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Relationship between cardiac dysfunction induced by chronic kidney disease (CKD) and Sirt 1

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Background I

- Chronic kidney disease (CKD) is a well-known risk factor for cardiovascular disease (CVD) and is associated with an increase in cardiovascular mortality rate.

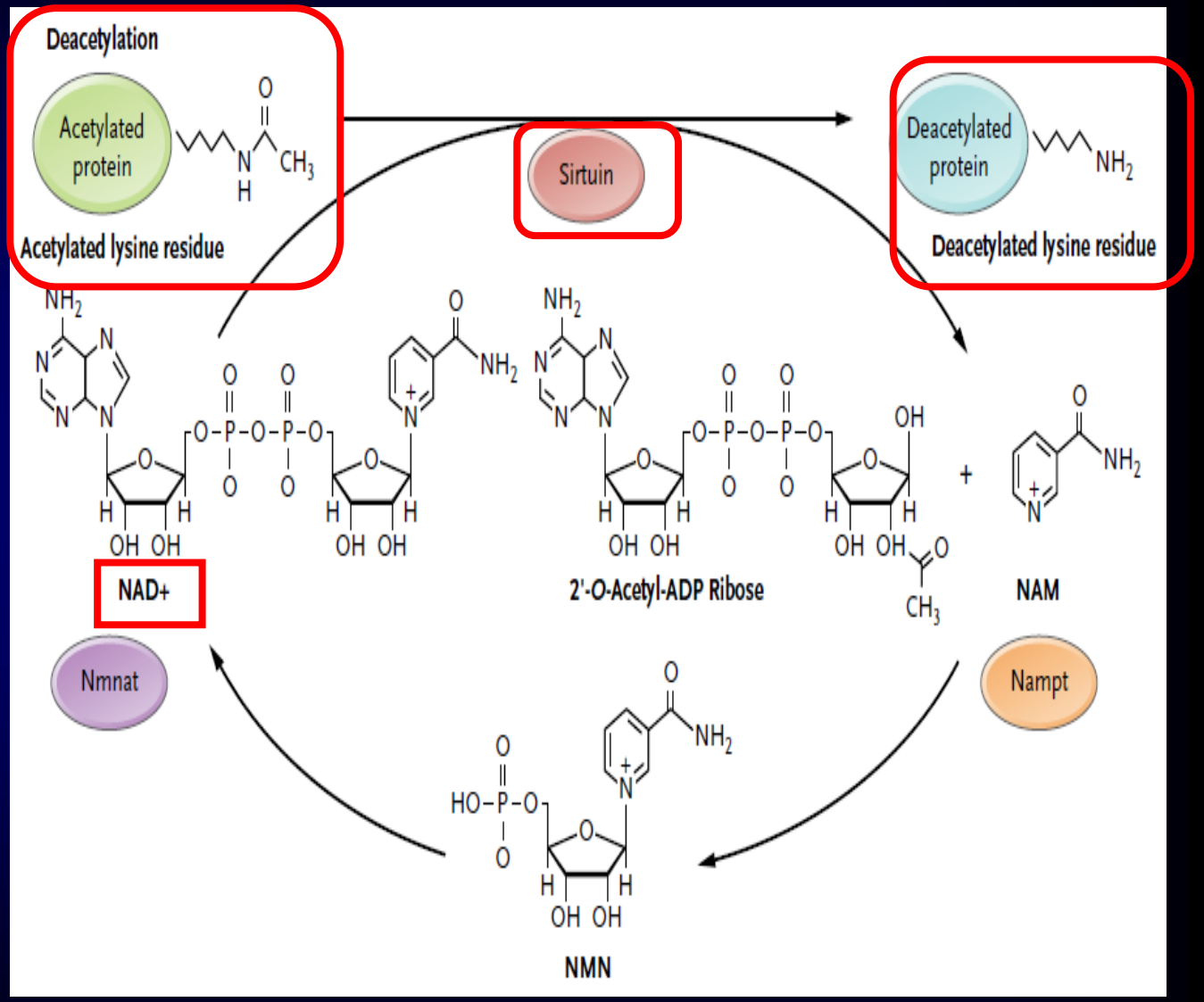
- Several studies have shown a strong association between CKD and cardiovascular disease, including atrial fibrillation(AF), myocardial infarctions (MIs), sudden cardiac death (SCD), and heart failure (HF). *(Front Physiol 2018;9:1726, Kidney Int. 2009;76:652-8, J Card Fail. 2019;25:286-300N Engl J Med. 1998;339:799-805)*

- Some studies have suggested that arrhythmic deaths and cardiac arrest in end-stage renal disease patients (ESRD) account for 22% of the total population. *(Am J Kidney Dis. 1998;32:853-906)*

- Cardiac disease is highly prevalent among patients with ESRD, and cardiovascular events are the main cause of death in these patients.

Background II

- Sirtuins (silent information regulator 2) proteins:
  - NAD-dependent deacetylases
  - highly conserve from bacteria to human
  - Splitting of NAD during each deacetylation cycle
  - activity : variety of phathophysiological process (oxidative stress, apoptosis, aging and caloric restrictions)
  - In mammals :
    1) seven sirtuins (Sirt1-7)
    2) different specific substrate and biological function
    3) found in various cell compartments
  - Location : Sirt1 is localize in the nucleus



N Engl J Med 2011;364:2235-44.

Background II

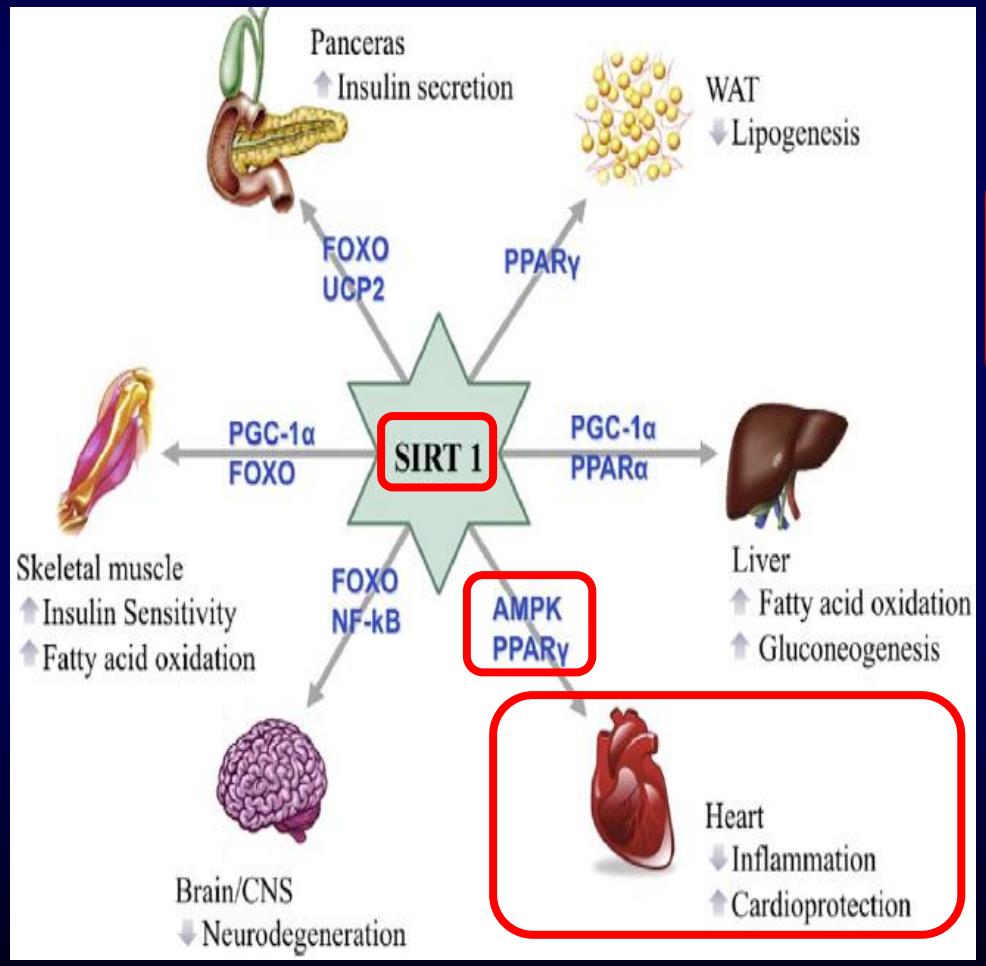
Role of Sirt1 protein :

