

Adrenergic Repression of the Epigenetic Reader MeCP2 Facilitates Cardiac Adaptation in Chronic Heart Failure

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methyl-CpG-binding protein 2
(MeCP2)



Expression Bead
Chips

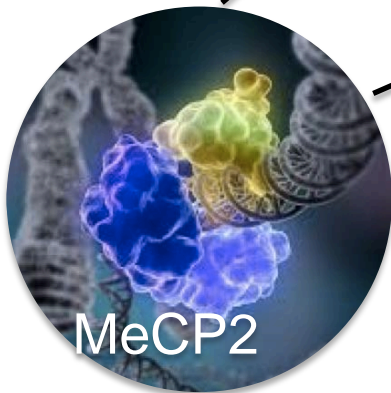


Mechanical unloading
(LVAD)



Pathogenesis of
chronic heart failure

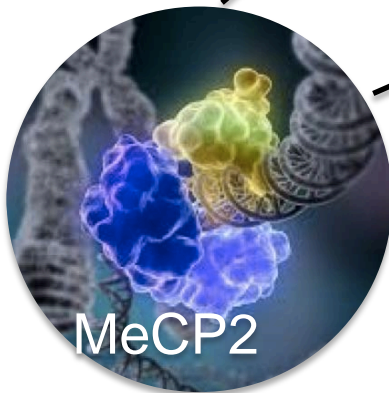
- Signaling mechanism (Intracellular kinase signalling pathways, nuclear transcription factors)
- Epigenetic processes (microRNA, DNA methylation, histone modification)



recognize and bind
to CH3-DNA

repress
transcription

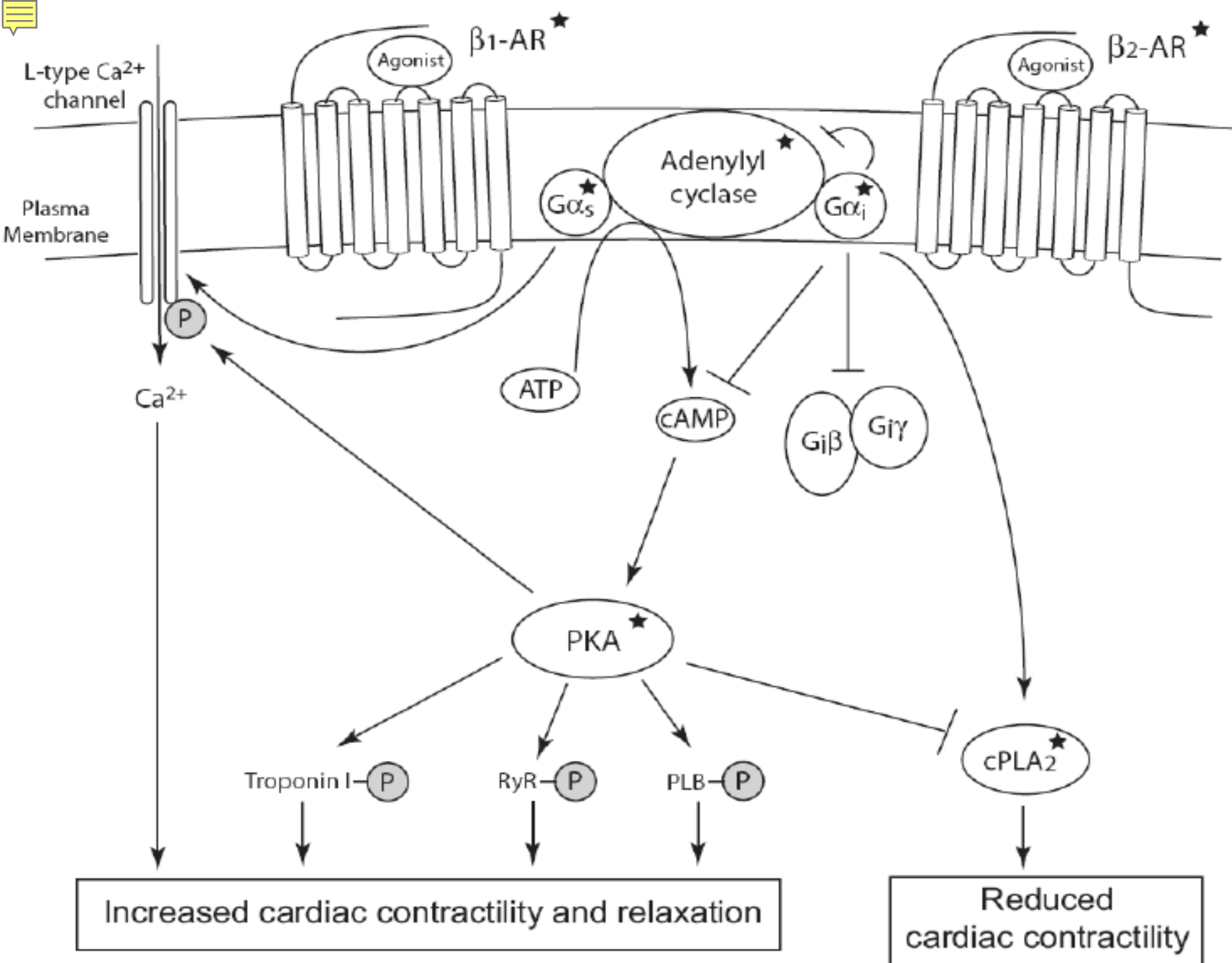
activate gene
expression
recruiting
coactivators



