Renoprotective effects of Citral on accelerated and severe lupus nephritis mice by inhibiting activation signal of NLRP3 inflammasome and enhancing Nrf2 activation

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Validation of renoprotective components from TCM against renal inflammation

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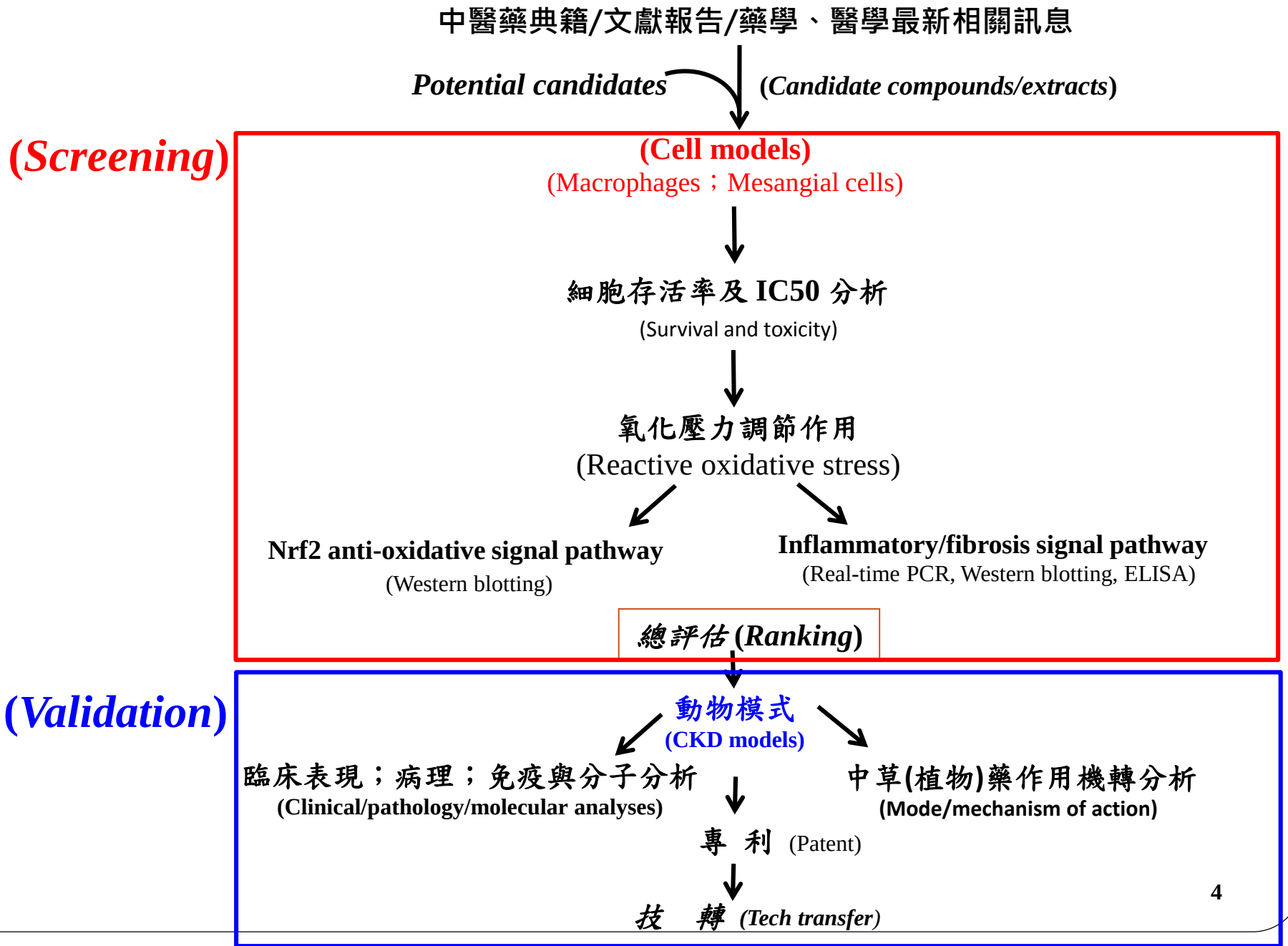
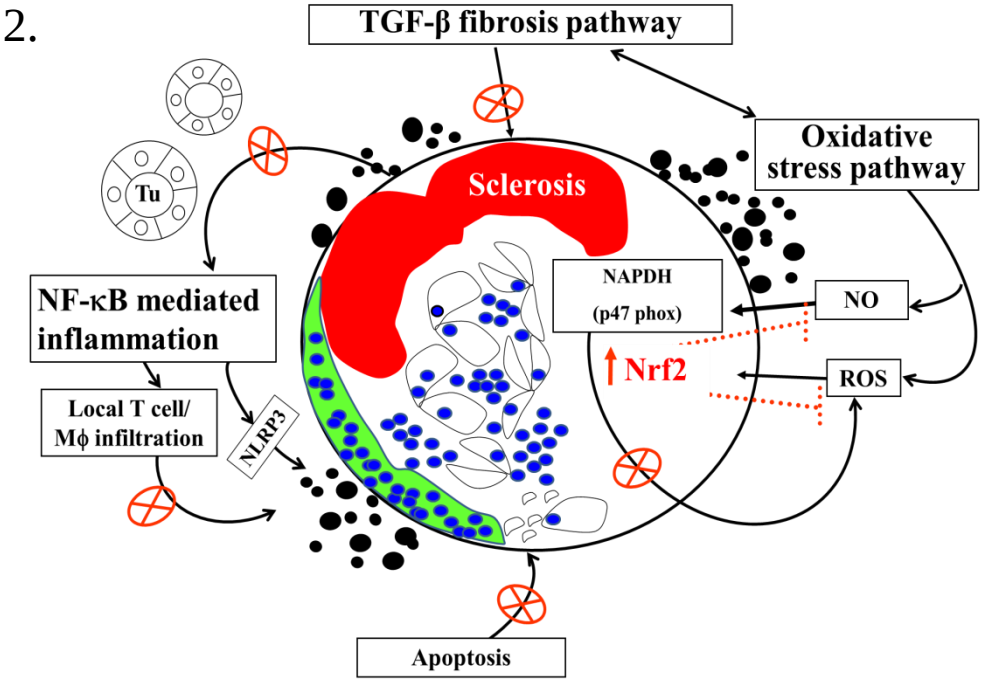

中醫藥典籍/文獻報告/藥學、醫學最新相關訊息
Potential candidates
(Candidate compounds/extracts)
(Screening)
(Cell models)
(Macrophages；Mesangial cells)
細胞存活率及 IC50 分析
(Survival and toxicity)
氧化壓力調節作用
(Reactive oxidative stress)
Nrf2 anti-oxidative signal pathway
(Western blotting)
Inflammatory/fibrosis signal pathway
(Real-time PCR, Western blotting, ELISA)
總評估 (Ranking)
(Validation)
動物模式
(CKD models)
臨床表現；病理；免疫與分子分析
(Clinical/pathology/molecular analyses)
中草(植物)藥作用機轉分析
(Mode/mechanism of action)
專 利 (Patent)
技 轉 (Tech transfer)

1. Among the 225 candidate compounds, 75 items passed the screening of the cell model platform, and totally 9 items were further validated in the mouse models of CKD; 6 items were proved to be reno-protective.

2.