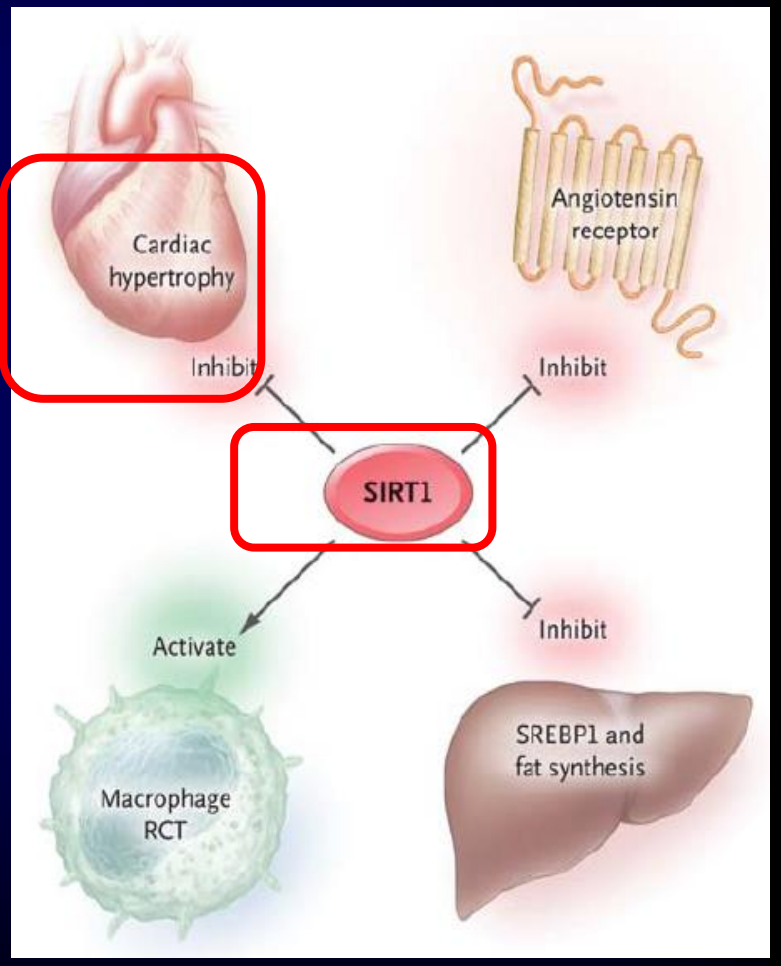
1) Sirt1 proteins regulate the life span, stress response, and metabolic regulation.

2) Sirt1 has been involved in neurodegenerative disorders, cancer, and aging processes as well as cardiovascular disease.

3) Increased sirt1 level were found in cardiac hypertrophy and heart failure.

Protective roles of SIRT1 in cardiovascular disease





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N Engl J Med 2011;364:2235-44.

Hypothesis

- The purpose of our study was to evaluate the association of Sirt1 with CKD-induced cardiac remodeling.
  We examined the expression of Sirt1 in CKD-induced cardiac remodeled tissue in mouse heart due to renal dysfunction.

Methods

- Animal Models :
  - Induction of renal fibrosis and CKD ; mice were fed a custom ready-made diet containing 0.2% (w/w) adenine for 6 weeks

-Heart and blood were collected for various analyses:

1) Serum chemistry analysis ; creatinine & blood urea nitrogen (BUN)
2) Urine ; microalbumin
3) Immunofluorescence staining ; Sirt1 expression in the cardiomyocytes
4) Hematoxylin and eosin (H&E) staining ; Cardiac structure (morphology & cellular dimensions)
5) Masson's trichrome staining ; interstitial fibrosis
6) Quantitative real-time PCR (qRT-PCR) ; Sirt1, BNP TGF-β and MMP-9 mRNA expression
7) Western-blotting ; - Sirt1 protein expression
   - Hypertrophy marker : β-MHC Protein level

Results

Kidney function in the sham and CKD group

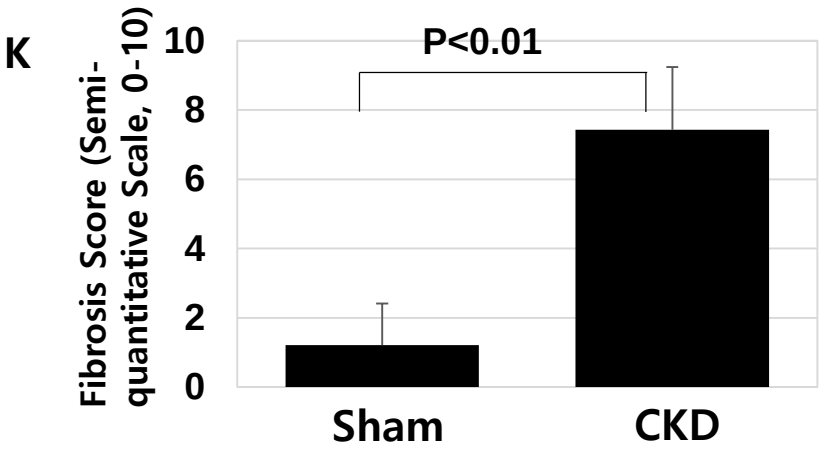
Kidney function Parameter	Sham group (n=6), (Week 6)	CKD group(n=6), (Week 6)
Body weight (g)	26.25±1.86	22.16±1.60**
Creatinine (mg/dL)	0.2±0.03	0.64±0.11**
BUN (mg/dL)	23.33±2.65	80.50±22.58**
Microalbumin(24h U)	0.00±0.003	0.04±0.03*