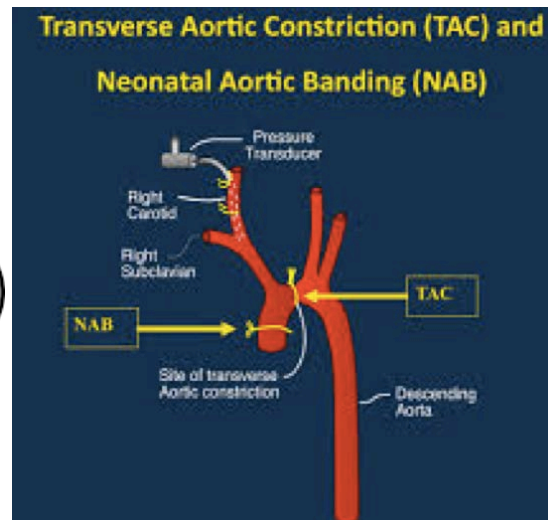
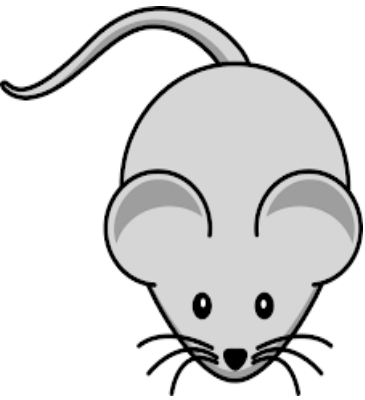
epigenetic factor
associated with
improvement of
heart failure

MeCP2 is repressed in
chronic heart failure

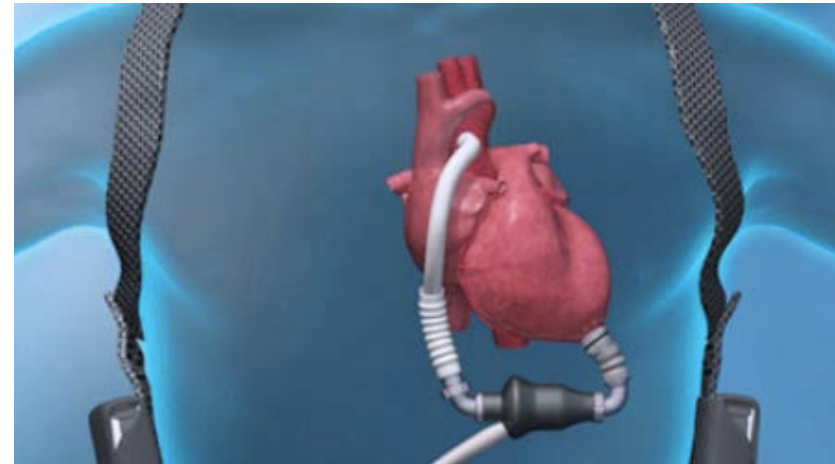
repression by
adrenergic
pathway



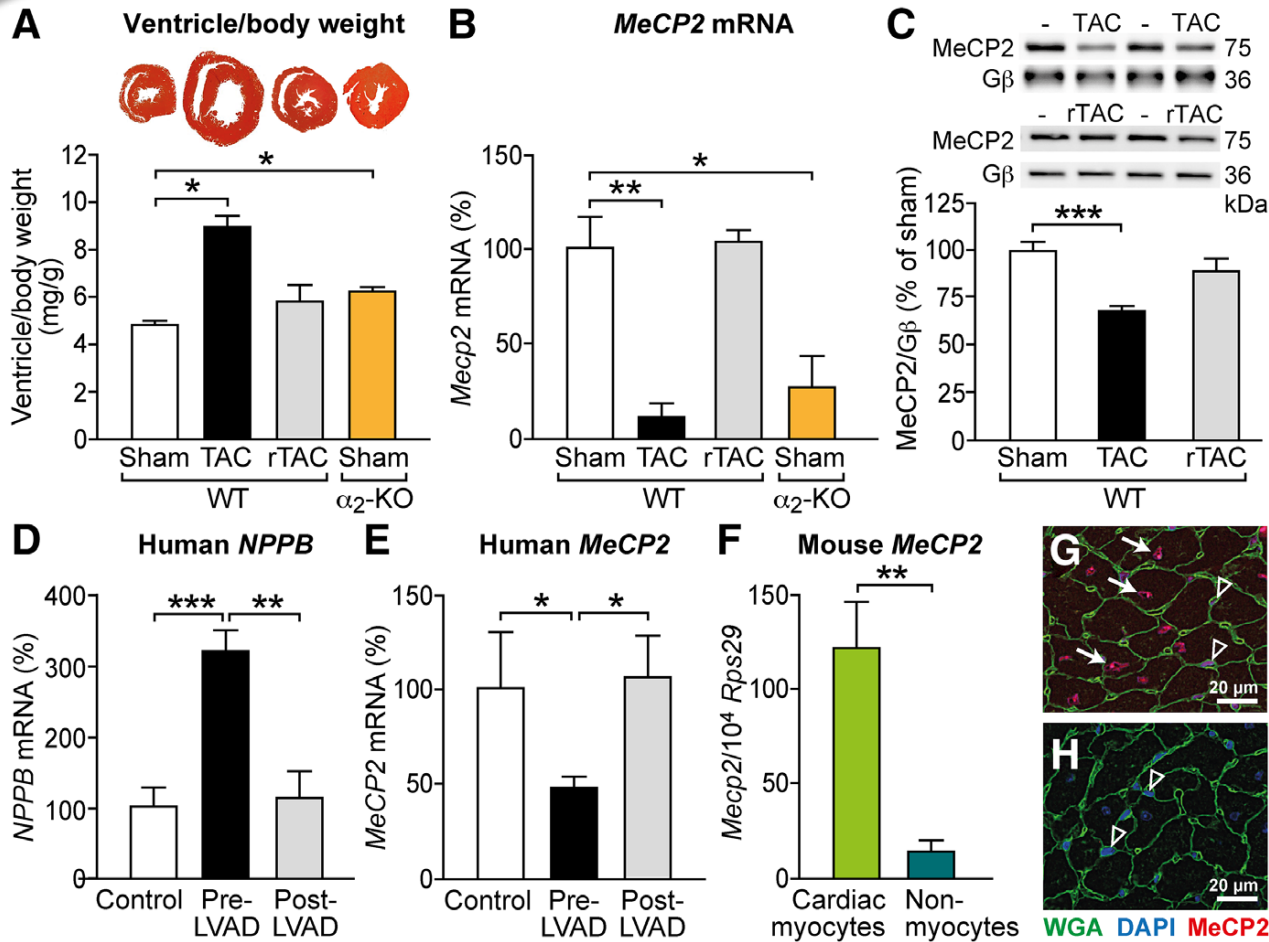
MeCP2 is repressed in mouse and human heart failure



VS.