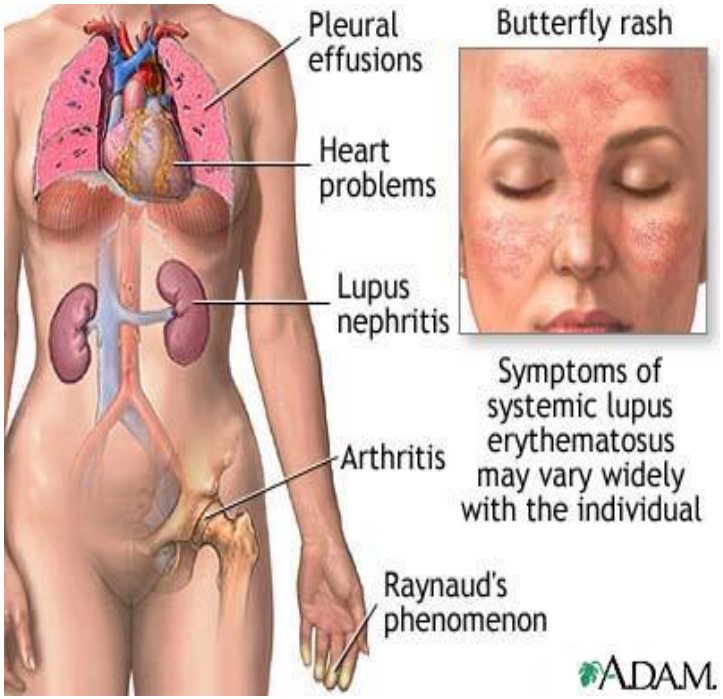


- Tsai PY, Ka SM, Chang JM, Lai JH, Dai MS, Jheng HL, Kuo MT, Chen P, Chen A. Arthritis Rheum. 2012 Jan;64 (1):232-42.
- Tsai PY, Ka SM, Chang JM, Chen HC, Shui HA, Li CY, Hua KF, Chang WL, Huang JJ, Yang SS, Chen A. Free Radic Biol Med. 2011 Aug 1;51 (3):744-54.
- Yang SM, Ka SM*, Hua KF, Wu TH, Chuang YP, Lin YW, Yang SS, Lin SH, Chang JM, Chen A. Free Radic Biol Med. 2013 Apr 6;61C:285-297.
- Tsai PY, Ka SM*, Chao TK, Chang JM, Lin SH, Li CY, Kuo MT, Chen P, Chen A. Free Radic Biol Med. 2011 Jun 1;50 (11):1503-16.
- Kuo-Feng Hua, Ju-Ching Chou, Yulin Lam, Yu-Ling Tasi, Ann Chen, Shuk-Man Ka, Zhanxiong Fang, May-Lan Liu, Feng-Ling Yang, Yu-Liang Yang, Yi-Chich Chiu, Shih-Hsiung Wu. PLoS ONE, 2013. Oct 7;8(10):e76754
- Chen-Lung Ho, Chai-Yi Lin, Shuk-Man Ka, Ann Chen, Yu-Ling Tasi, May-Lan Liu, Yi-Chich Chiu, Kuo-Feng Hua. PLoS ONE, 2013 Oct 4;8(10):e75738.
- Kuo-Feng Hua, Shun-Min Yang, Tzu-Yang Kao, Jia-Ming Chang, Hui-Ling Chen, Yung-Jen Tsai, Ann Chen, Sung-Sen Yang, Louis Kuoping Chao, Shuk-Man Ka. PLOS ONE 2013 Oct 28;8(10):e77794.
- Yang SM, Hua KF, Lin YC, Chen A, Chang JM, Kuoping Chao L, Ho CL, Ka SM*. PLoS One. 2013 Sep 17;8(9):e74871.
- Tsai PY, Ka SM, Chang JM, Chang WL, Huang YJ, Hung LM, Jheng HL, Wu RY, Chen A. Am J Physiol Renal Physiol. 2011 Oct;301 (4):F751-64.
- Ka SM, Kuo YC, Ho PJ, Tsai PY, Hsu YJ, Tsai WJ, Lin YL, Shen CC, Chen A. Rheumatol, 2010 ;49(10):1840-51

Systemic lupus erythematosus (SLE)

- A chronic autoimmune connective tissue disease that can affect any part of the body.
- The disease occurs nine times more often in women than in men, especially child-bearing female
- Produce autoantibodies
  → inflammation and tissue damage
- Kidney involvement of SLE is a common, major complication and can lead to end-stage renal disease (uremia).

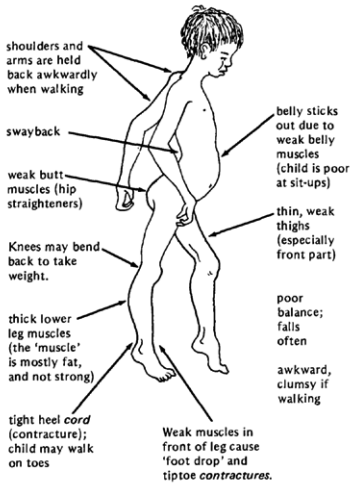
Crispin *et al.*, 2010, *Trends Mol Med*



Current treatment for lupus nephritis

The current therapy for ASLN is to the mainly use corticosteroids or combined corticosteroids with other cytotoxic agents or immunomodulators (such as cyclophosphamide, azathioprine or cyclosporine), although many of them are found to have severe systemic side effects.

- Cyclosphosphamide
- Chlorambucil
- Mycophenolate mofetil
- NSAIDs
- ACE inhibitors



Molino C *et al.*, *Eur J Intern Med*, 20: 447-453, 2009; Yee CS *et al.*, *Ann Rheum Dis*, 63: 525-529, 2004; Benseler SM *et al.*, *Rheumatology (Oxford)*, 48: 176-182, 2009.

Current use of Chinese herbal medicines

- Herbal medicines have been widely used around the world since ancient times.
- Traditional herbs are now widely acknowledged for their immunomodulatory and antiinflammatory activities.

Kuo-Feng Hua et al., PLoS One 2013 8:e77794; Yang SM et al., Free Radic Biol Med. 2013 6. doi:pii; Yang SM et al., PLoS One. 2013 8:e74871; Tsai PY et al., Arthritis Rheum. 2012 64:232-42.; Tsai PY et al., Free Radic Biol Med. 2011 50:1503-16; Tsai PY et al., Free Radic Biol Med. 2011 51:744-54; Tsai PY et al., Am J Physiol Renal Physiol. 2011 301:F751-64.

Citral, a pure compound extract from *Litsea cubeba*

Microcirculation. 2010 Jul;17(5):321-32.

Lemon grass (Cymbopogon citratus) ameliorates murine spontaneous ileitis by decreasing lymphocyte recruitment to the inflamed intestine.

