Activation of CXCL16/CXCR6 pathway by inflammation accelerates the progression of atherosclerosis in ESRD patients

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Background

Chronic inflammation plays a crucial role in the progression of atherosclerosis (AS). We observed the effects of CXC chemokine ligand 16 (CXCL16)/CXC chemokine receptor 6 (CXCR6) pathway on cholesterol accumulation in the radial arteries of end-stage renal disease (ESRD) patients under inflammatory stress and further investigated its potential mechanisms modulated by purinergic receptor P2X ligand-gated ion channel 7 (P2X7R).

Methods

Fourty ESRD patients were divided into control group (n=17) and inflamed group (n=26) according to plasma C-reactive protein (CRP) level. Biochemical index and lipid profile of patients were measured. Surgically removed tissues from the radial arteries of patients receiving arteriovenostomy were used in the experiments for preliminary evaluation of AS. Foam cell formation was observed by Hematoxylin-eosin (HE) and Filipin staining. CXCL16/CXCR6 pathway related protein expressions, P2X7R protein expressions and the expressions of monocyte chmotactic protein 1 (MCP-1), tumor necrosis factor α (TNFα), and CD68 were detected by immunohistochemistry staining or immunofluorescent staining.

Results

1. Basic clinical data of the patients in the two groups.

Table 1.Basic clinical and biochemical data for the patients

Parameters	Control(n=17)	Inflamed group(n=26)
Weight (kg)	61.22±11.00	61.80±8.59
BMI(kg/m^2)	22.73±3.29	22.72±2.05
WC (cm)	79.75±10.81	81.17±8.43
Age (y)	52.53±9.40	55.12±13.33
RBC (10^{12}/L)	2.60±0.61	2.78±0.63
Hb (g/L)	78.00(55.50,85.50)	81.00(63.75,92.75)
TP (g/L)	62.12±8.21	60.43±8.28
ALB (g/L)	36.88±4.25	35.36±4.16
ALT (IU/L)	13.00(11.00,18.00)	12.00(7.75,23.00)
AST (IU/L)	16.00(12.50,20.00)	17.00(13.00,20.00)
TG (mmol/L)	1.30(0.68,2.10)	1.26(1.00,1.70)
T-CHO (mmol/L)	3.56(2.75,4.12)	3.75(3.02,4.59)
LDL (mmol/L)	1.81±0.58	2.07±0.74
HDL (mmol/L)	1.01(0.81,1.21)	1.06(0.81,1.25)
ApoA1 (mmol/L)	1.13(1.03,1.28)	1.12(0.96,1.38)
ApoB (mmol/L)	0.71±0.22	0.78±0.23
Lp(a) (mmol/L)	207.00(134.00,324.00)	249.00(154.00,415.00)
Ca (mmol/L)	2.10±0.24	2.00±0.25
P (mmol/L)	2.08±0.53	1.96±0.74
Ca × P (mmol/L)^2	54.41±11.26	50.13±19.58
iPTH (pg/mL)	335.30(194.05,854.70)	323.00(144.32,467.30)

There was no difference compared every index in the inflamed group with that in the control, P>0.05