* P<0.05 vs. sham

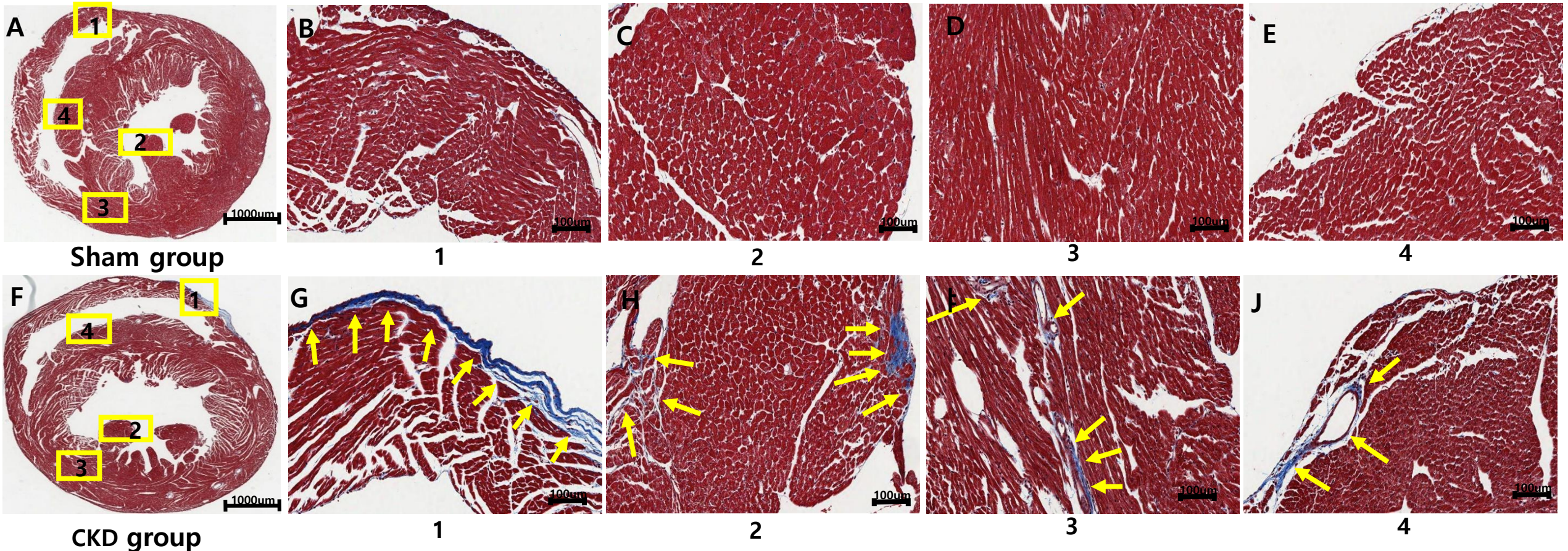
**P<0.01 vs sham

Cardiac fibrosis

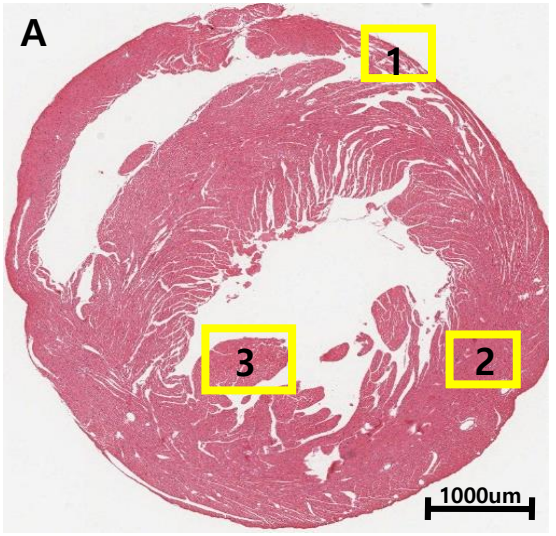
The calculated percent(%) area of the cardiac interstitial fibrosis:(k)



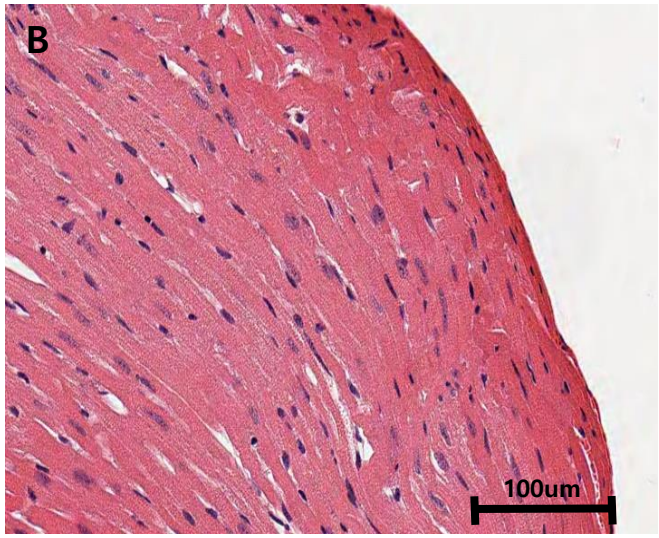
Degree of heart fibrosis deposition: (A to J)



Myocardial structure



Sham group



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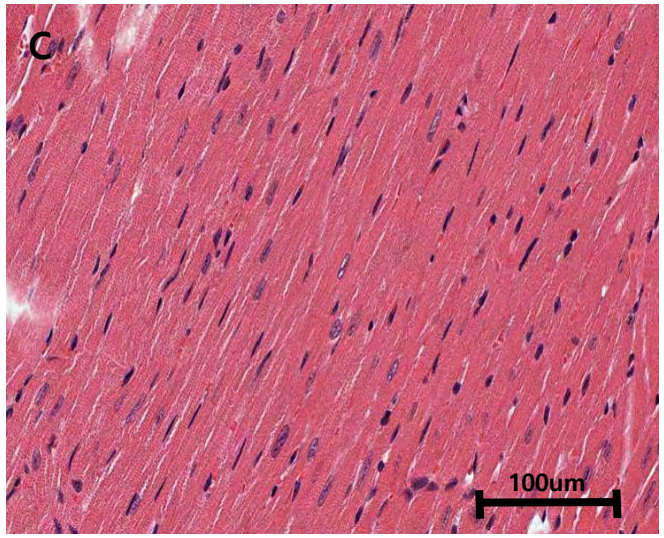

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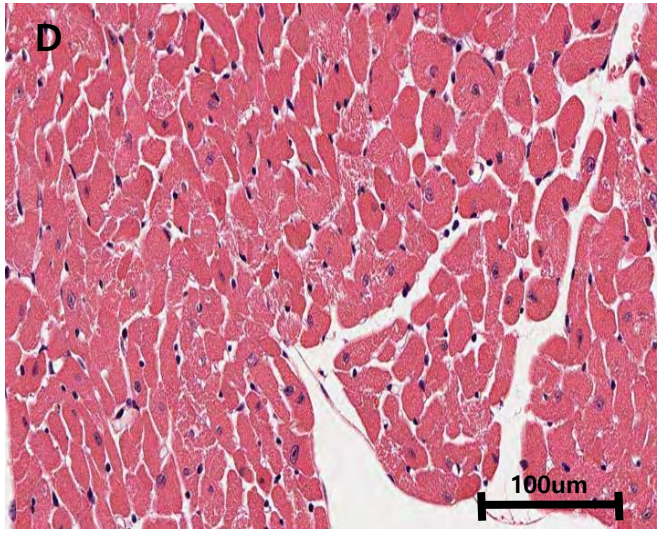

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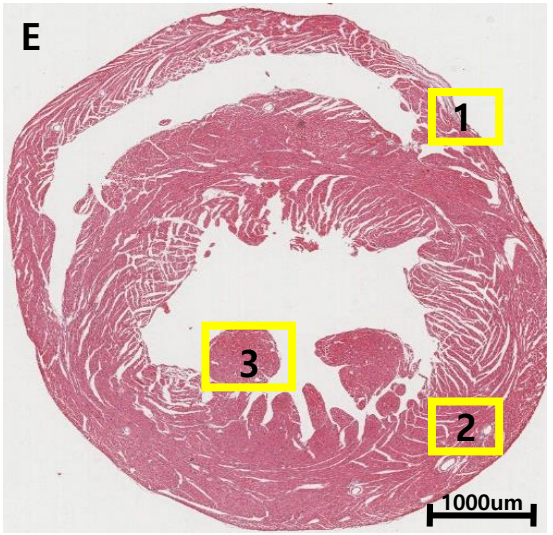
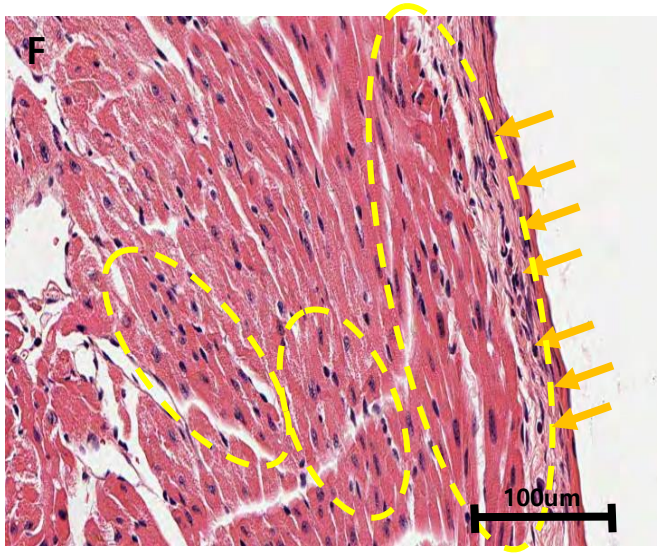