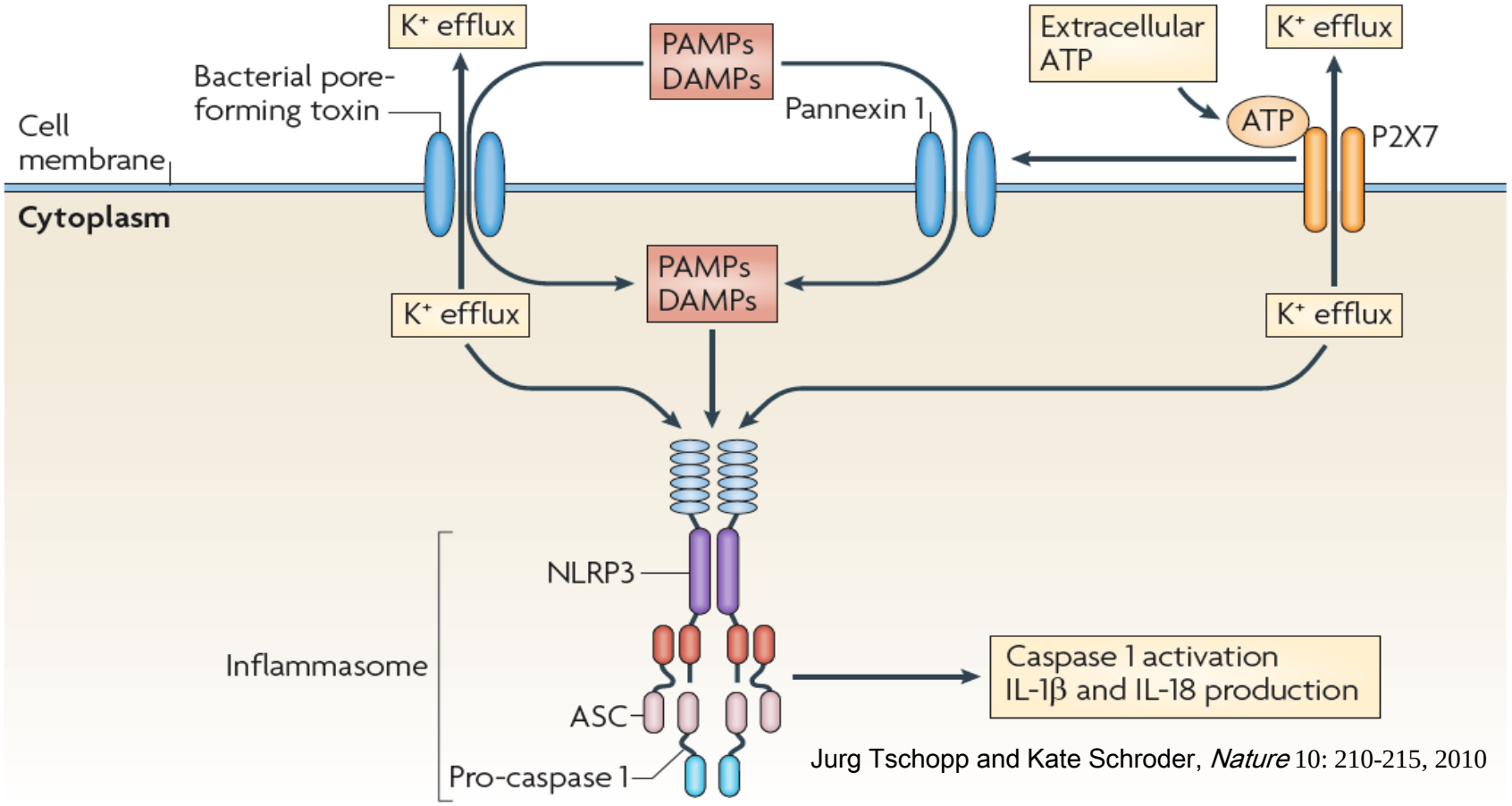
Watanabe C, Hokari R, Komoto S, Kurihara C, Okada Y, Matsunaga H, Takebayashi K, Kawaguchi A, Nagao S, Tsuzuki Y, Yokoyama H, Hibi T, Miura S.

J Agric Food Chem. 2011 May 11;59(9):5062-72. Epub 2011 Apr 4.

Flavored waters: influence of ingredients on antioxidant capacity and terpenoid profile by HS-SPME/GC-MS.

Barroso MF, Noronha JP, Delerue-Matos C, Oliveira MB.

