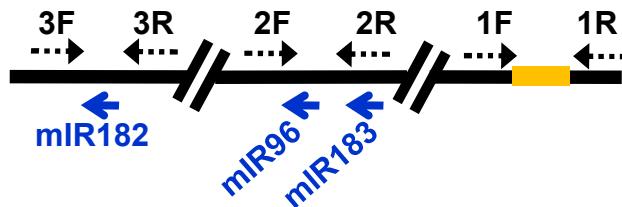
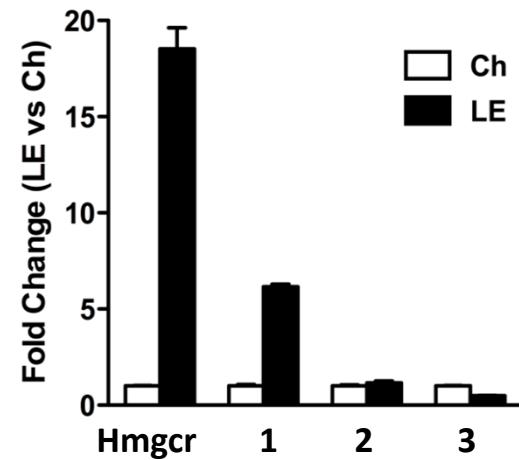
miR-182-96-183 cluster



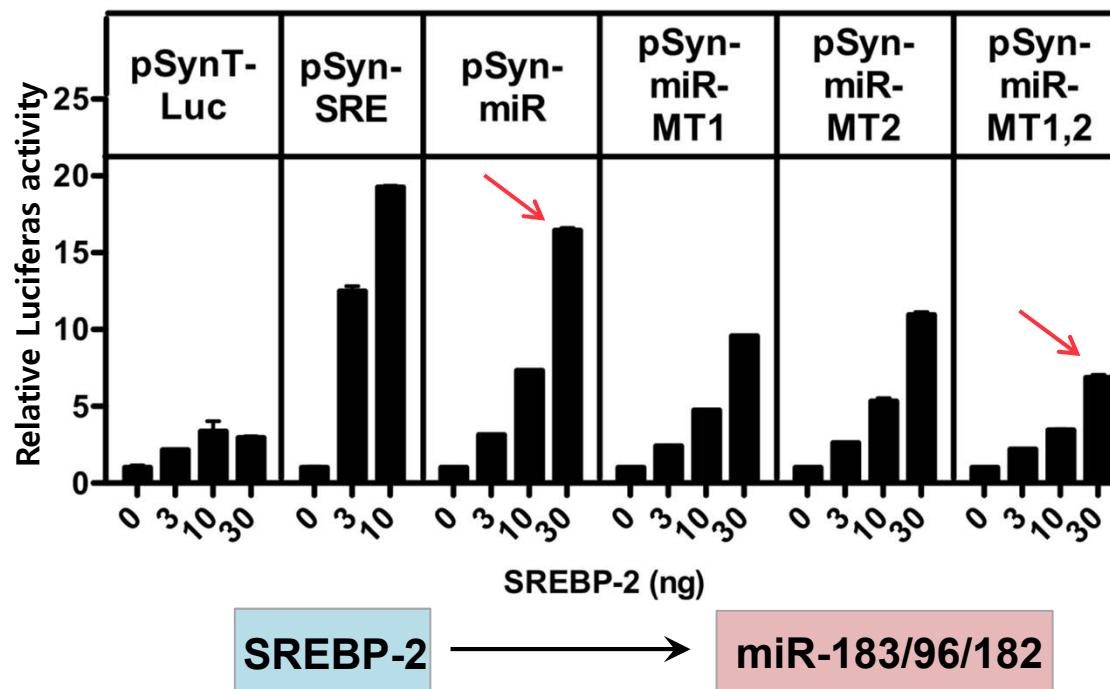
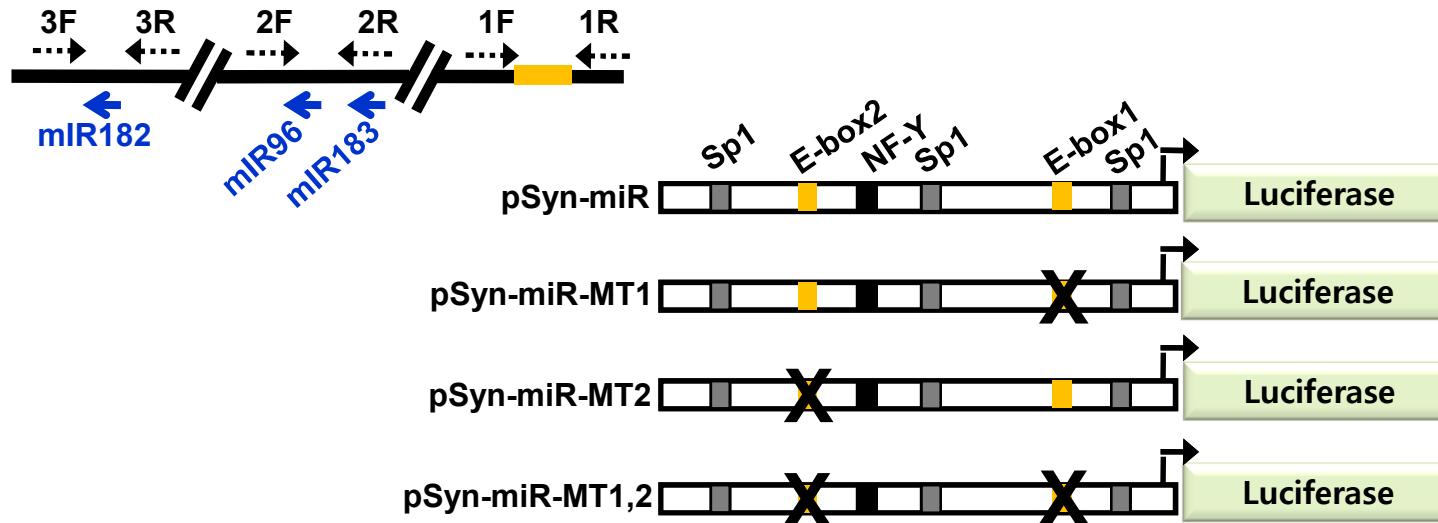
Legend:

