MP255

ATF4/p16 signaling activation accelerates premature senescence of renal tubular epithelial cells （RTECs）in diabetic nephropathy

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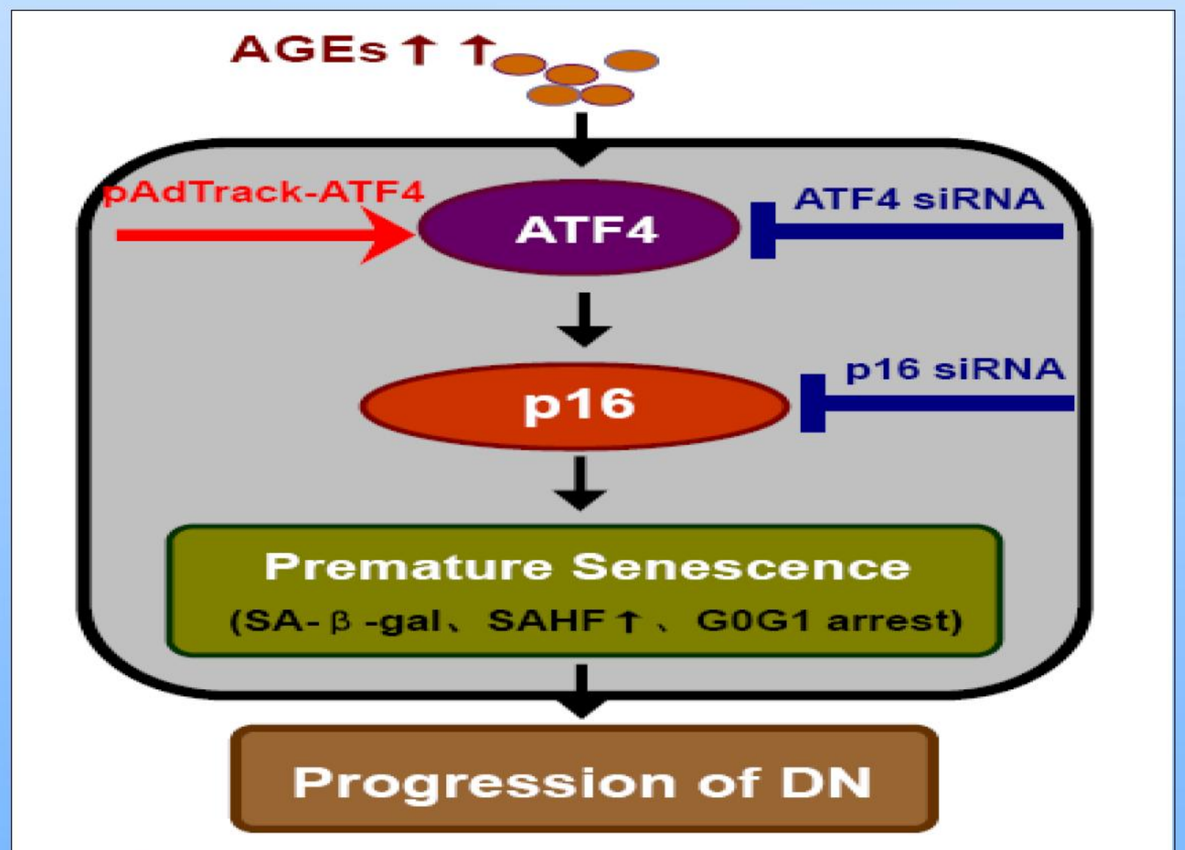
Objective

Recent studies reveal an accelerated senescence of RTECs in DN. However, its mechanism remains unclear. ATF4 activation is linked to p16 expression in oncogene-induced cellular senescence. This study focused on the role of ATF4/p16 activation in premature senescence of RTECs in DN.