CKD group



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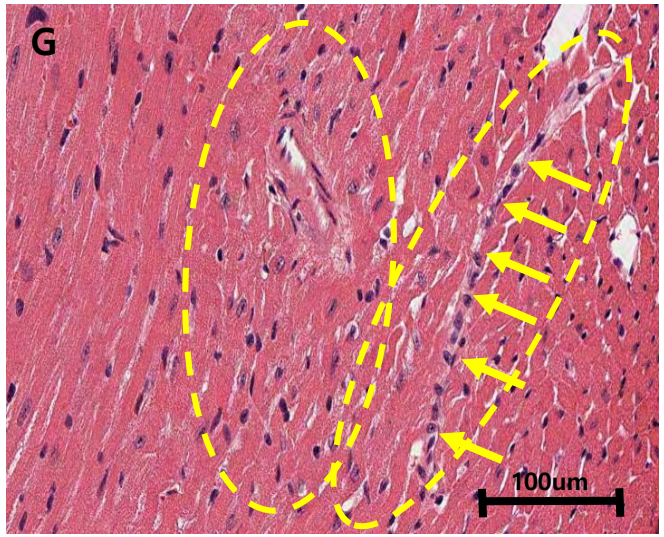

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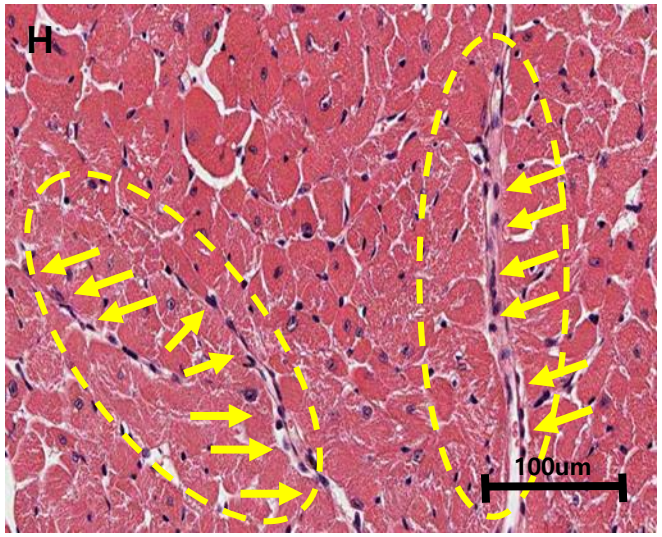

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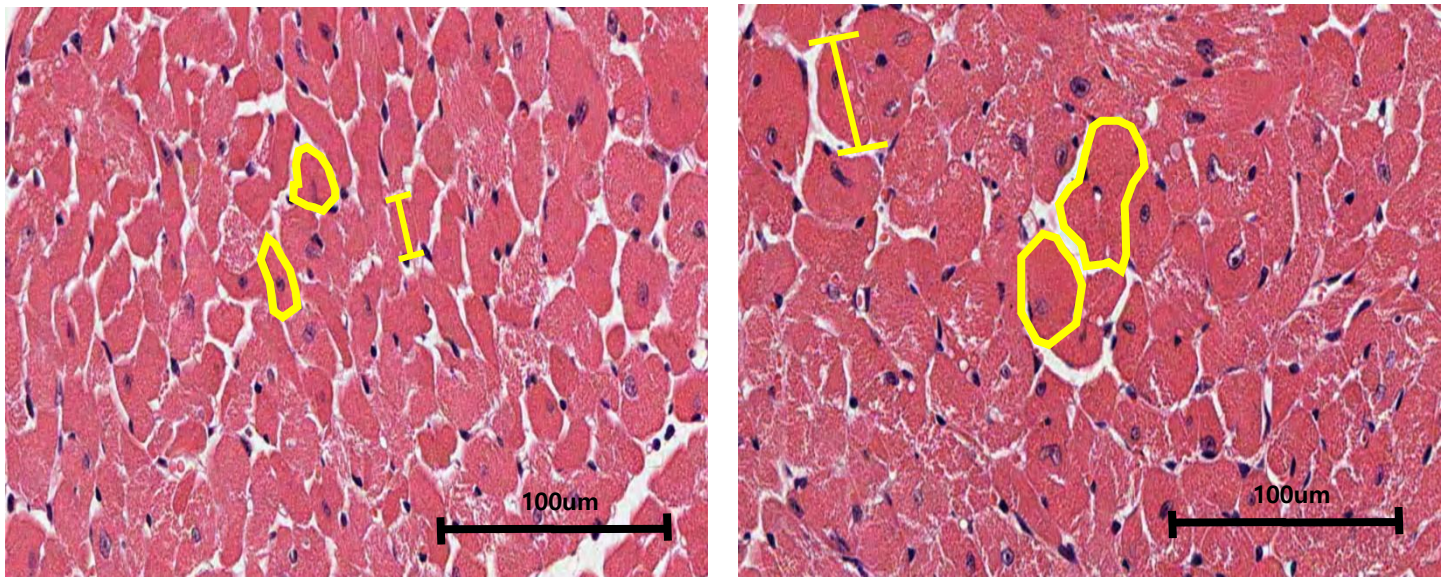
Results