- WT
- Tg-SREBP-1a
- Tg-SREBP-1c
- Tg-SREBP-2

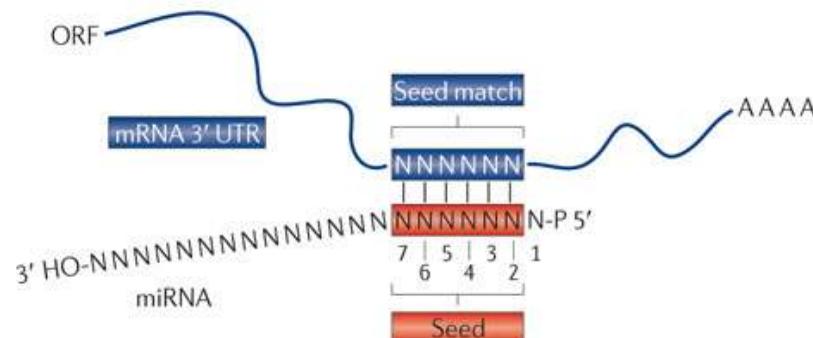
SREBP-2 regulatory region



Promoter region of miR-182-96-183 cluster



miRNA target prediction



A. 1st binding site of miR-182 in fbxw7 3'UTR

| | | | | | |
|-------------|--------------------|---------------------|------------------|----|-----|
| miR-182 | 3' CACACUCAAGAUGGU | AACGGUUU | 5' | | |
| | | | | | |
| Fbxw7 3'UTR | | | | | |
| Mouse | 573 | 5' UUUUCUUUUUUUUUUU | UUGCCAA C | 3' | 595 |
| Human | | UUUUUUUUUUUUUUUU | UUGCCAA C | | |
| Chimpanzee | | UUUUUUUUUUUUUUUU | UUGCCAA C | | |
| Rat | | UUUUUUUUUUUUUUUU | UUGCCAA C | | |