MeCP2 is repressed in mouse and human heart failure



A- 4 weeks TAC

B- mRNA level

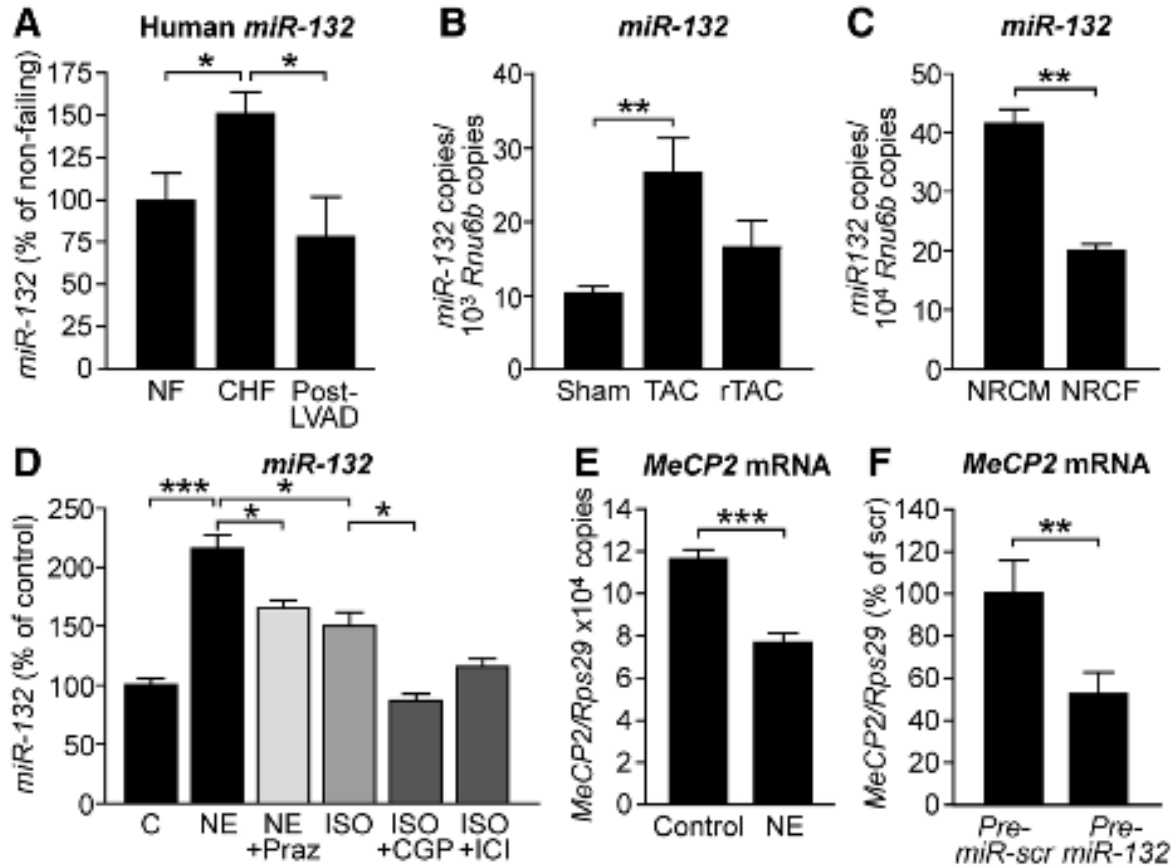
C- protein level

D+E- mRNA from heart biopsies

F- mRNA

G+H- mouse tissue

MiR-212/132 is upregulated by adrenergic activation and targets MeCP2



A- NF(non-failing); CHF (chronic heart)

B- mouse model

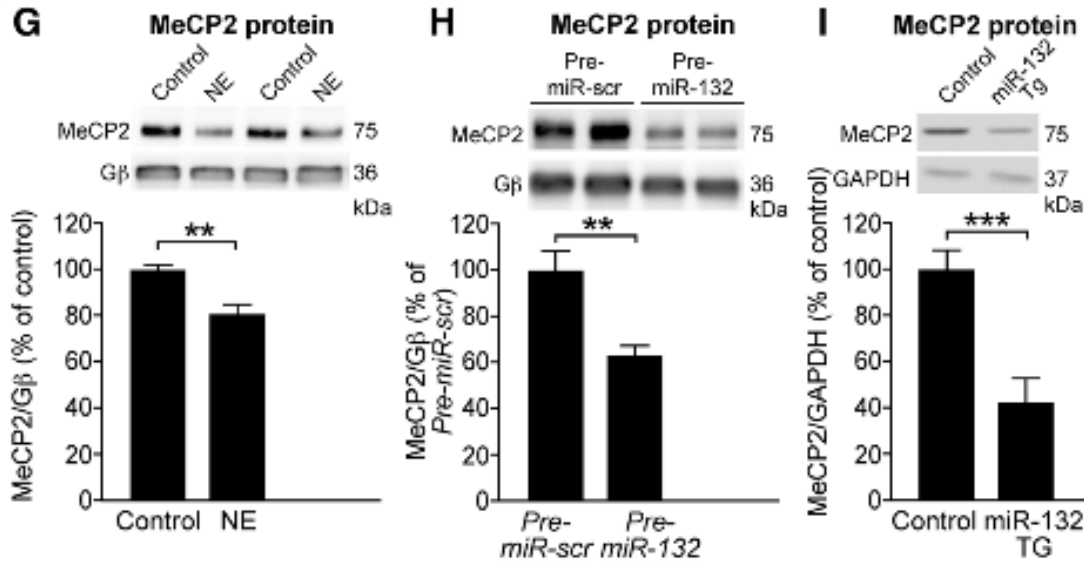
C- NRCM(neonatal rat cardiomyocytes);NRCF (neonatal rat non-myocytes)