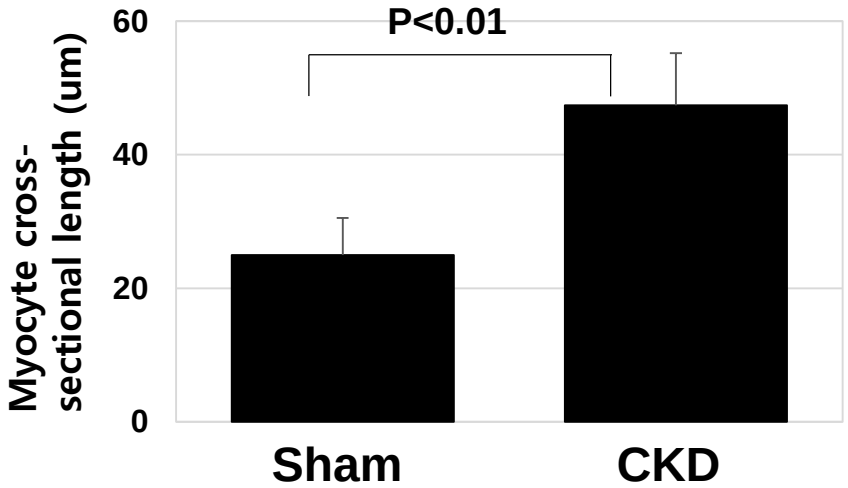
Myocyte cross-sectional area & length

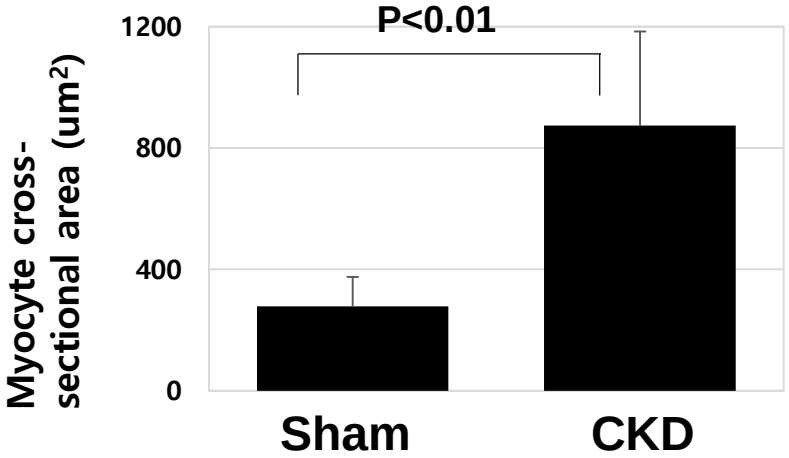
A



Sham CKD

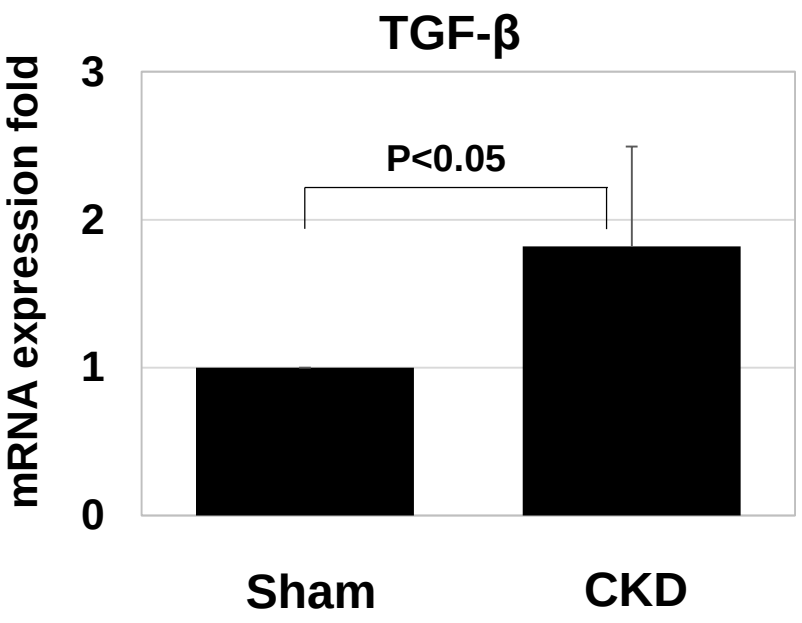
B

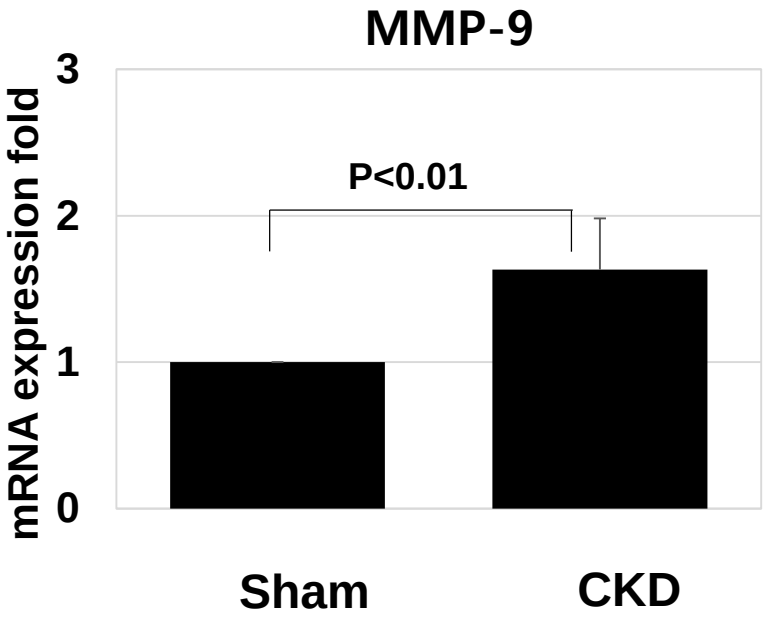


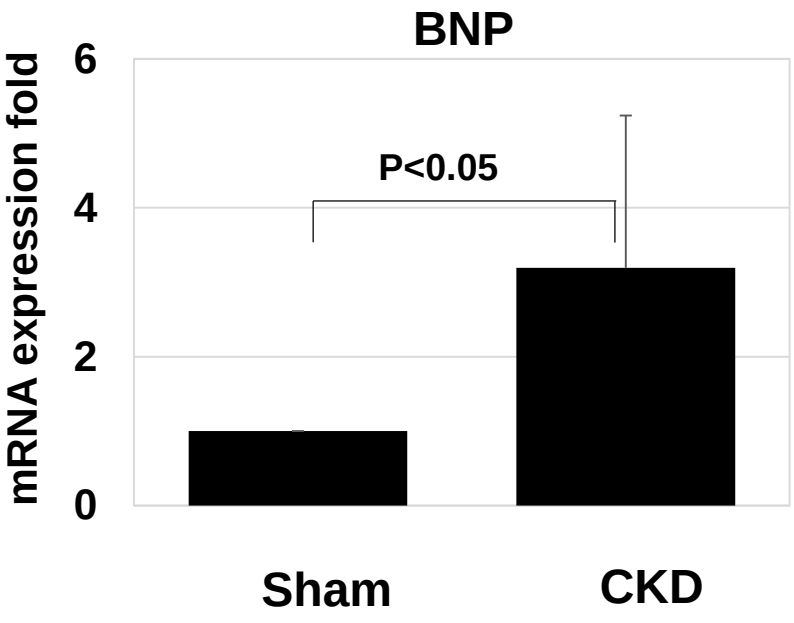


Results

mRNA expression level in cardiac remodeling induced by CKD

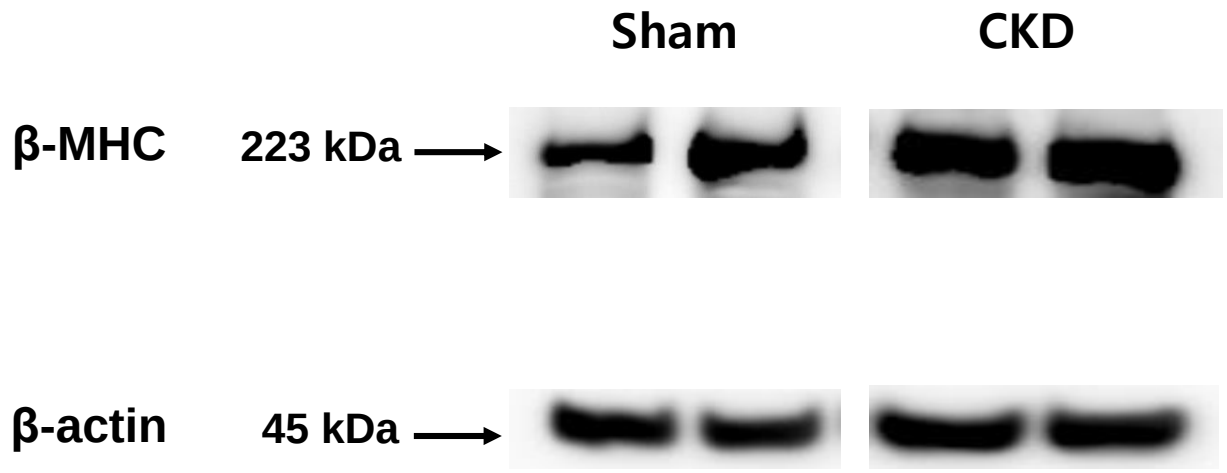


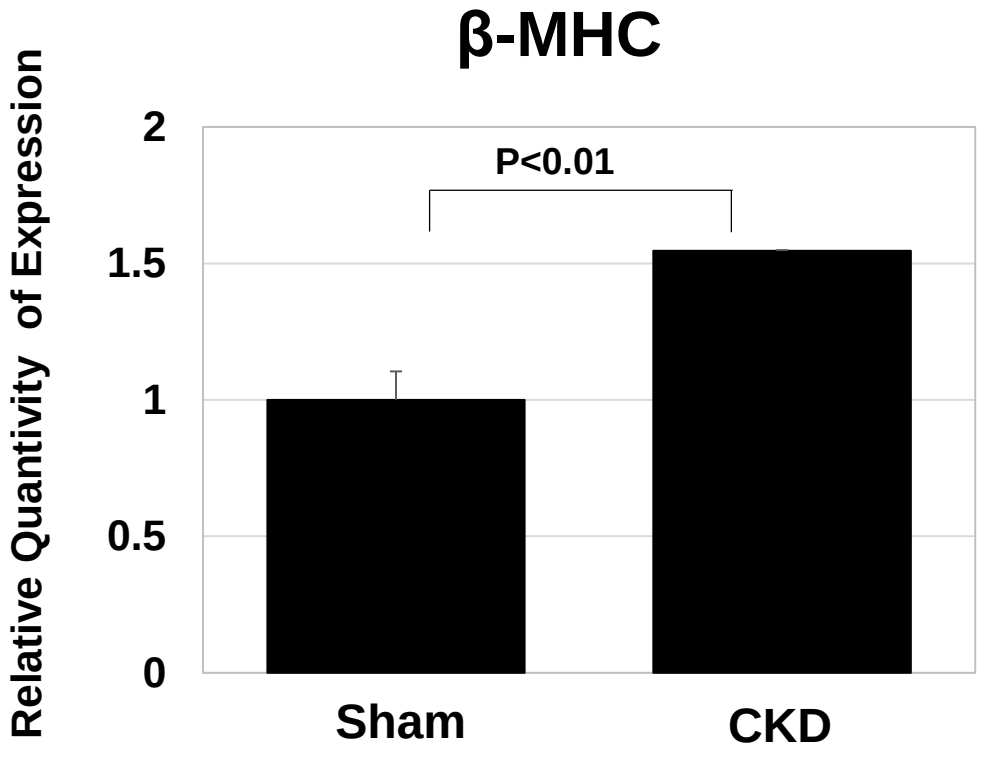




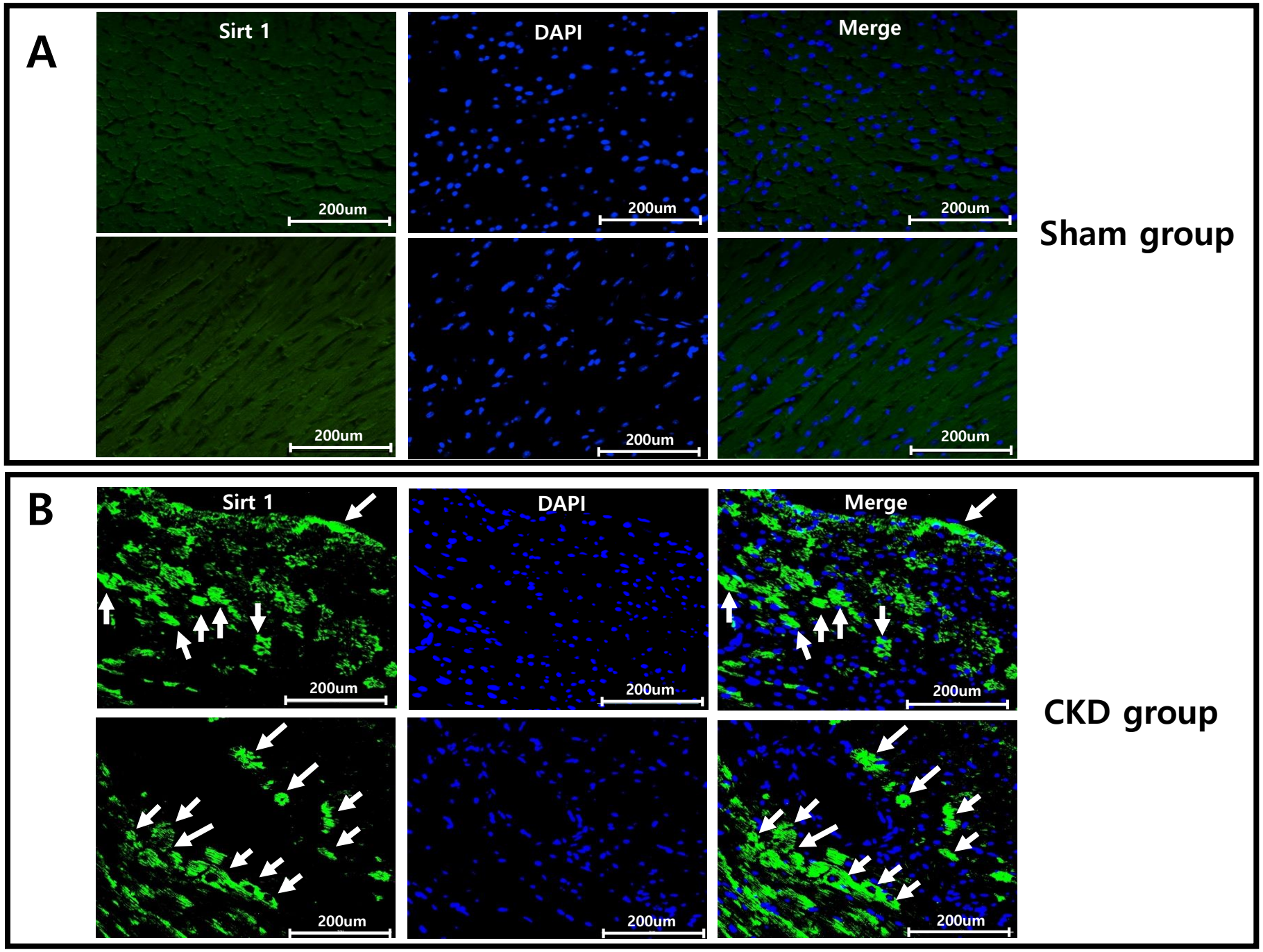