B. 2nd binding site of miR-182 in fbxw7 3'UTR

| | | | | | |
|-------------|--------------------|---------------------|-----------------|----|-----|
| miR-182 | 3' CACACUCAAGAUGGU | AACGGUUU | 5' | | |
| | | | | | |
| Fbxw7 3'UTR | | | | | |
| Mouse | 583 | 5' UUUUUUUUGCCAACCA | UUGCCAAU | 3' | 605 |
| Human | | UUUUUUUGCCAACCA | UUGCCAAU | | |
| Chimpanzee | | UUUUUUUGCCAACCA | UUGCCAAU | | |
| Rat | | UUUUUUUGCCAACCA | UUGCCAAU | | |

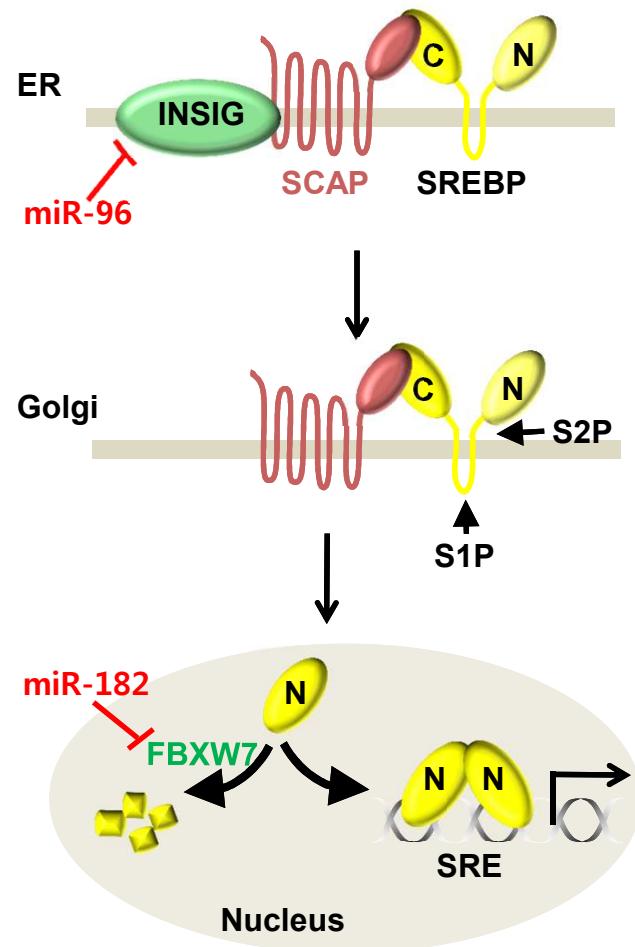
C. Binding site of miR-96 in Insig-2 3'UTR

| | | | | | |
|---------------|-----------------|-----------------|------------------|----|-----|
| miR-96 | 3' UUUUUACACGAU | CACGGUUU | 5' | | |
| | | | | | |
| Insig-2 3'UTR | | | | | |
| Mouse | 280 | 5' CACAAUGUCAAU | GUGCCAAA | 3' | 302 |
| Human | | CACAAUGUUAAU | GUGCCAA G | | |
| Chimpanzee | | CACAAUGUUAAU | GUGCCAA G | | |
| Rat | | CACAAUGUUGAU | GUGCCAAA | | |