Route



Results

1. AGEs-induced premature senescence is dependent on p16 activation.

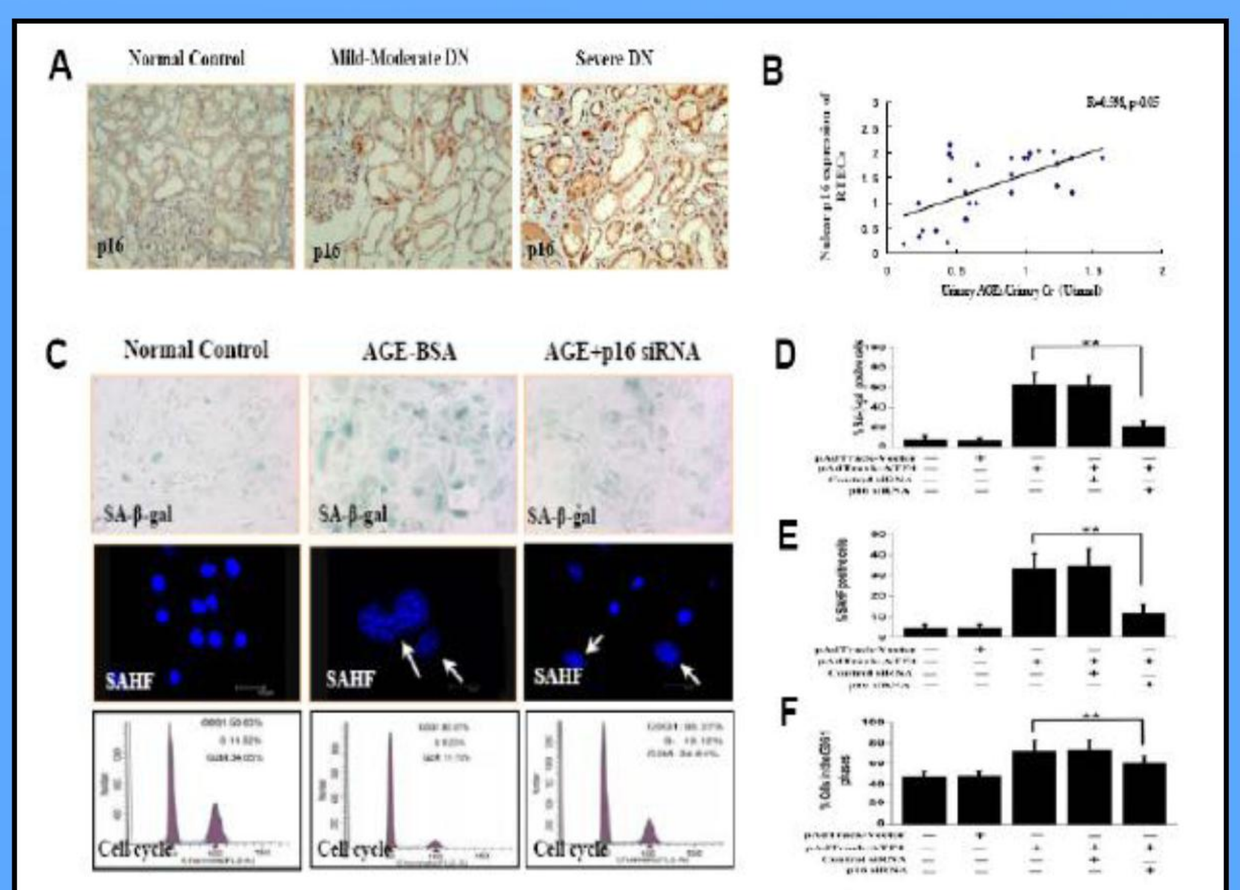


Figure 1. AGEs-induced premature senescence is dependent on p16 activation.

A:Immunohistochemistry showed p16 expression extensively increased in RTECs of DN patients ;

B:Correlation analyses showed p16 expression was positively correlated with U_{AGEs}/Ucr in DN patients;

C–F: p16 gene silencing suppressed AGE-induced premature senescence.

2. ATF4/p16 pathway activation is essential for AGEs-induced premature senescence.

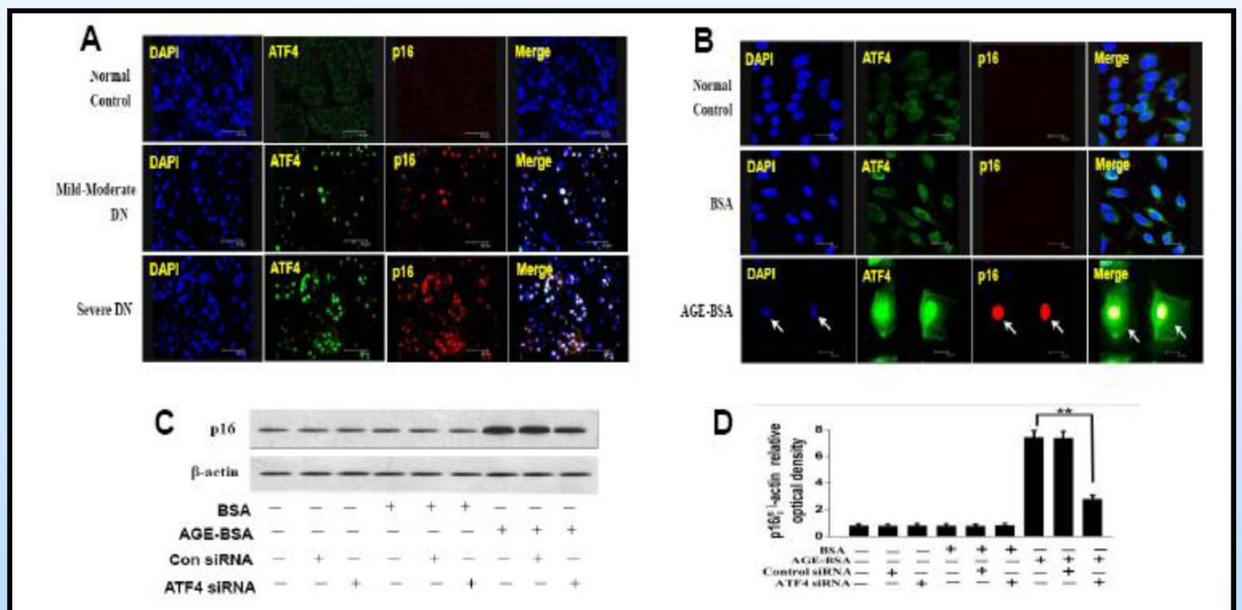


Figure 2. Activation of the ATF4/p16 pathway mediates AGEs-induced premature senescence.