D- NE(norepinephrine); PRA (prazosine); ISO(iso-proterenol); CGP(CGP207); ICI (ICI118551)

E- cell culture experiment with NRCM

F- transfected NRCM

MiR-132 is upregulated by adrenergic activation and targets MeCP2

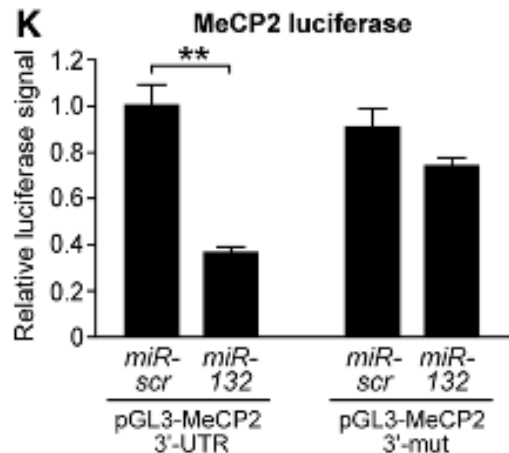
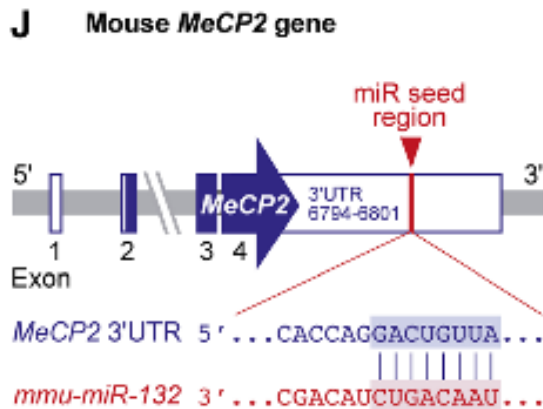


G- NE(norepinephrine)

H- transfected NRCM

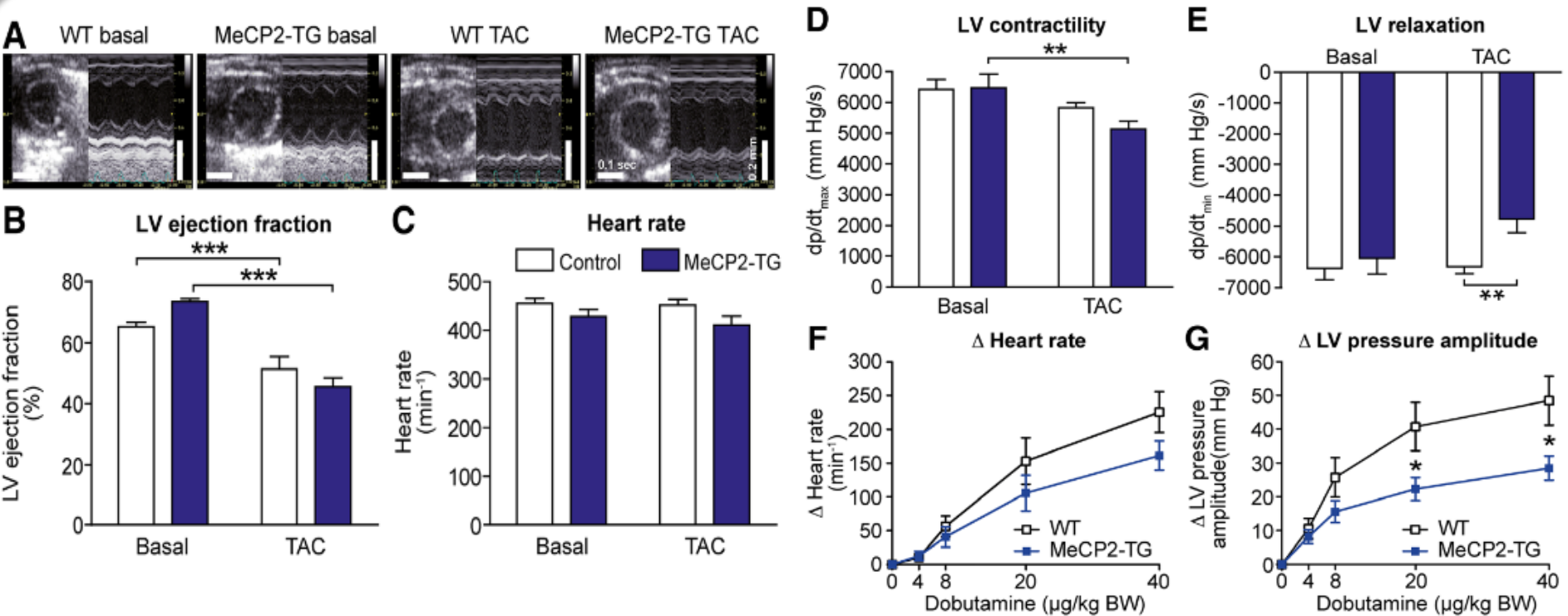
I- transgenic mouse model over-expressing miR-132