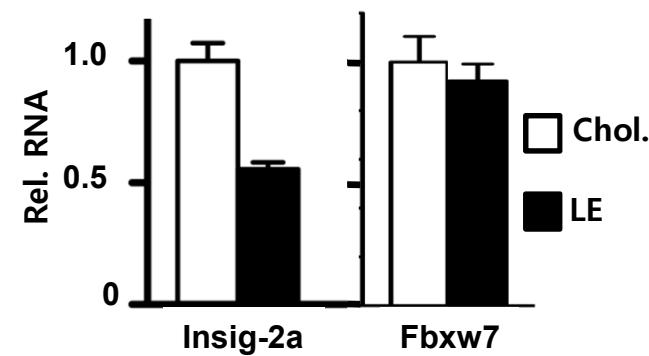
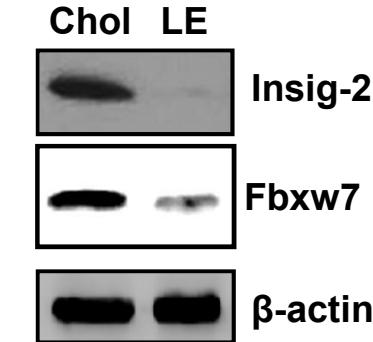
FBXW7

INSIG2

SREBP processing



Insig-2
Fbxw7 → SREBPs



A. 1st binding site of miR-182 in fbxw7 3'UTR

miR-182 3' CACACUCAAGAUGGU **AACGGUU** U 5'
 Fbxw7 3'UTR
 Mouse 573 5' UUUUCUUUUUUUUUUU **UUGCCAA** C 3' 595
 Human
 Chimpanzee
 Rat UUUUUUUUUUUUUUUUU **UUGCCAA** C

B. 2nd binding site of miR-182 in fbxw7 3'UTR

miR-182 3' CACACUCAAGAUGGU **AACGGUU** U 5'
 Fbxw7 3'UTR
 Mouse 583 5' UUUUUUUUGCCAACCA **UUGCCAA** U 3' 605
 Human
 Chimpanzee
 Rat UUUUUUUUGCCAACCA **UUGCCAA** U

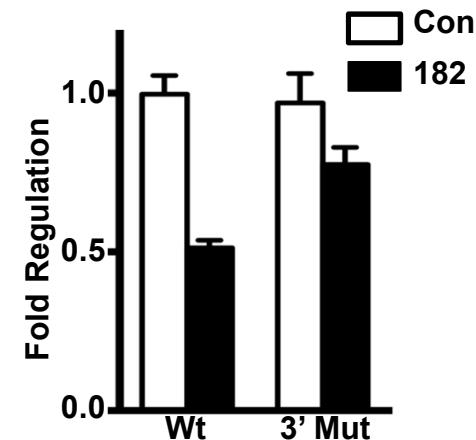
C. Binding site of miR-96 in Insig-2 3'UTR

miR-96 3' UUUUUACACGAU **CACGGUUU** 5'
 Insig-2 3'UTR
 Mouse 280 5' CACAAUGUCAAU **GUGCCAA** 3' 302
 Human
 Chimpanzee
 Rat CACAAUGUUAAU **GUGCCAA**
 CACAAUGUUGAU **GUGCCAA**