A: Immunofluorescence showed ATF4 and p16 were co-located in RTECs of DN patients ;

B: Immunofluorescence showed ATF4 and p16 were co-located in the nucleus of the same SAHF positive cells after AGEs stimulation;

C—G：ATF4 gene silencing suppressed AGE-induced p16 expression and premature senescence.

3. ATF4/p16 pathway activation directly induces premature senescence.

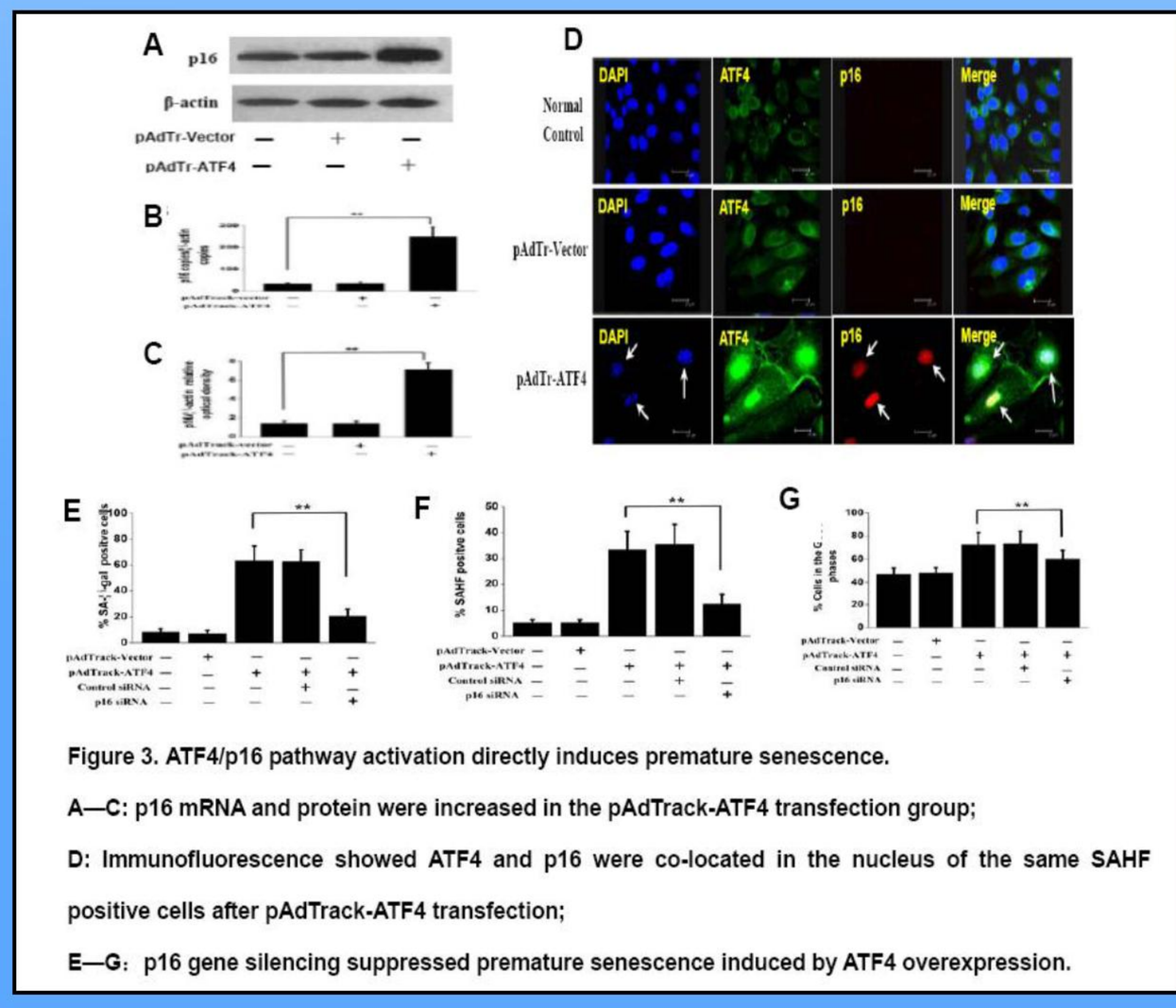


Figure 3. ATF4/p16 pathway activation directly induces premature senescence.

A—C: p16 mRNA and protein were increased in the pAdTrack-ATF4 transfection group;

D: Immunofluorescence showed ATF4 and p16 were co-located in the nucleus of the same SAHF positive cells after pAdTrack-ATF4 transfection;

E—G：p16 gene silencing suppressed premature senescence induced by ATF4 overexpression.

Conclusion

Our study indicates that ATF4/p16 signaling activation is an important mechanism of AGEs-induced premature senescence of RTECs during DN.