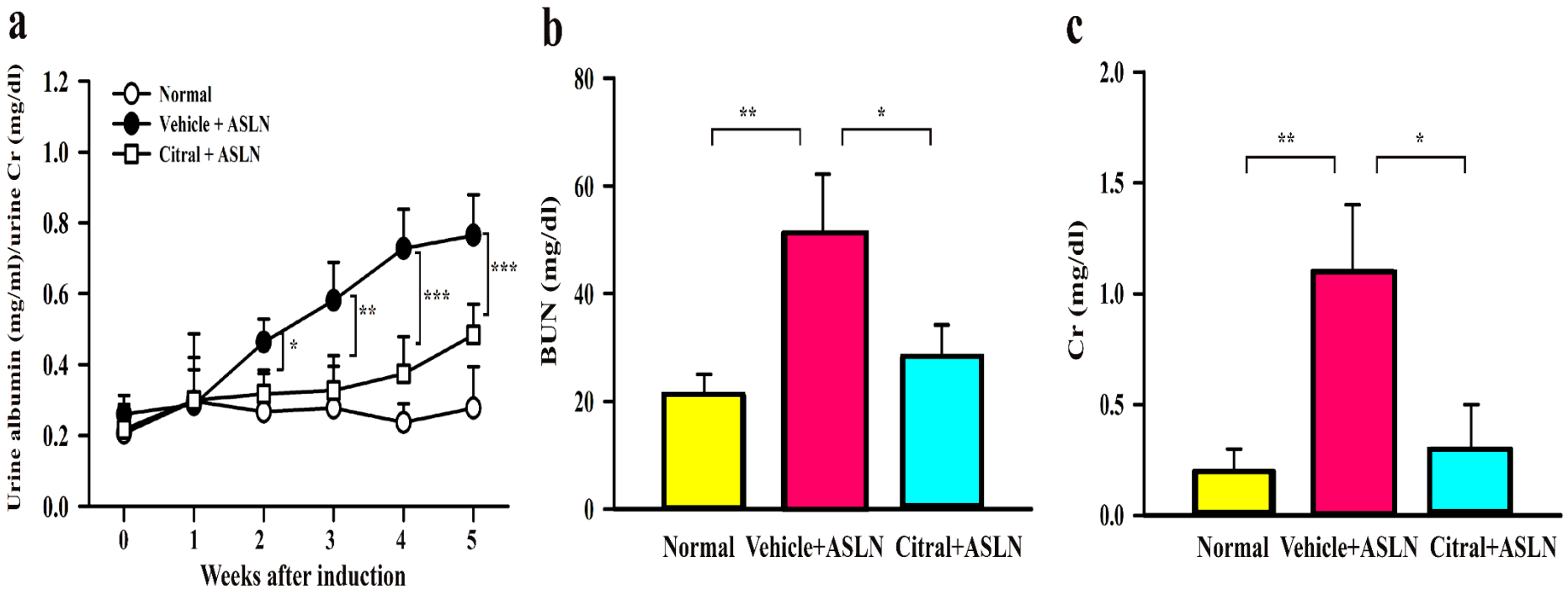
NLRP3 inflammsome



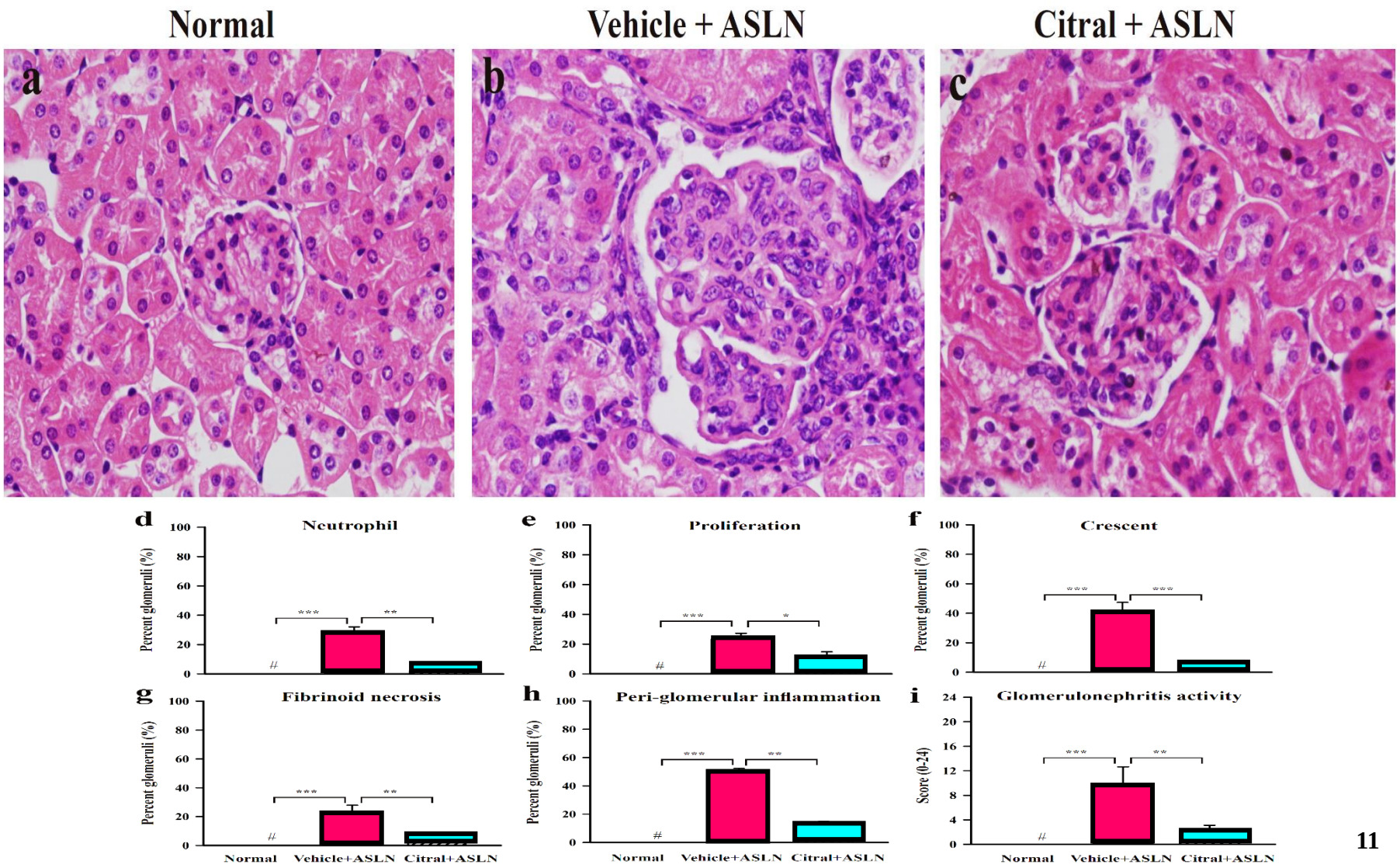
Jurg Tschopp and Kate Schroder, *Nature* 10: 210-215, 2010

PAMPs, pathogen-associated molecular patterns; DAMPS, danger associated molecular patterns; ASC, apoptosis-associated speck-like protein containing a CARD; NACHT, nucleotide-binding and oligomerization domain;LRR, leucine-rich repeat; PYD, pyrin domain