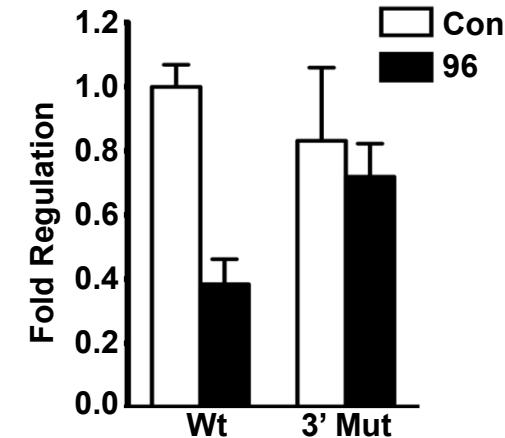
miR-183/96/182

Insig-2
Fbxw7

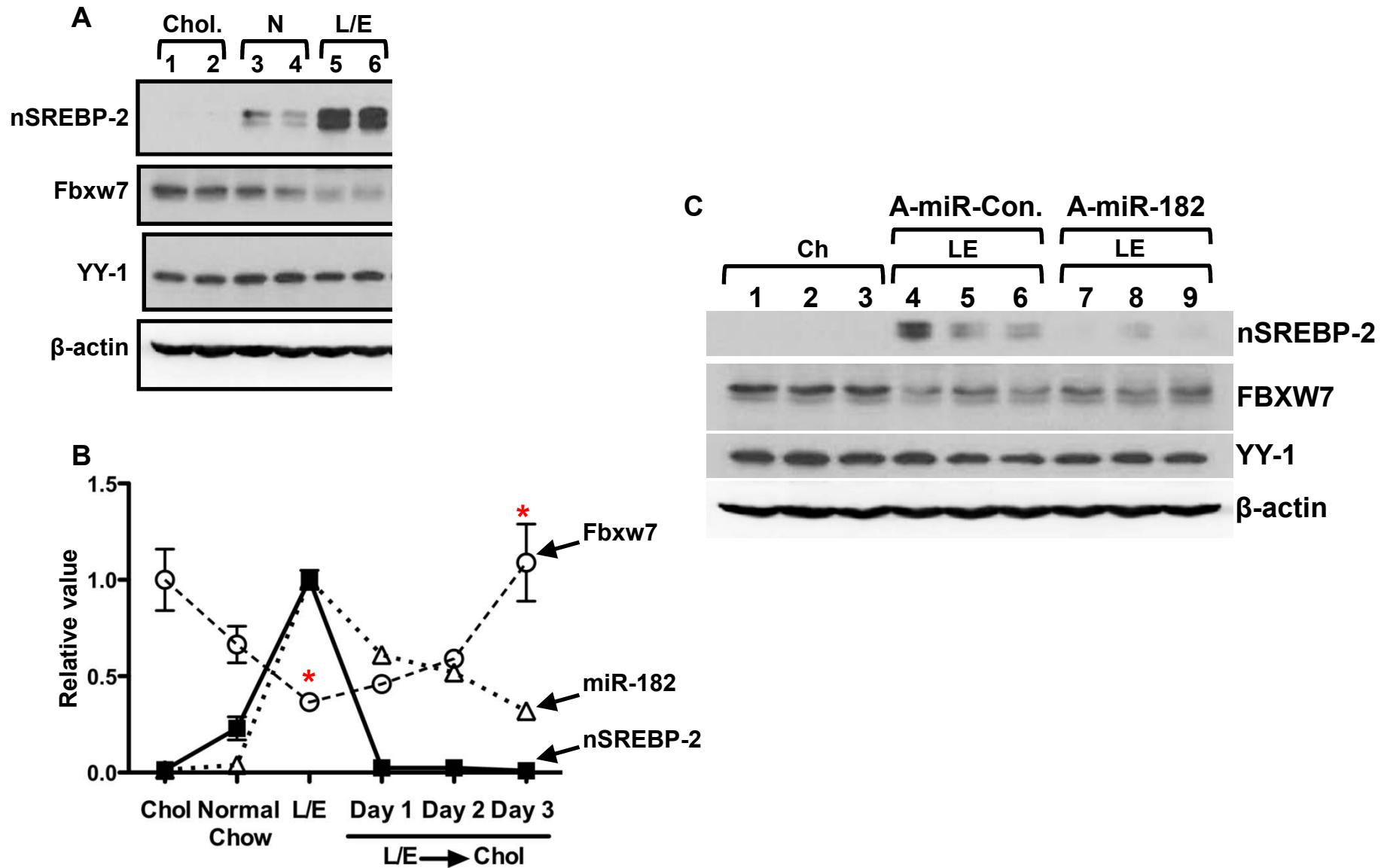
A FBXW7 3'UTR



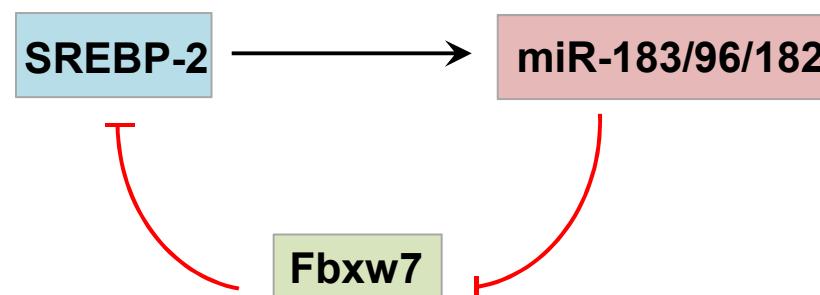
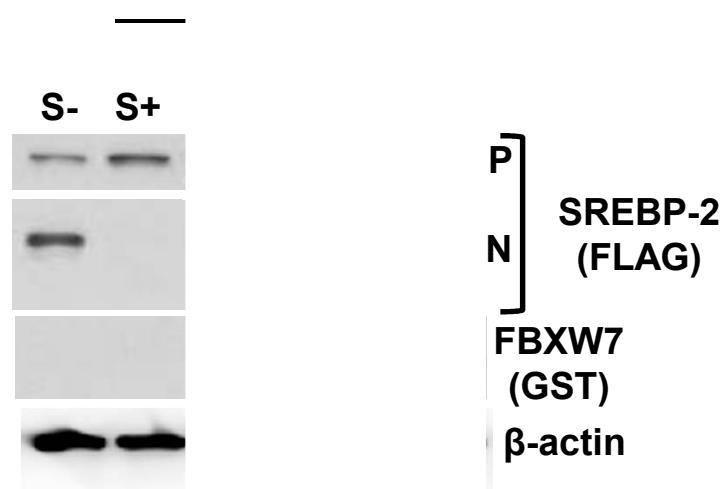