Results

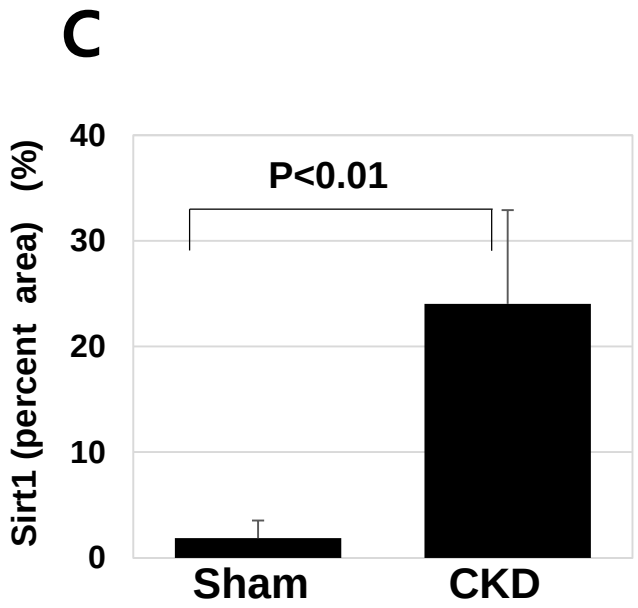
β-MHC protein expression level





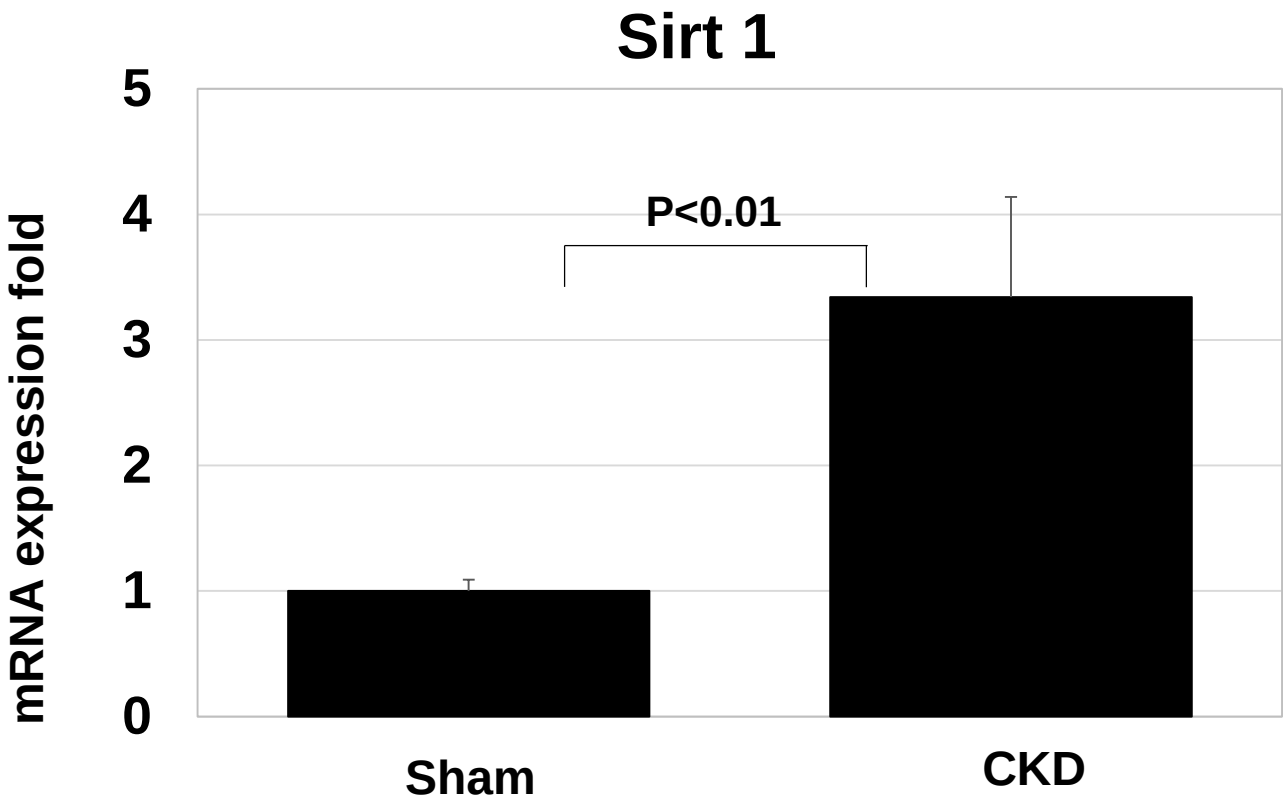
Distribution and expression of Sirt1





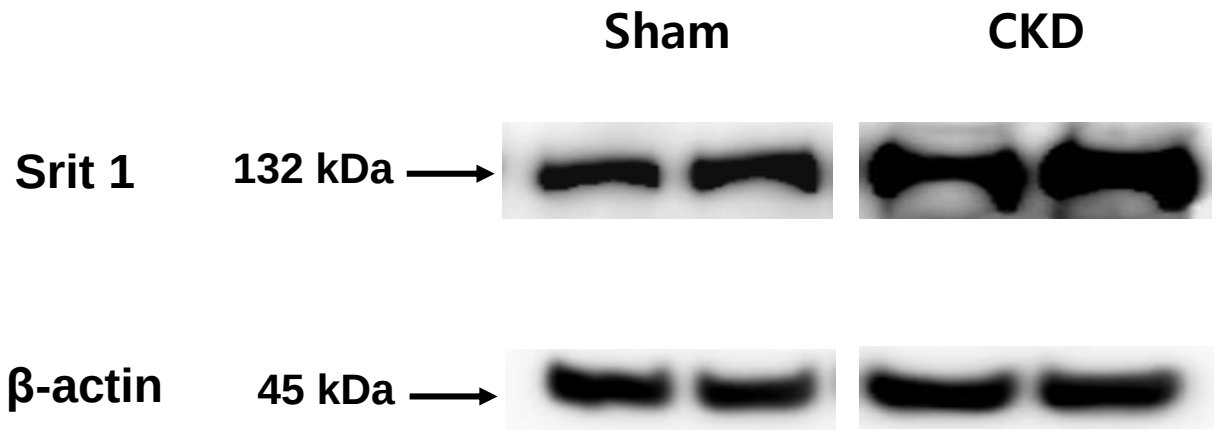
Results

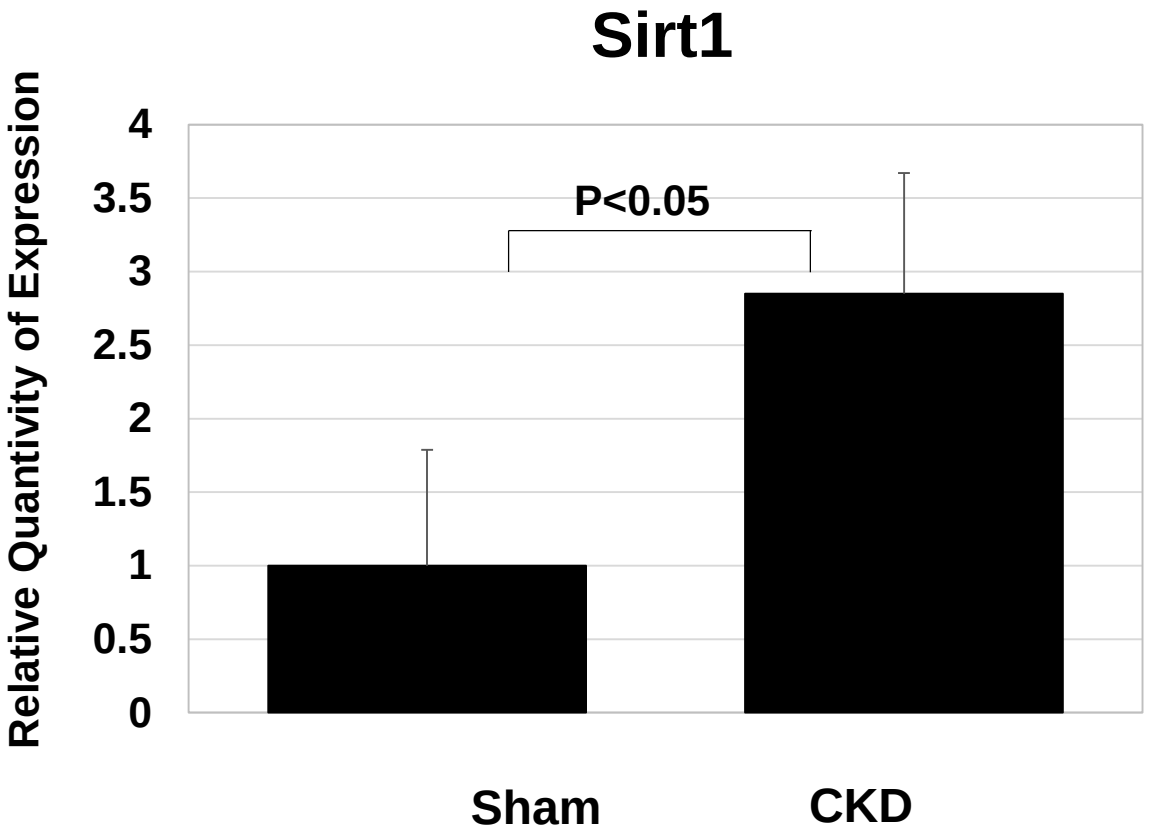
mRNA expression of Sirt1



Results

Sirt1 protein expression level





Summary

- We confirmed that CKD induces cardiac remodeling, including cardiac fibrosis, nuclei infiltration, and myocardial hypertrophy.

- Cardiac remodeling was evidenced by changes in various BNP, TGF-β, MMP-9 and β-MHC markers. In addition, to observing the relationship between the Sirt1 and CKD-induced cardiac remodeling, the expression of Sirt1 was observed by protein, mRNA, and immunofluorescence staining in remodeled heart.

- Thus, we have also demonstrated that the expression of the Sirt1 mRNA and protein was increased in CKD-induced cardiac remodeling in mice.