2. Inflammation increased inflammatory cytokines expression and macrophage infiltration.

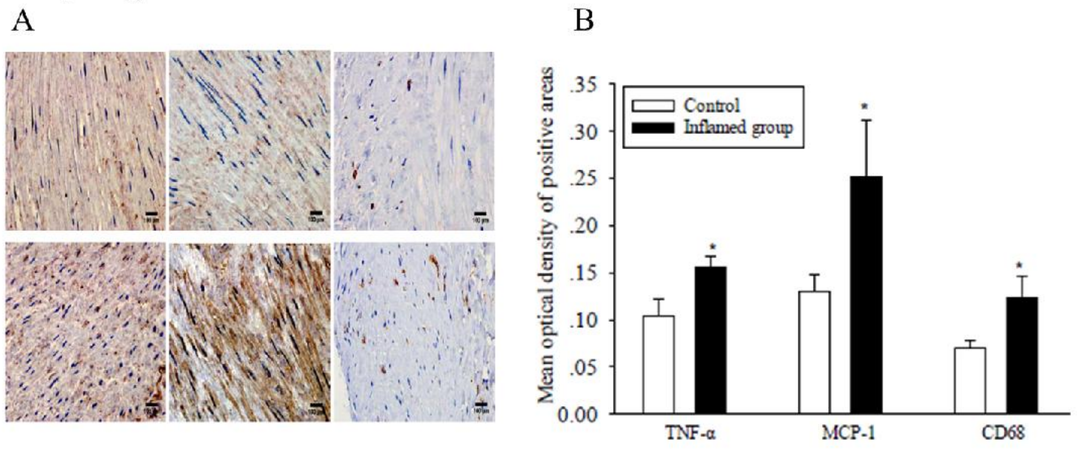


Fig.1 The local inflammation status in the radial artery was examined by immunohistochemical staining. (A, brown color,original magnification ×400). The values of semiquantitative analysis for the positive areas were expressed as the mean ±SD from five patients in each group(n=27 for control, n=26 for inflamed group). * P<0.05 vs control. (B). The protein expression of CD68 in the kidneys of the mice was measured by immunohistochemical staining. The positive areas were stained brown in cross-sections of kidneys (C, original magnification, ×400). The values of semiquantitative analysis for the positive areas were expressed as the mean ±SD (n=17 for control, n=26 for inflamed group). *P<0.05vs. control .

3. Inflammation induced foam cell formation of radial arteries.

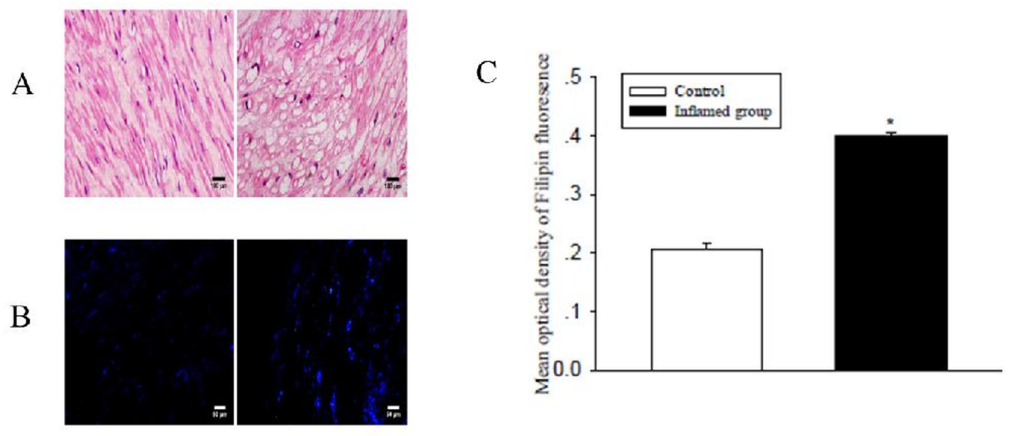
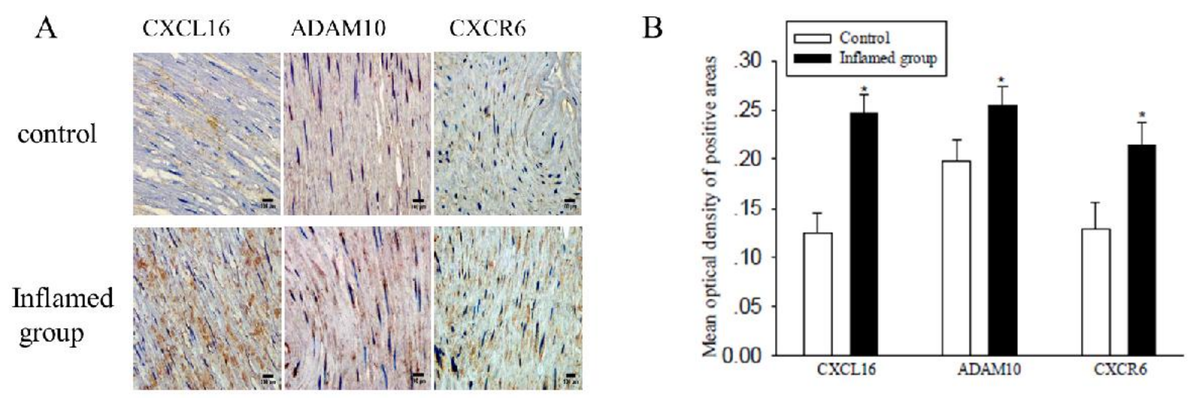


Fig.2 The lipid accumulation in the radial arteries was checked by hematoxylin-eosin staining (A, original magnification × 400) and Filipin staining(B, original magnification ×200) . The values of semiquantitative analysis for the positive areas were expressed as the mean ±SD from five patients in each group (n=17 for control, n=26 for inflamed group). *P<0.05 *vs.* control (C).