B INSIG-2 3'UTR



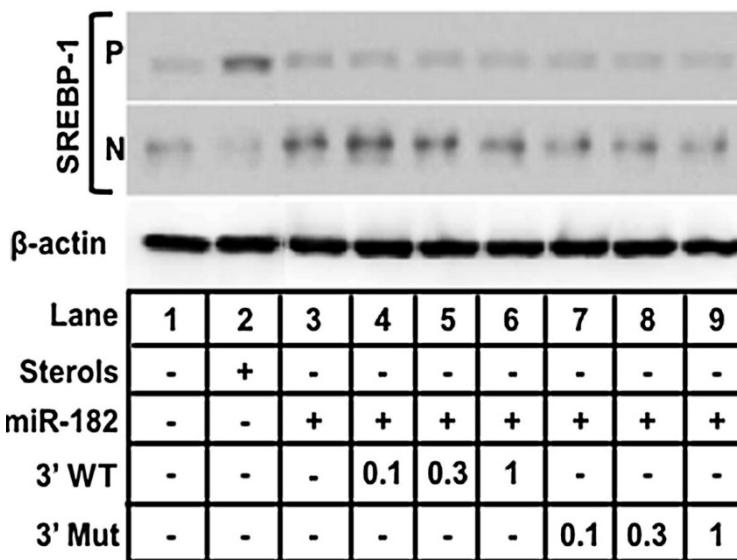
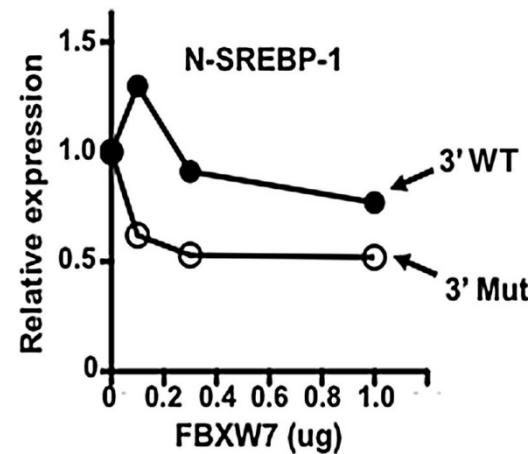
Coordinate and reciprocal regulation of nSREBP-2 with miR-182 or Fbxw7