J- The mouse MeCP2 gene displaying the 3' part with the seed region for miR-132

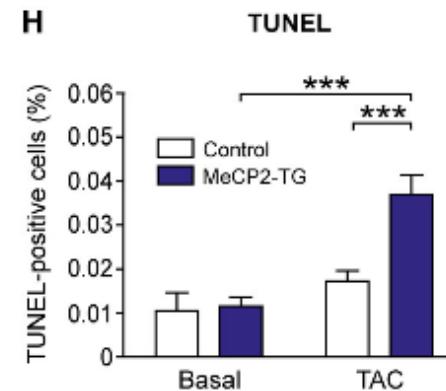
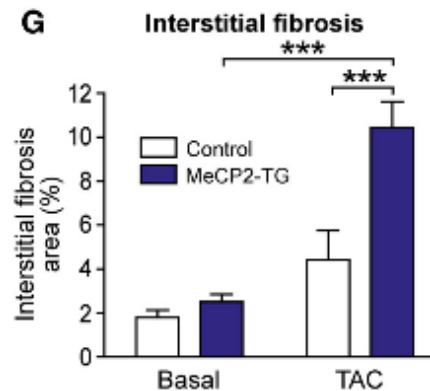
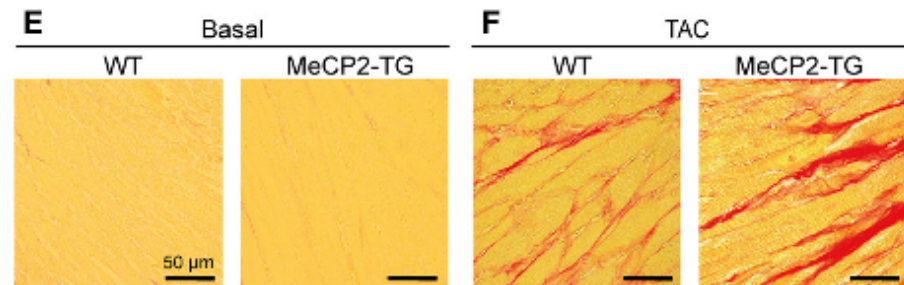
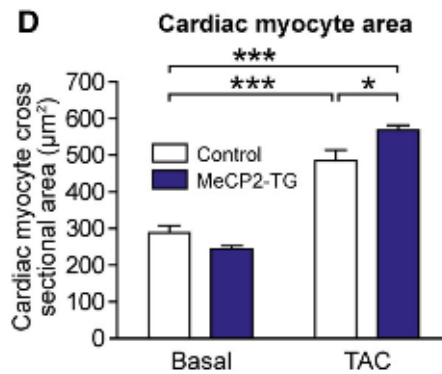
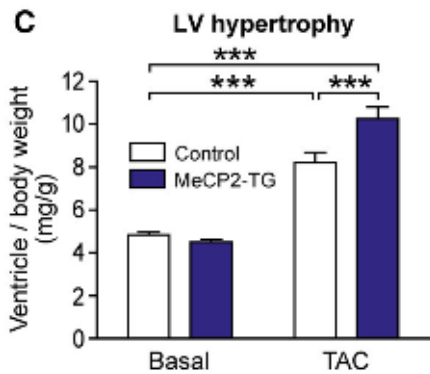
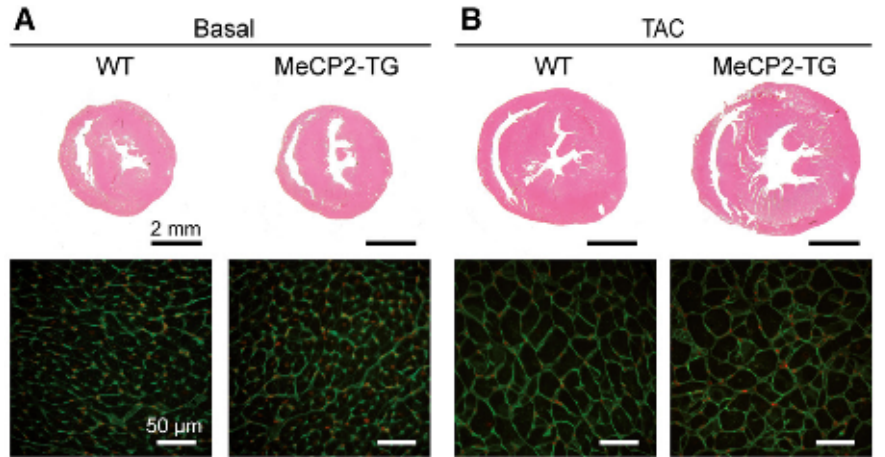