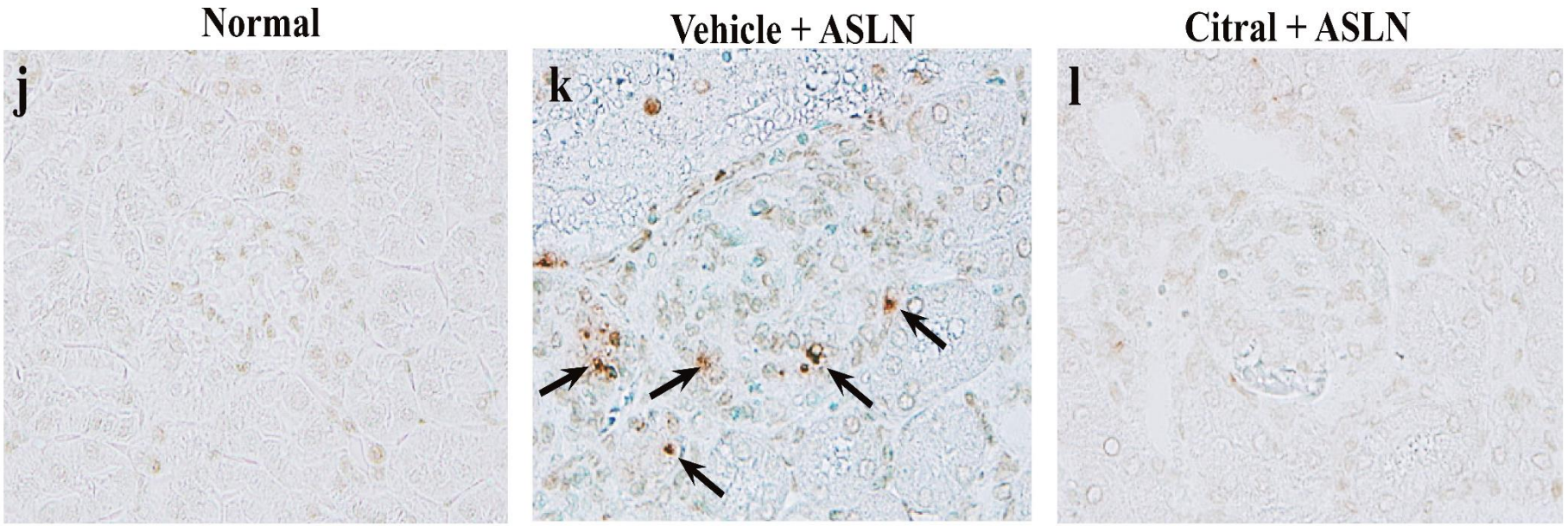
Albuminuria and renal function

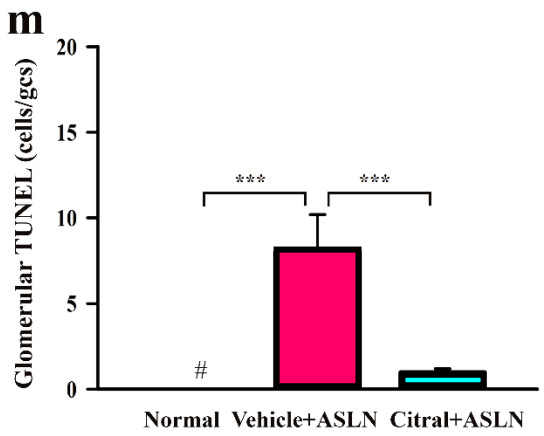


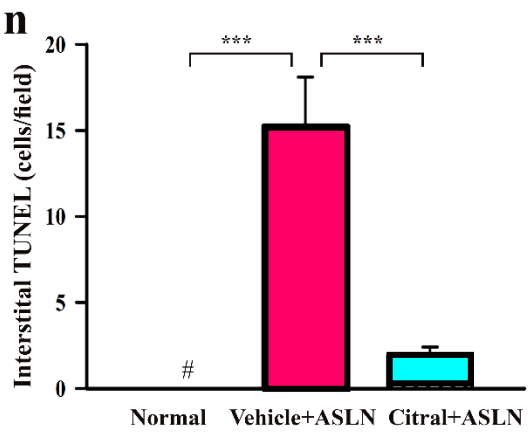
Renal pathology



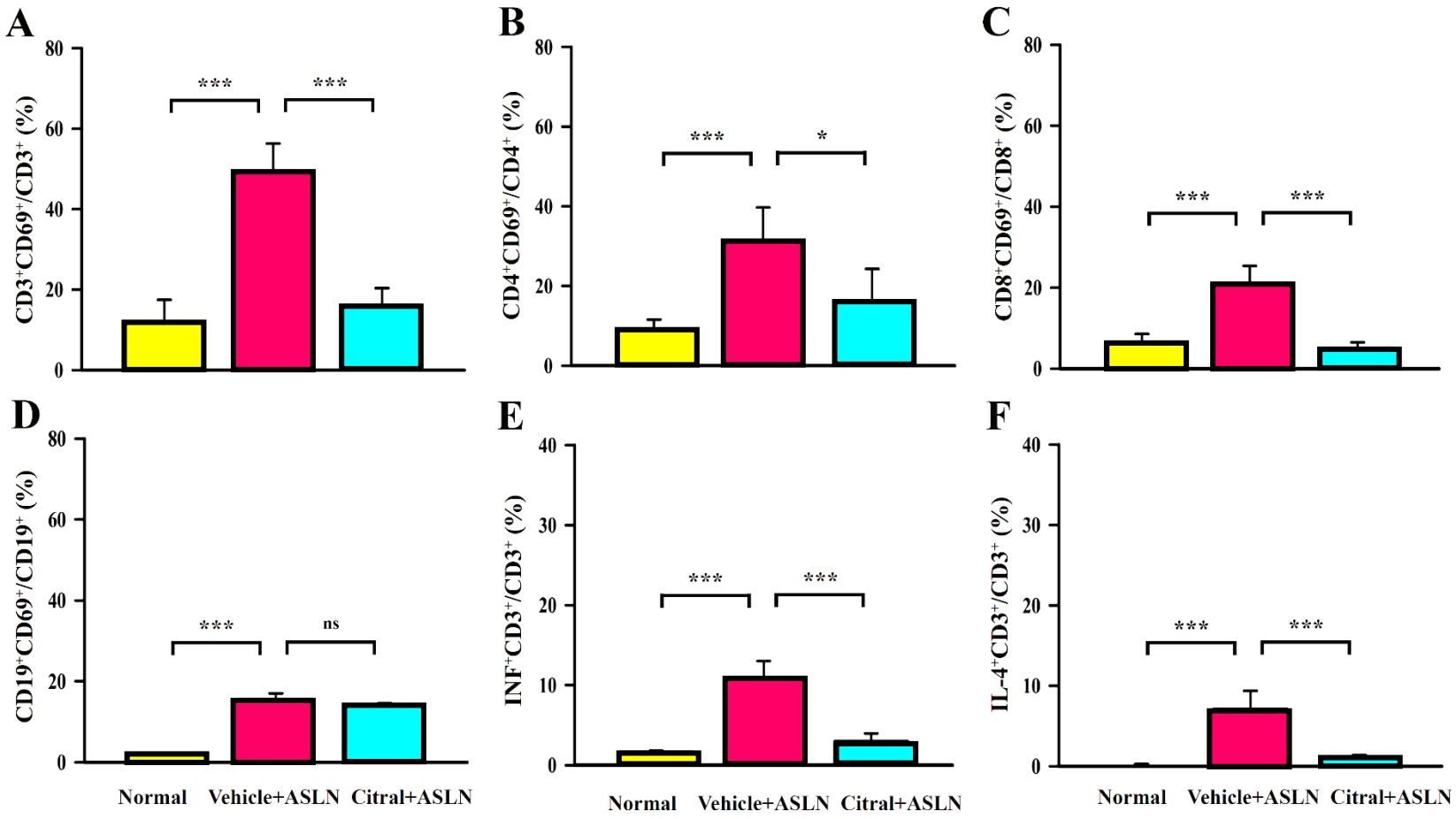