FBXW7 overexpression rescues nSREBP-2 accumulation by miR-182



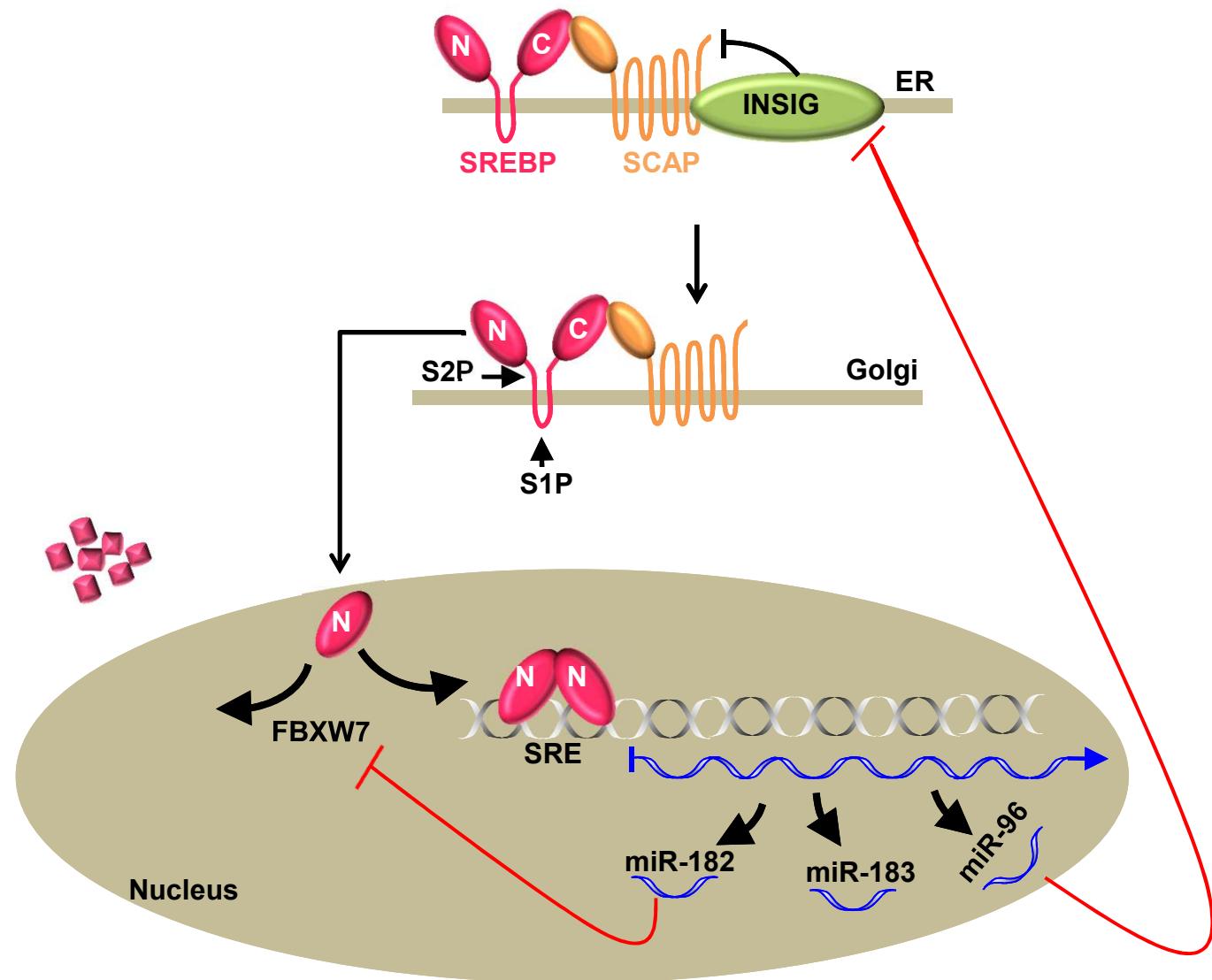
Effect of ectopic *FBXW7* on nSREBPs is sensitive to miR-182-binding sites in the *FBXW7* 3'UTR



miR regulation of SREBP levels induces lipid biosynthesis



An SREBP-2 regulated miR operon regulates lipid metabolism



ACKNOWLEDGEMENTS



Functional Genomics Core facility (SBMRI)

Christine C. Esau (Regulus Therapeutics)



Sanford | Burnham
Medical Research Institute