K- vectors containing the wild-type or mutated 3' MeCP2 region

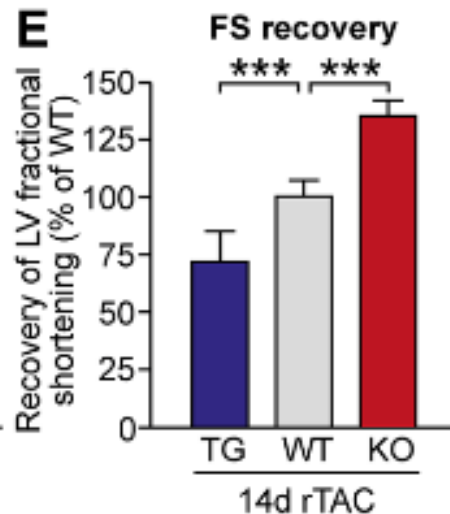
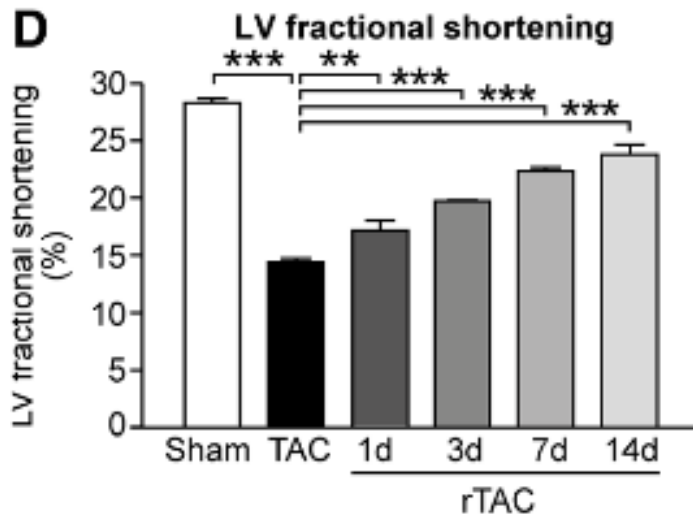
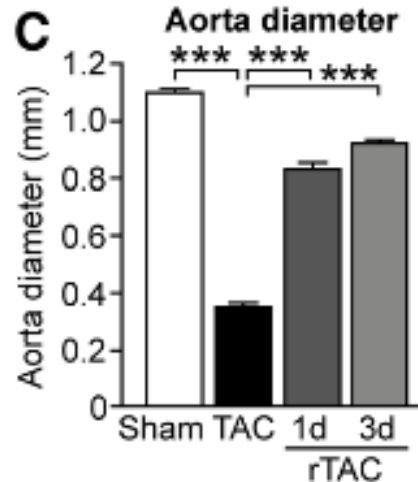
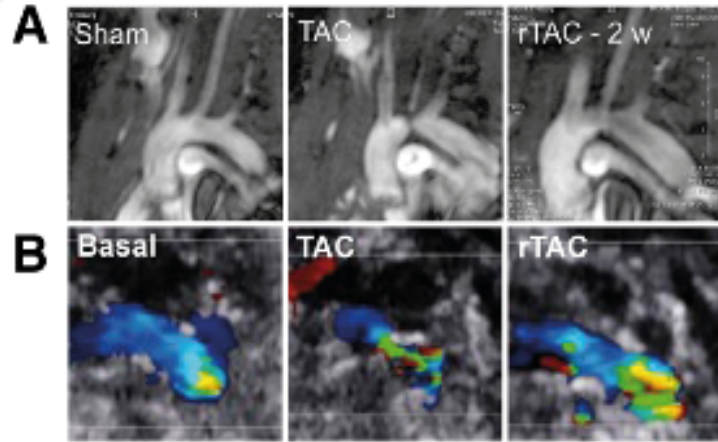
Mouse models with cardiomyocytes specific- expression or ablation of MeCP2



Cardiac hypertrophy and fibrosis in MeCP2-TG mice



Ablation of MeCP2 expression facilitates recovery from pressure overload



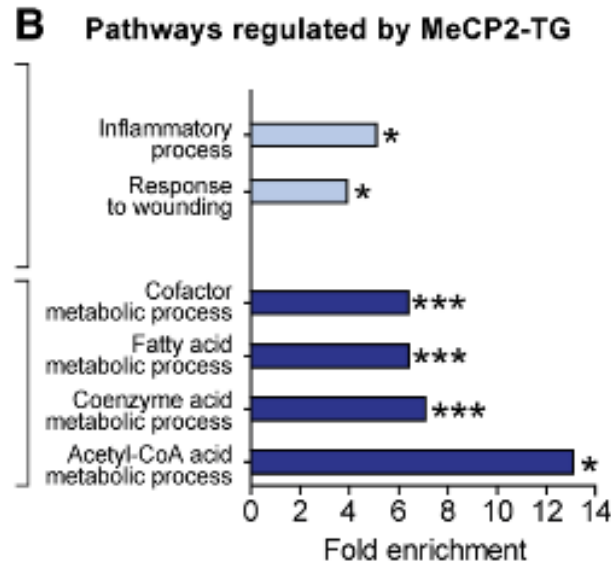
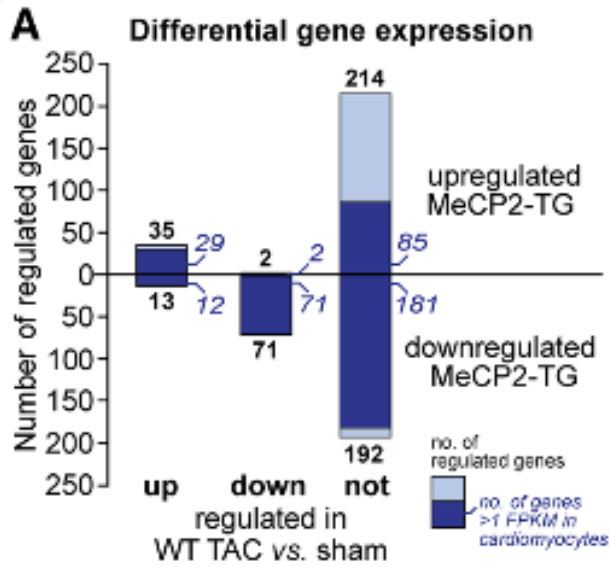
A- MRI

B- color Doppler echo-
cardiography

C- rTAC (removal of
stenosis)

E- TG (MeCP2-
transgenic mice); WT
(wild type); KO (MeCP2
knock-out)

