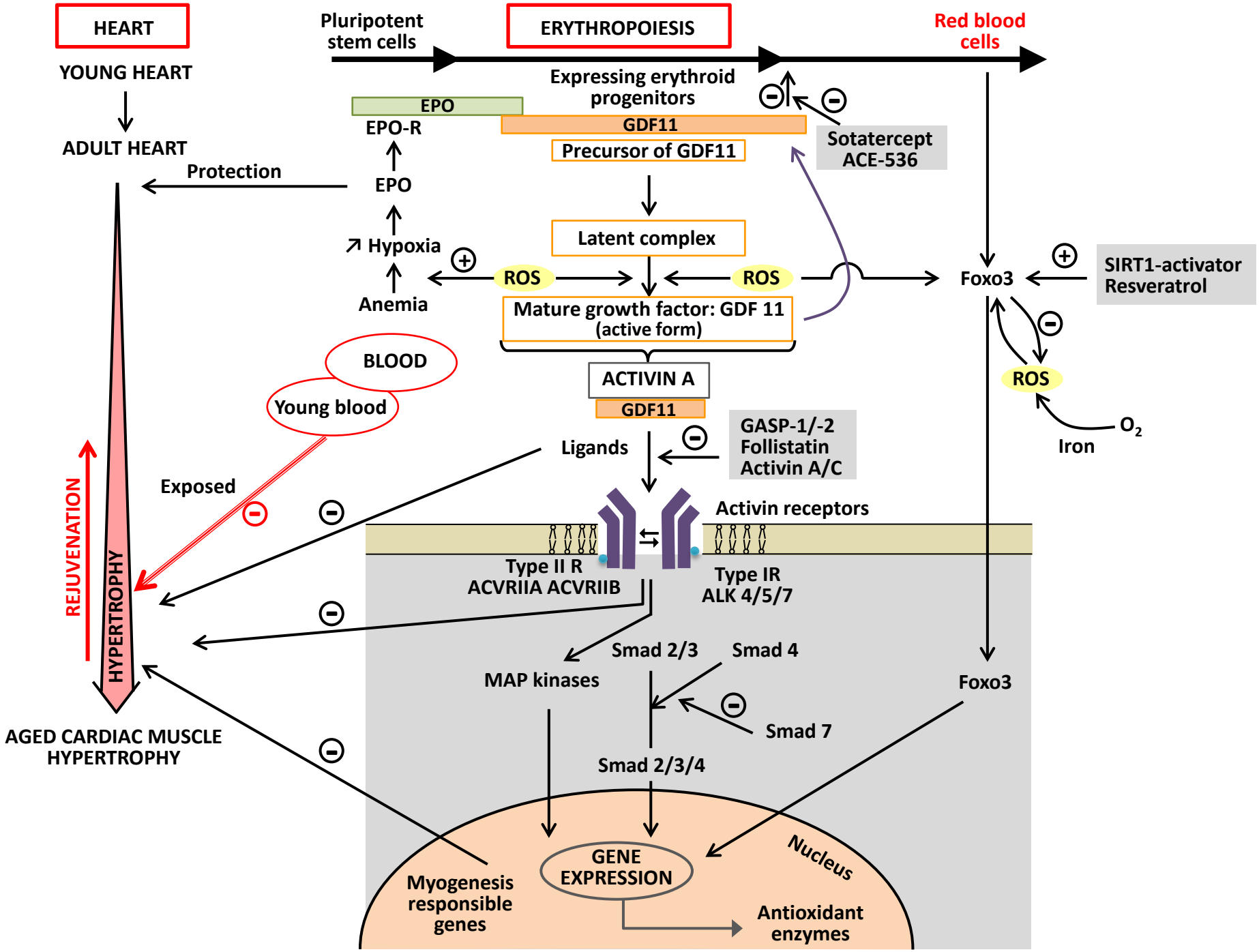
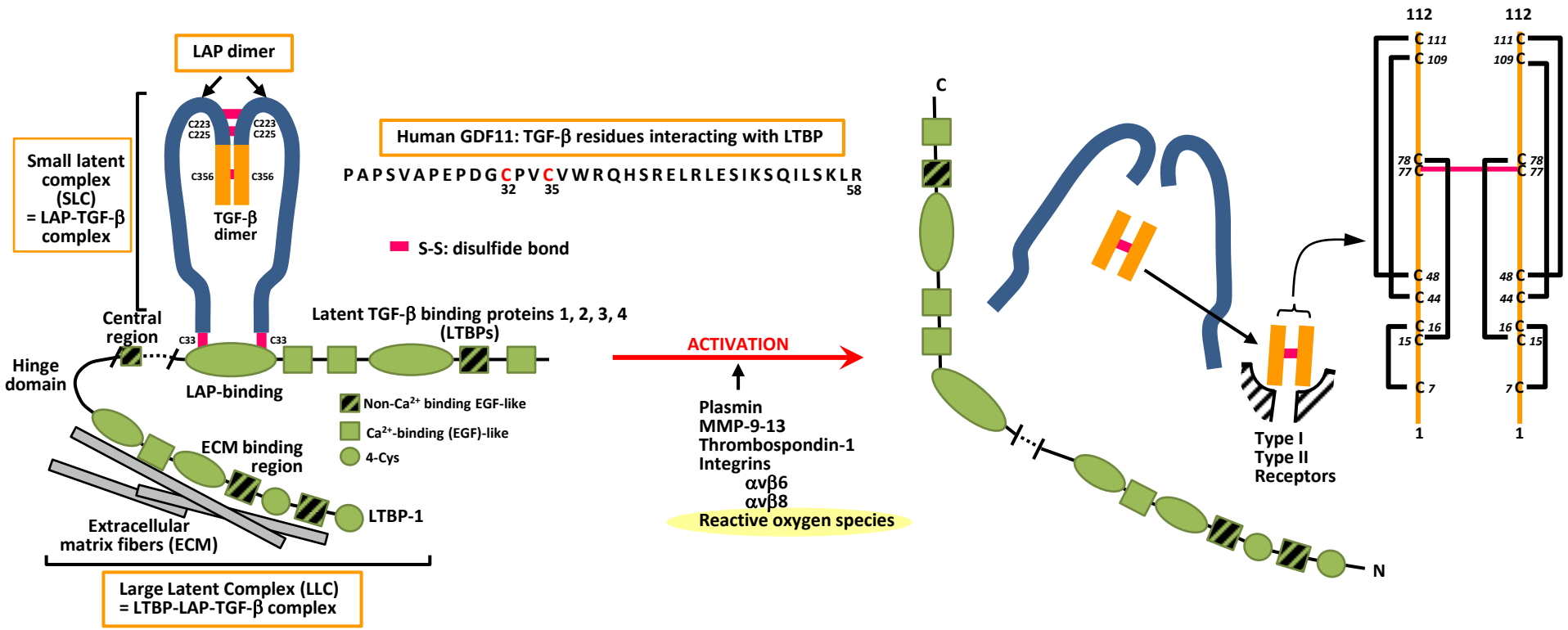
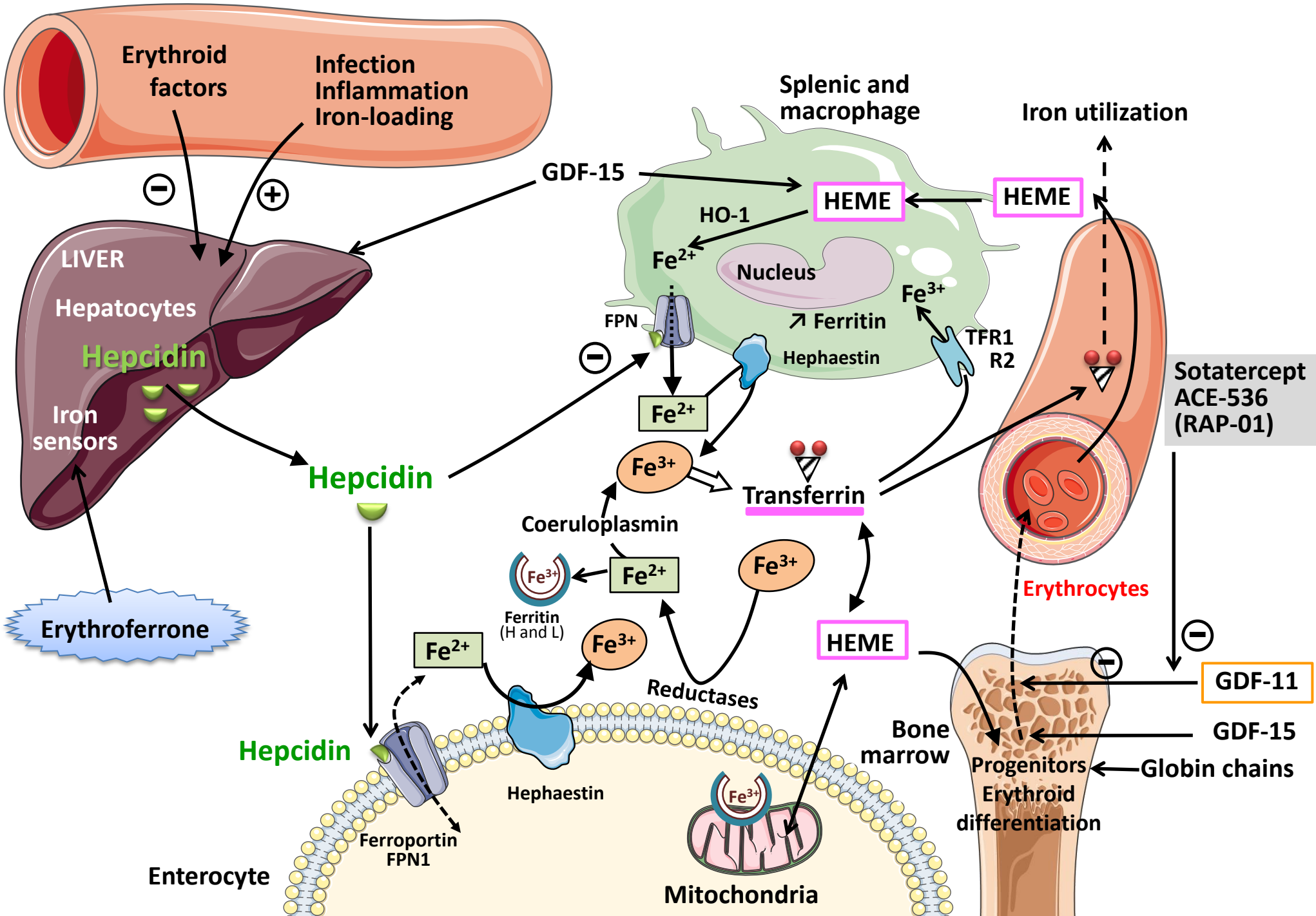

HEART
YOUNG HEART
ADULT HEART
Protection
Pluripotent stem cells
ERYTHROPOIESIS
Red blood cells
Expressing erythroid progenitors
EPO
EPO-R
EPO
Hypoxia
Anemia
GDF11
Precursor of GDF11
Sotatercept
ACE-536
Latent complex
ROS
ROS
Mature growth factor: GDF 11
(active form)
ACTIVIN A
GDF11
Foxo3
SIRT1-activator
Resveratrol
ROS
O_2
Iron
BLOOD
Young blood
Exposed
REJUVENATION
HYPERTROPHY
AGED CARDIAC MUSCLE HYPERTROPHY
Ligands
GASP-1/-2
Follistatin
Activin A/C
Activin receptors
Type II R
ACVRIIA ACVRIIB
Type IR
ALK 4/5/7
Smad 2/3
Smad 4
MAP kinases
Smad 7
Smad 2/3/4