Renal apoptosis



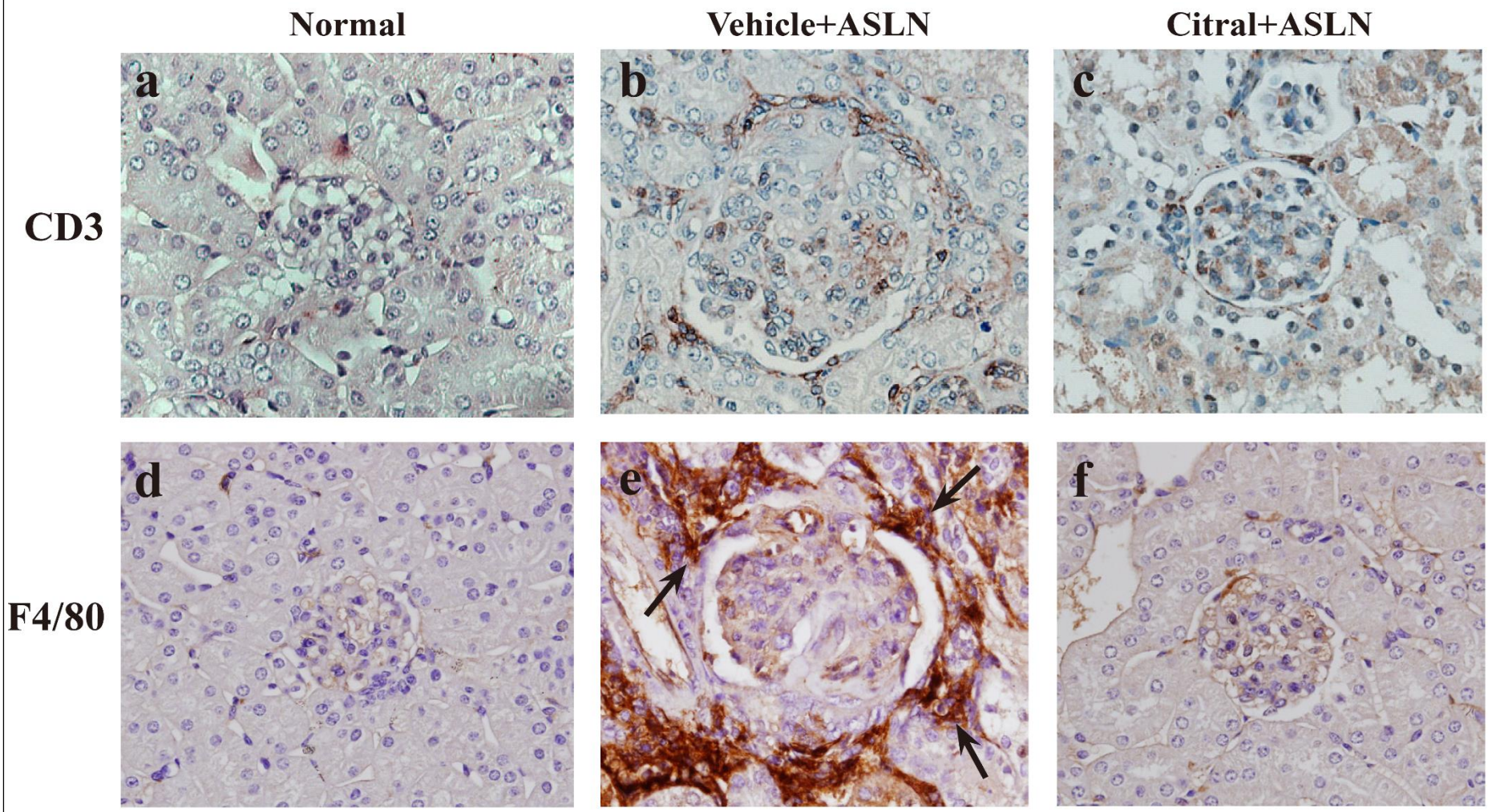




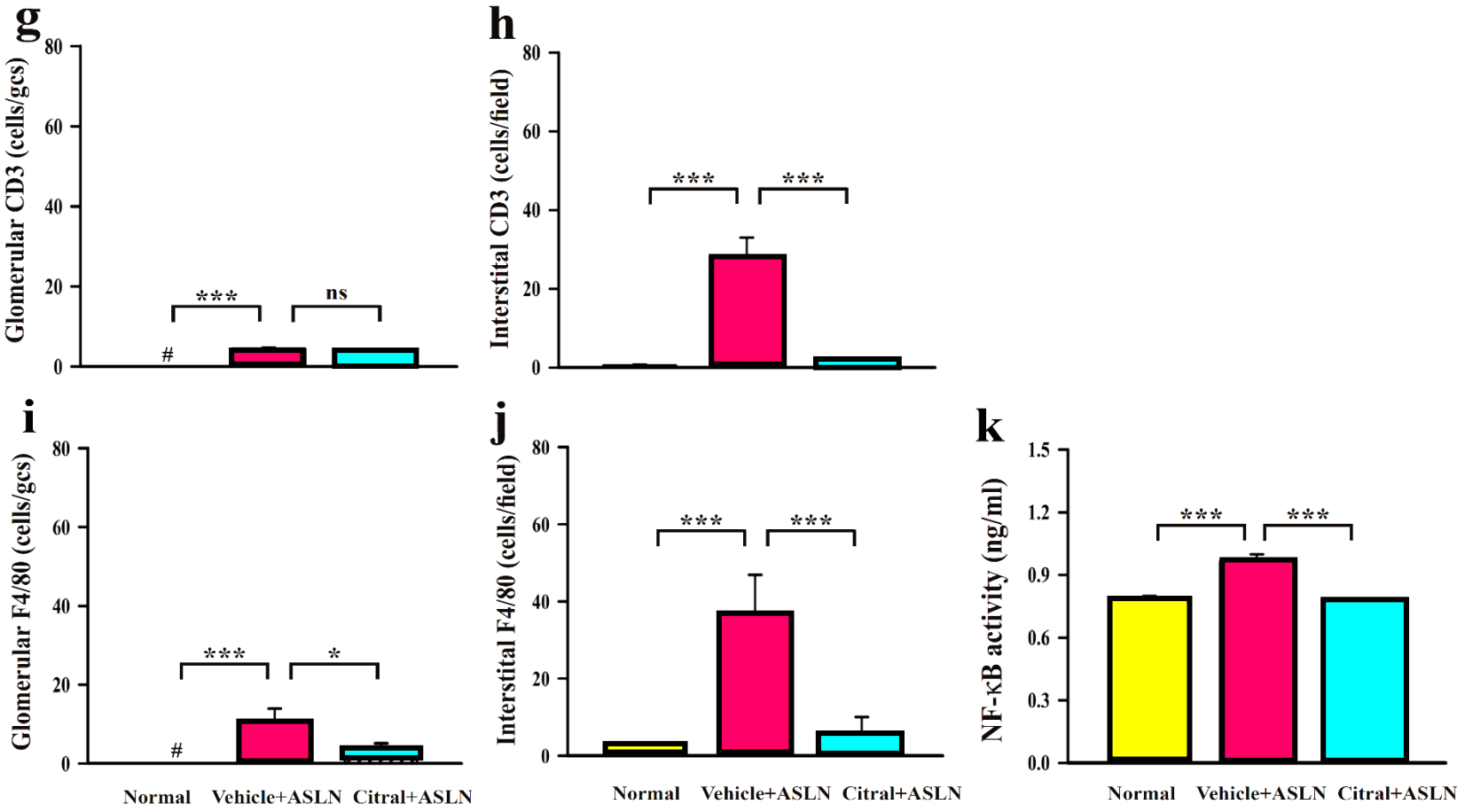
Systemic T cell activation



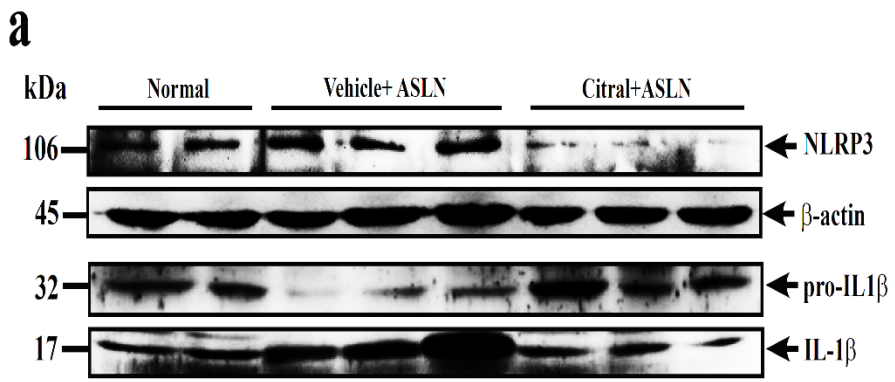
Renal T cell and macrophage infiltration