Differential Gene Expression in Mouse Hearts

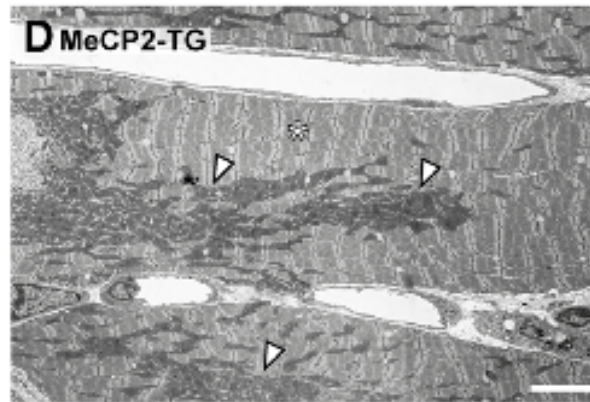
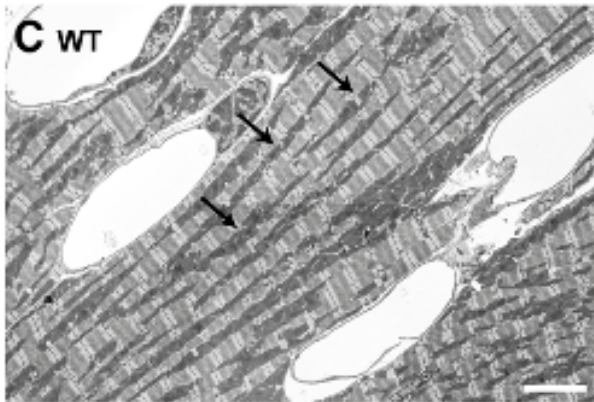