4. Inflammation increased protein expressions of CXCL16 pathway in radial arteries.



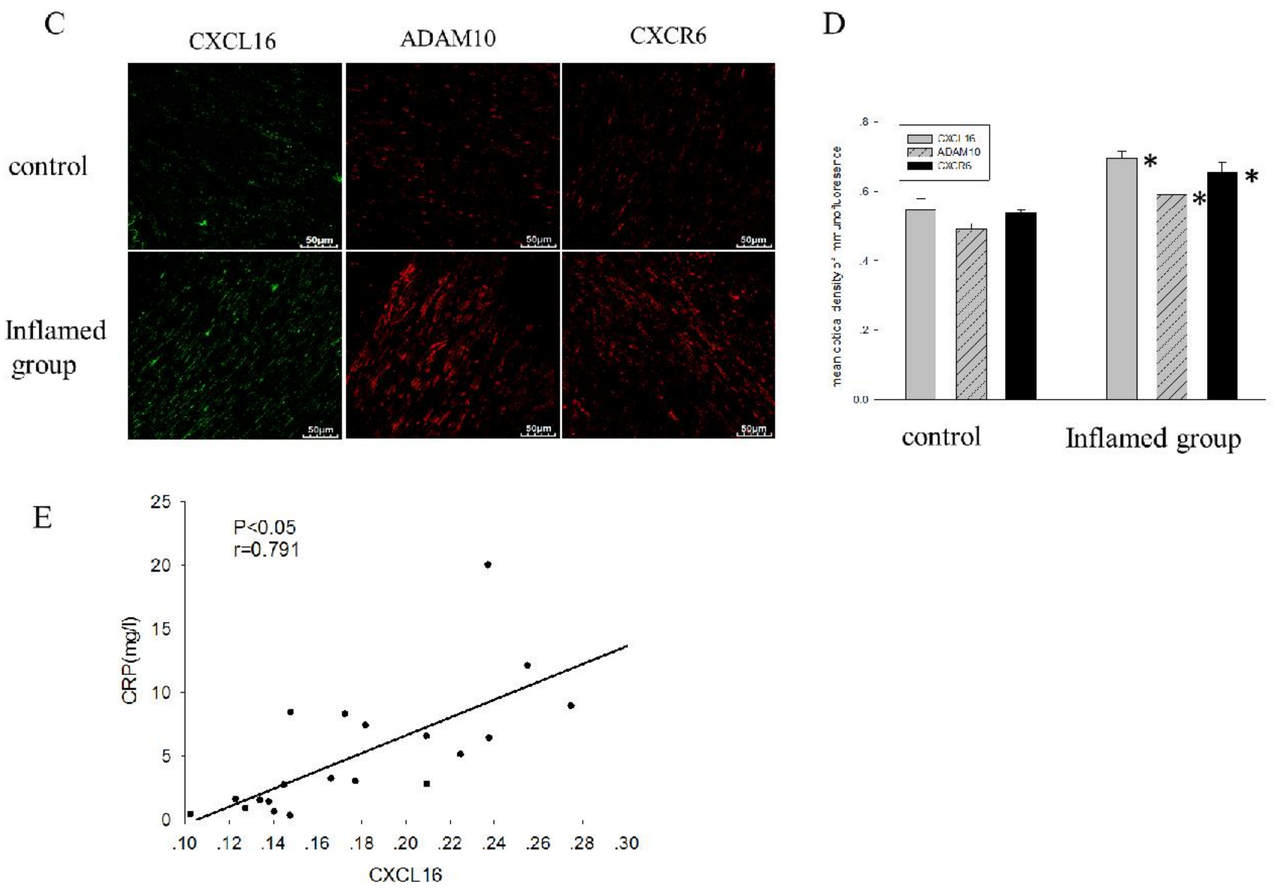
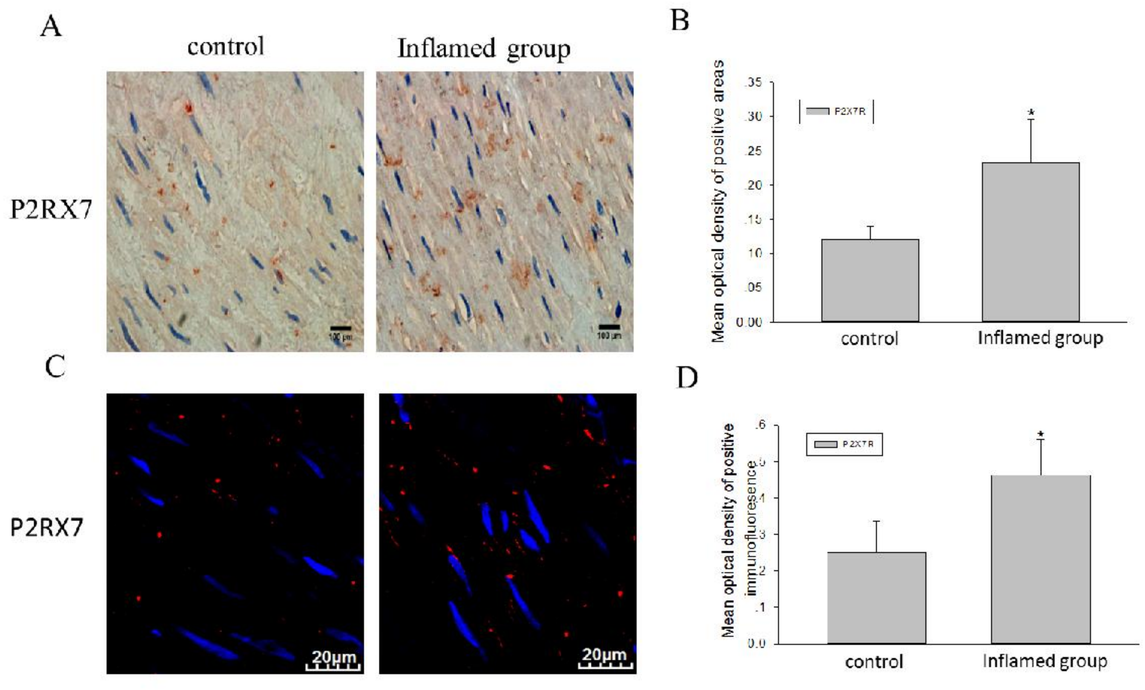
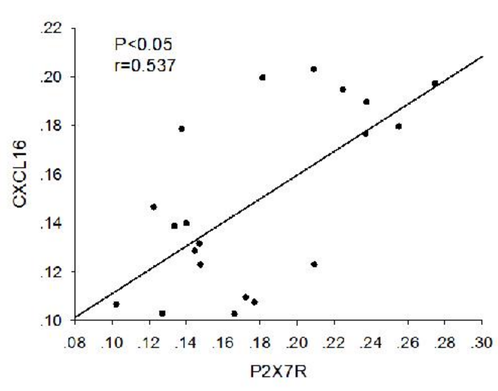


Fig.3 The protein expression of CXCL16, ADAM10 and CXCR6 in the radial artery were measured by immunohistochemical staining (A, brown colour, original magnification×400) and immunofluorescent staining (C, original magnification×400) . The values of semiquantitative analysis for the positive areas were expressed as the mean ±SD from five patients in each group(n=16 for control, n=27 for inflamed group). * P<0.05 *vs* control(B,D) Correlation analysis of plasma CRP level with CXCL16 expression (E).

5. The increased protein expressions of the CXCL16 pathway was relevant with P2X7R expression of the radial arteries.





Conclusion

Inflammation contributed to foam cell formation in the radial arteries of ESRD patients via the activation of the CXCL16/CXCR6 pathway, which is possibly regulated by P2X7R activation.

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