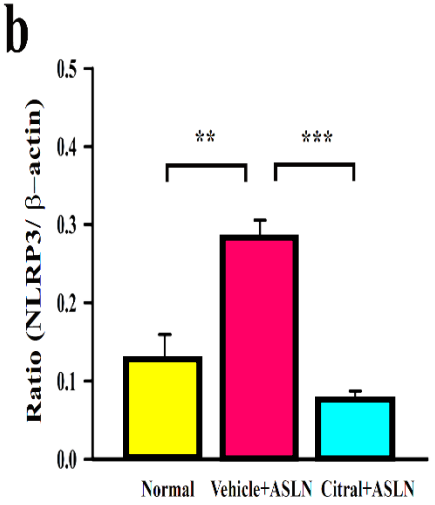


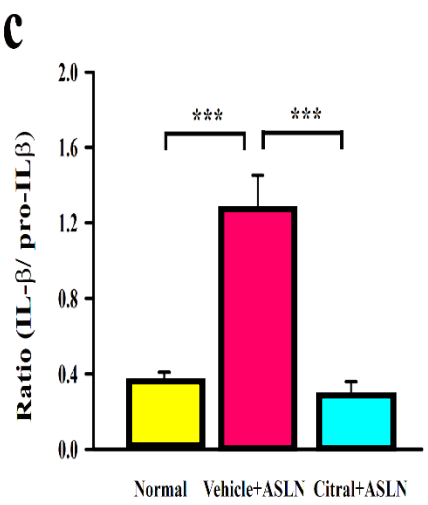
Quantitative analysis

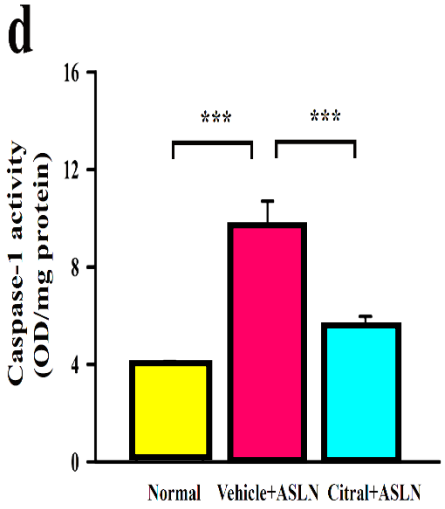


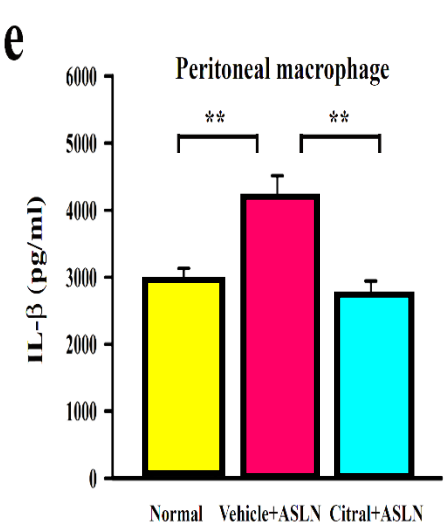
Renal NLRP3 inflammasome signal pathway



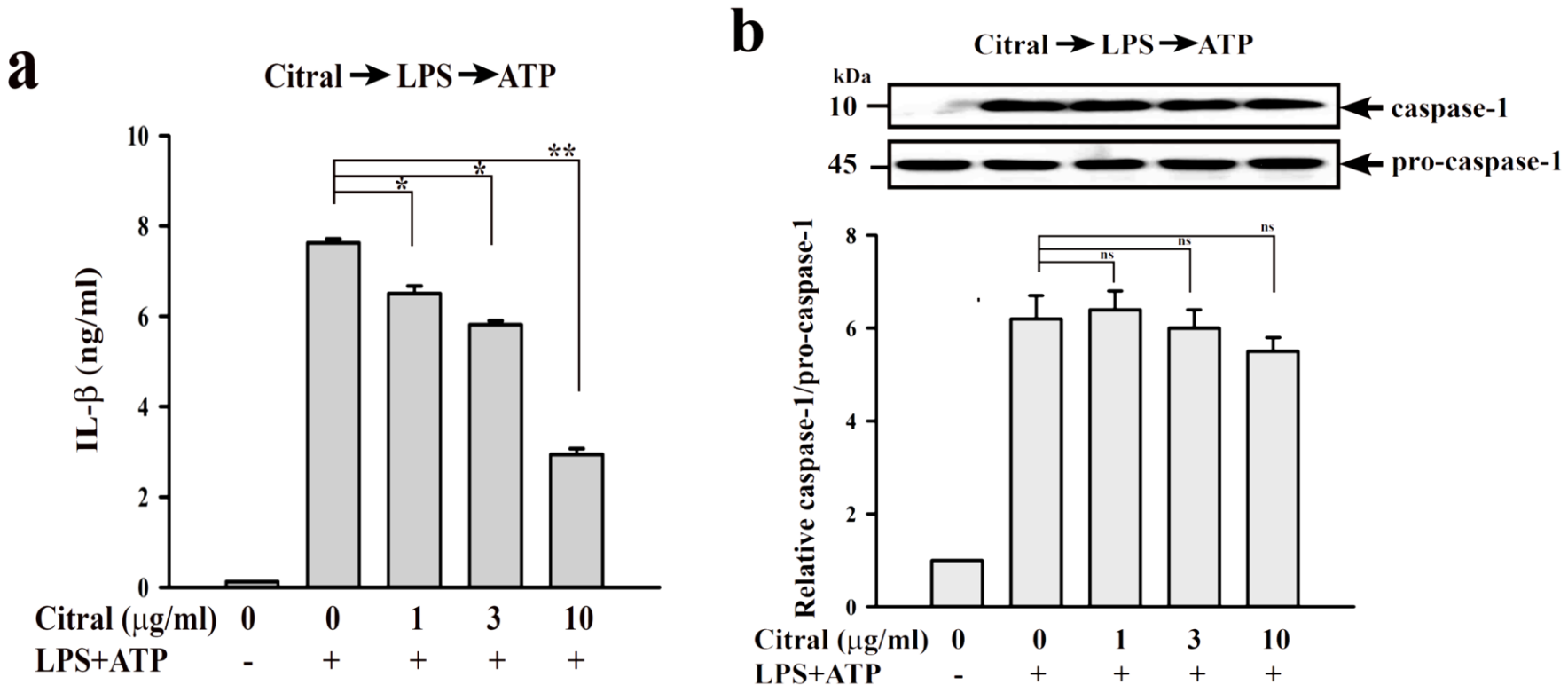




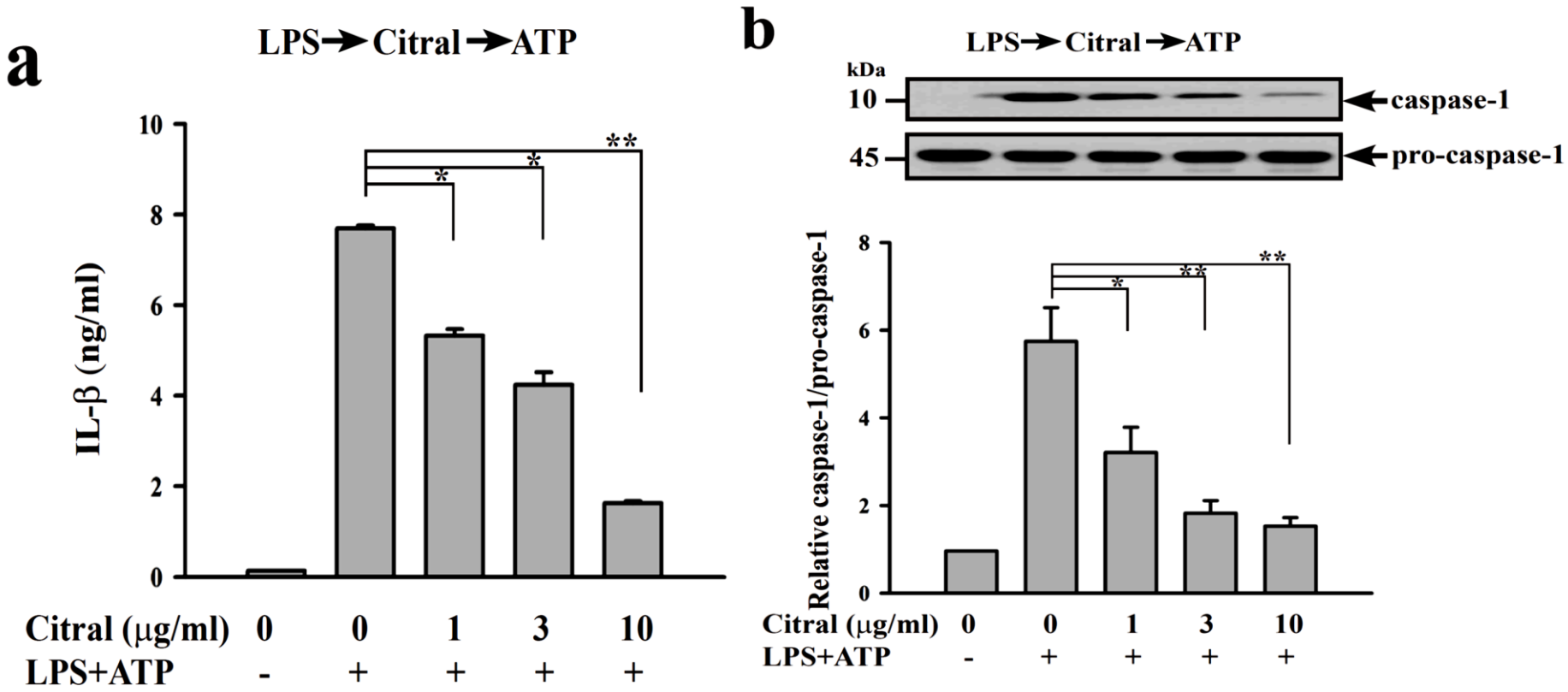




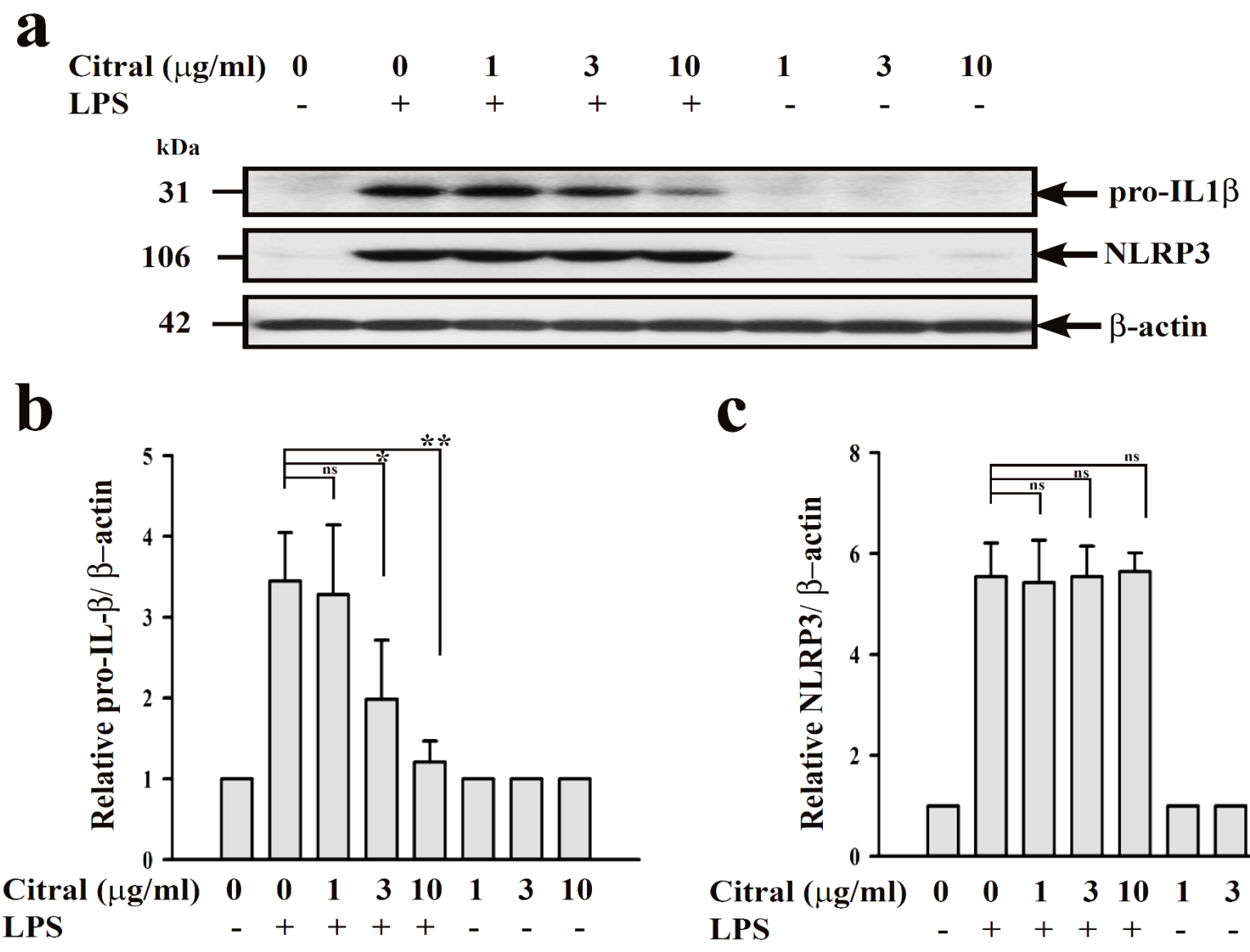
NLRP3 inflammasome -- priming signal



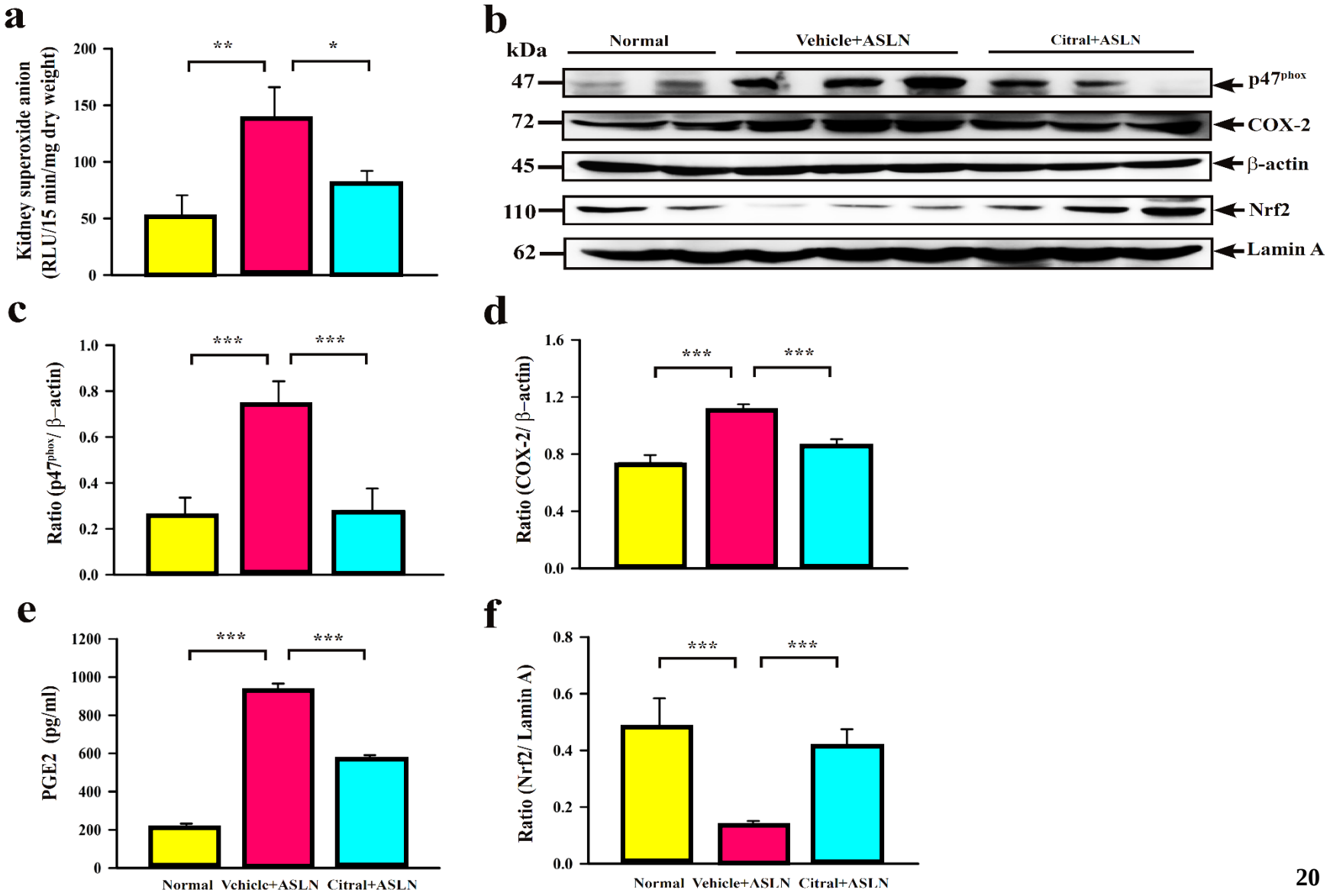
NLRP3 inflammasome -- activation signal



NLRP3 inflammasome–pro-IL-b and NLRP3



Renal Nrf2 pathway activation



Discussion and conclusion

1. Citral inhibited the development of the lupus nephritis model (ASLN), as demonstrated by its effects of reducing albuminuria and improving renal function as well as renal histopathology.
2. The major mechanism (mode) of action of Citral for its renoprotective effect involves inhibition of the activation signal of NLRP3 inflammasome and enhanced activation of Nrf2 antioxidant pathway.
3. Further studies should include pharmacology and toxicology for the compound that is derived a commonly used traditional Chinese medicine (TCM).
4. This work has been considered by Arthritis Ther Res (In revision)

Acknowledgements

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1. MOST 103-2321-B-016-002

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Tri-Service General Hospital, National Defense Medical Center, Taiwan

TSGH-C104-073

Sky lantern festival, Taipei

Thank you very much