Foxo3
Nucleus
GENE EXPRESSION
Myogenesis responsible genes
Antioxidant enzymes


LAP dimer
Small latent complex (SLC) = LAP-TGF-β complex
C223
C225
C223
C225
C356
C356
TGF-β dimer
Human GDF11: TGF-β residues interacting with LTBP
P A P S V A P E P D G C P V C V W R Q H S R E L R L E S I K S Q I L S K L R
32
35
58
S-S: disulfide bond
Central region
C33
C33
Latent TGF-β binding proteins 1, 2, 3, 4 (LTBPs)
Hinge domain
LAP-binding
Non-Ca2+ binding EGF-like
Ca2+-binding (EGF)-like
4-Cys
ECM binding region
LTBP-1
Extracellular matrix fibers (ECM)
Large Latent Complex (LLC) = LTBP-LAP-TGF-β complex
ACTIVATION
Plasmin
MMP-9-13
Thrombospondin-1
Integrins
αvβ6
αvβ8
Reactive oxygen species
C
N
Type I
Type II
Receptors
112
112
C 111
C 109
111 C
109 C
78 C
77 C
C 78
C 77
C 48
C 44
C 16
15 C
C 7
48 C
44 C
16 C
C 15
7 C
1
1


Erythroid factors
Infection
Inflammation
Iron-loading
GDF-15
Splenic and macrophage
Iron utilization
HEME
HEME
HO-1
Fe^{2+}
Nucleus
Fe^{3+}
FPN
↗ Ferritin
TFR1
R2
Hephaestin
LIVER
Hepatocytes
Hepcidin
Iron sensors
Fe^{2+}
Fe^{3+}
Transferrin
Sotatercept
ACE-536
(RAP-01)
Hepcidin
Coeruloplasmin
Fe^{3+}
Fe^{2+}
Fe^{3+}
Ferritin
(H and L)
Erythrocytes
Erythroferrone
Fe^{2+}
Fe^{3+}
HEME
GDF-11
Reductases
Bone marrow
GDF-15
Hepcidin
Hephaestin
Progenitors
Globin chains
Erythroid differentiation
Ferroportin
FPN1
Enterocyte
Mitochondria