A- MeCP2-TG vs. WT mouse after TAC

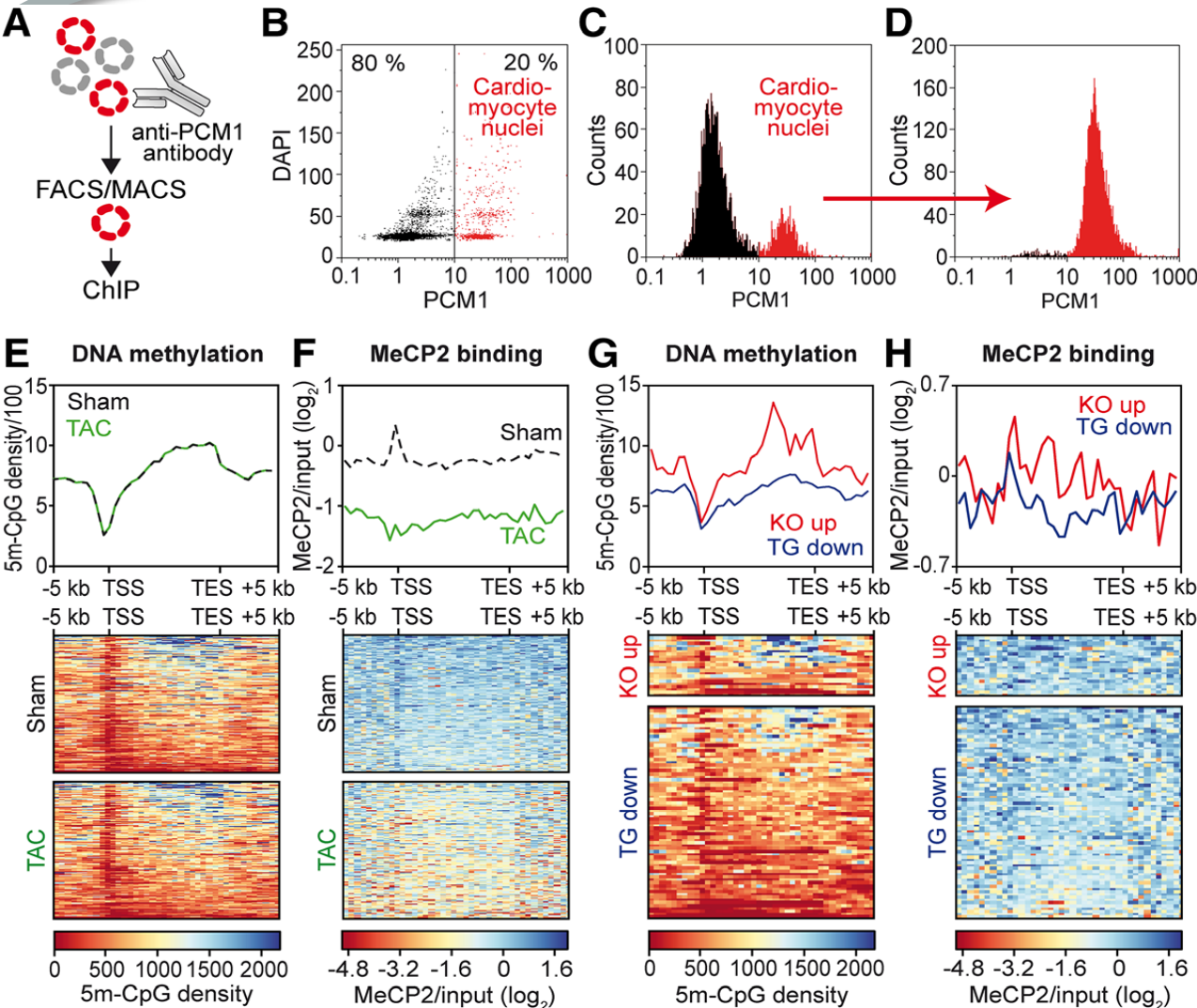
B- Gene ontology pathway

C- 10-week odl male WT mouse

D- MeCP2-transgenic mice



MeCP2 is bound to methylated genes in cardiomyocytes



A-D- Isolation of cardiomyocyte nuclei

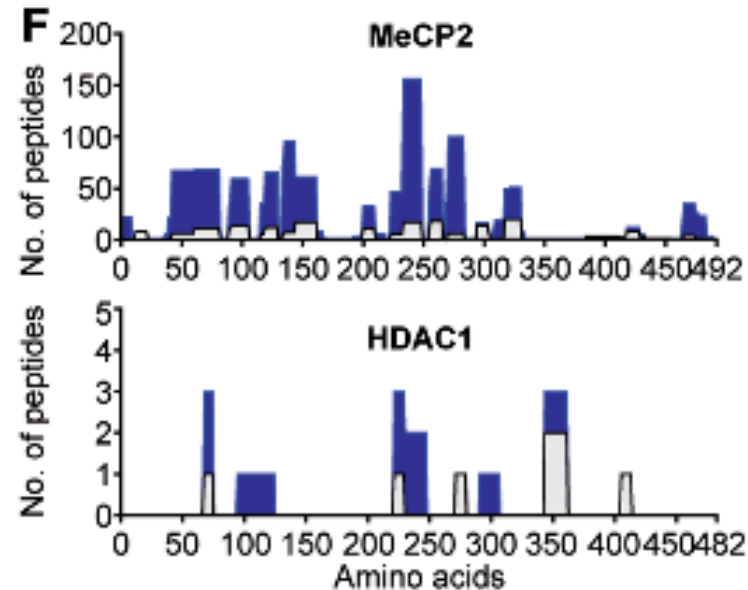
E+F- Differentially regulated genes by MeCP2 in WT-mouse (upper-average levels, heat maps-individual genes)

G+H- Differentially regulated genes by MeCP2 in transgenic and knockout mouse

MeCP2 interaction partners

E

	C1	C2	C3	
MeCP2	28.2	49.4	57.3	∞
HDAC1	2.4	∞	57.7	90
HDAC2	2.3	n.d.	n.d.	80
HDAC3	∞	n.d.	n.d.	70
HDAC6	n.d.	∞	n.d.	60
SIN3A	n.d.	n.d.	n.d.	50
NCOR1	∞	n.d.	n.d.	40
NCOR2	n.d.	n.d.	n.d.	30
DNMT1	6.4	∞	n.d.	20
DNMT3A	2.1	∞	n.d.	10
DNMT3B	n.d.	n.d.	n.d.	1
CREB1	∞	n.d.	n.d.	n.d.

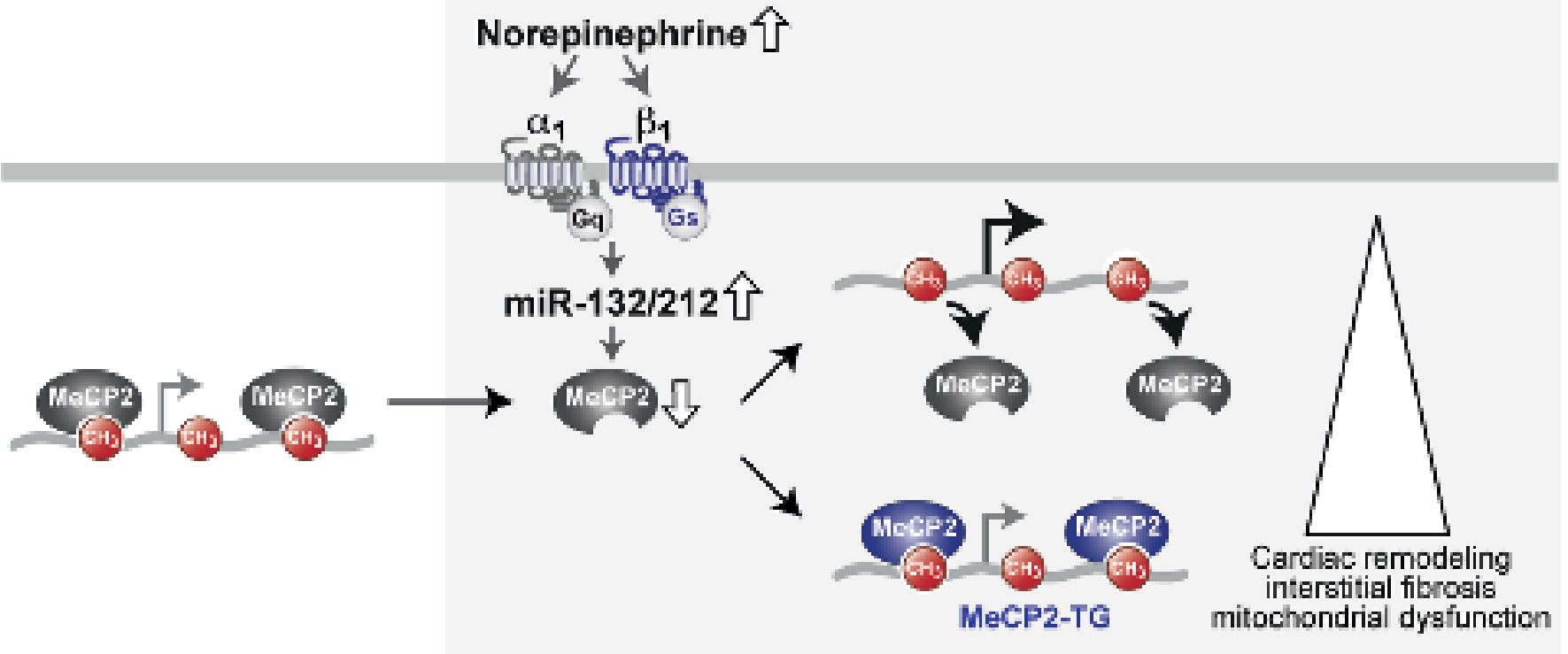


E- interaction partners of MeCP2 in NRCM with adenoviral expression of MeCP2, values=intensity ratio(control transduced cardiomyocytes /adenoviral transduced myocytes), (C1, C2, C3- different lysing conditions)

F- Peptide coverage in NRCM with adenoviral expression of MeCP2

G Sham

TAC



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