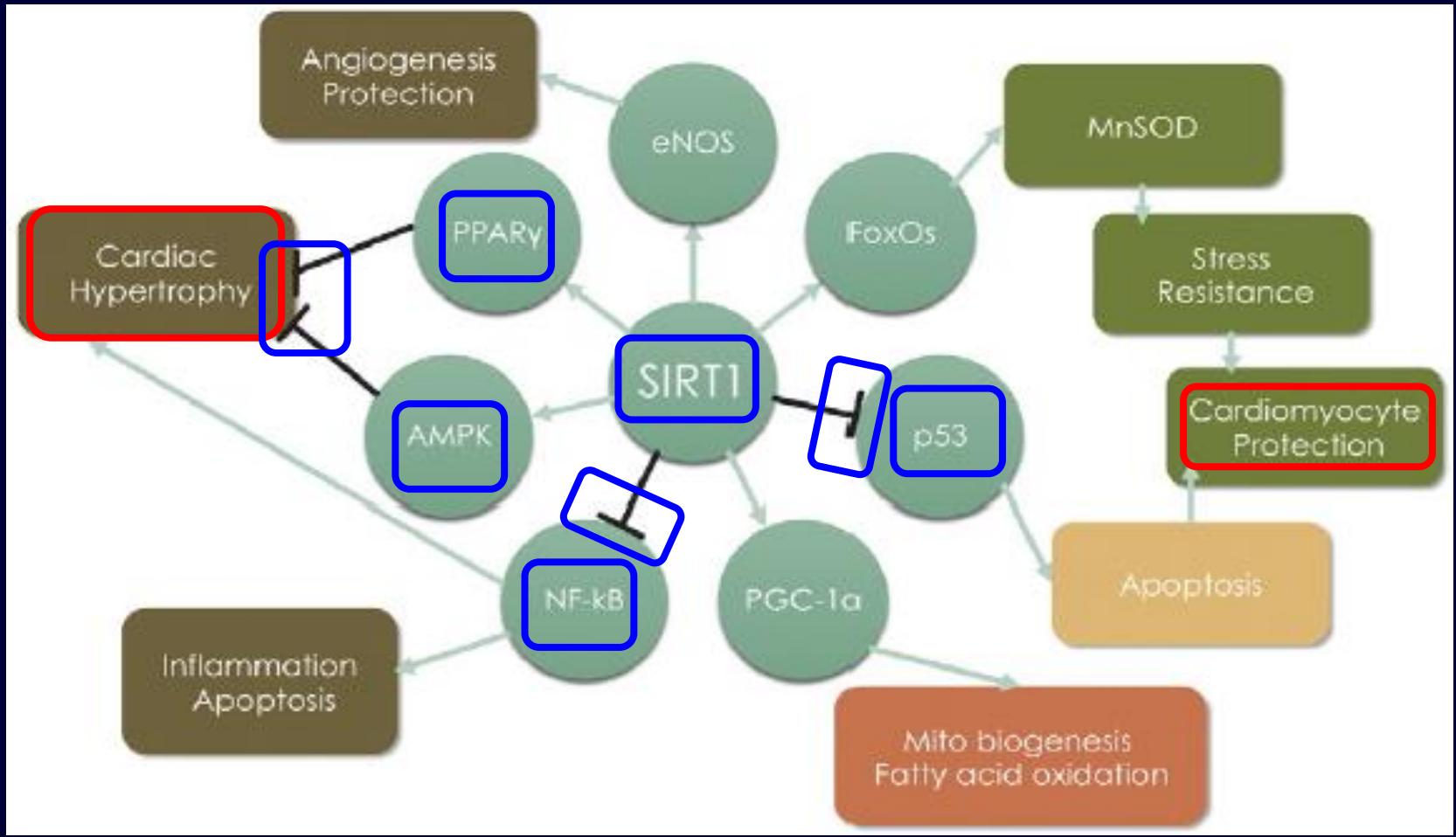
Conclusion

- Our study confirmed CKD-induced cardiac remodeling through various cardiac remodeling markers (BNP, MMP-9, TGF-β and β-MHC) and immunohistochemical staining.

- In addition, our study identified that the increase in the Sirt1 mRNA and protein expression in the heart was associated with CKD-induced cardiac remodeling.

- Thus, an increased expression of sirt1 in the heart during cardiac remodeling appears to be a compensatory response in CKD-induced cardiac remodeling.

Thank you for attention



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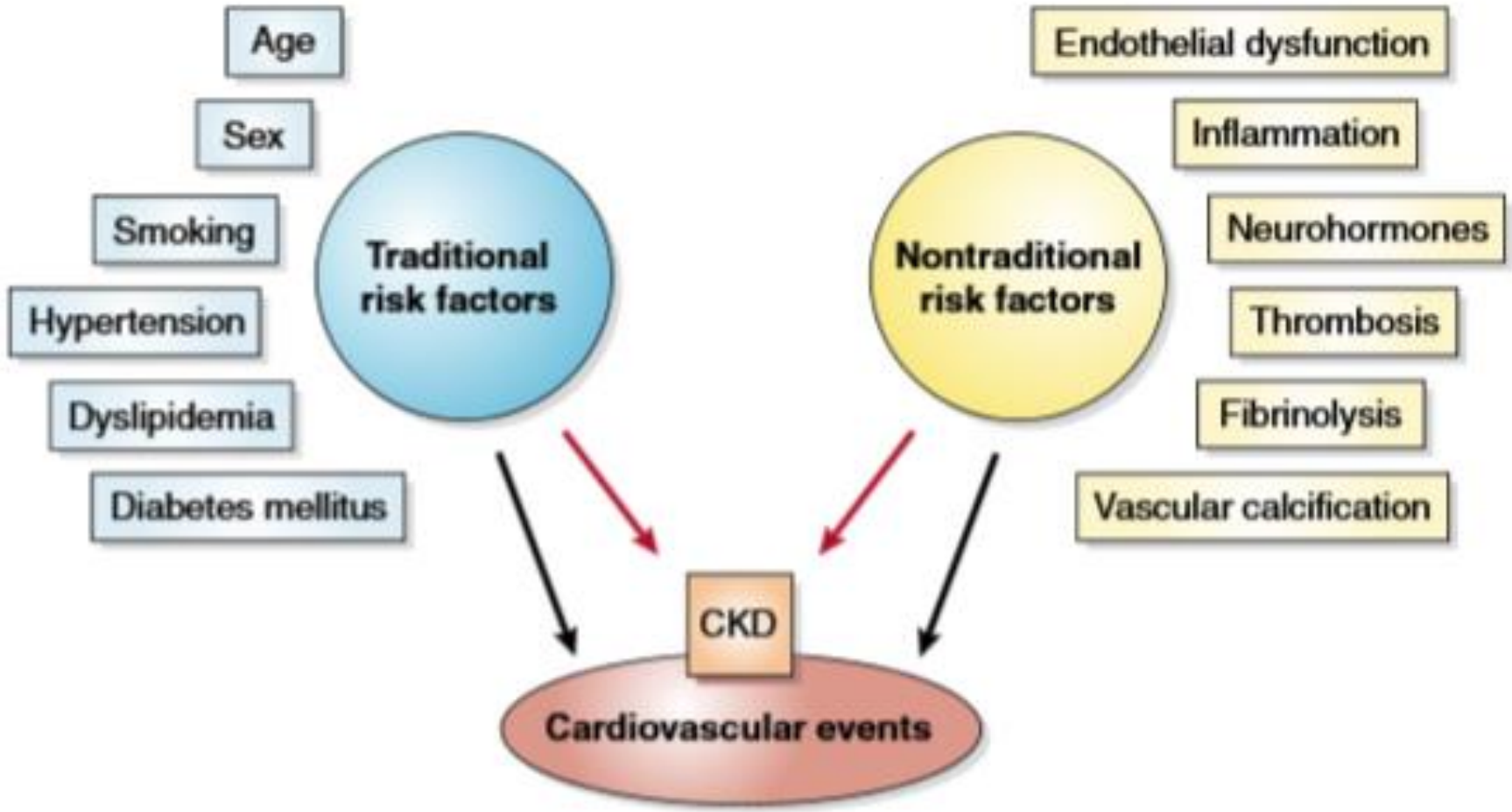
Impact of traditional and nontraditional risk factors and CKD on cardiovascular events



Kidney International (2008) 73 1340–1342