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Erythropoiesis stimulating agent inhibit proximal tubular cell G2/M arrest to attenuate renal fibrosis

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Objectives: G2/M cell cycle arrest of proximal tubular epithelial cells(PTC) after severe acute kidney injury results in maladaptive repair that promote progression to chronic kidney disease(CKD). Aim of the study is to investigate whether erythropoiesis stimulating agent may regulate G2/M arrest and ameliorate renal fibrosis.

Methods: Human kidney 2(HK-2) cells were cultured in hypoxic chamber for 48 hours with or without darbepoetin alfa(DARB) at low(0.5ug/ml) or high(5ug/ml) concentration and cell cycles were assessed using flow cytometry analysis. DARB(0.5 ug/kg, 25 ug/kg) was given intraperitoneally to mouse model of unilateral ureteral obstruction(UUO) and immunohistochemistry as well as western blot analysis were performed to assess renal fibrosis and cell cycle regulatory proteins.

Results: In HK-2 cell, the 48 hours of hypoxia induced significant increase in the proportion of HK-2 cells in G2/M phase arrest (31.7±0.5%vs16.9±3.7%, P<0.05), whereas both low and high dose DARB significantly decreased proportion of G2/M arrest cells (31.7±0.5%vs24.1±0.7% and 18.7±4.7%, P<0.05, respectively). Vehicle treated UUO kidneys(UUO+PBS) showed increased tubular injury (15.92±6.96vs1.00±0.21, P<0.05), greater tubulointerstitial fibrosis(TIF, 10.80±1.43 vs 1.00±0.37, P<0.05), higher TGF-β1 and α-SMA expressions than the sham-operated kidneys (13.52±0.96 vs 1.00±0.65 ;14.03±2.25 vs 1.00±0.48, P<0.05, respectively). DARB dose dependently attenuated tubular injury (11.83±3.29 vs 11.15±3.53 vs15.92±6.96, P<0.05), TIF (6.79±1.32 vs 2.92±0.88 vs 10.80±1.43, P<0.05), TGF-β1 and α-SMA expression (7.15±0.69 vs 3.91±0.41 vs 13.52±0.96 ;8.26±0.64 vs 2.65±1.03 vs 14.03±2.25, P<0.05). UUO+PBS showed increase in p53, p21 and p-Histone H3 expression (8.67±1.81 vs 1.00±0.13, 61.18±5.71 vs 1.00±0.14, 11.58±1.90 vs 1.00±0.17, P<0.05, respectively) indicating increased G2/M arrest of PTC and these features were dose dependently attenuated by DARB (0.64±0.29 vs 0.38±0.26 vs 8.67±1.81; 8.11±1.64 vs 0.83±0.07 vs 61.18±5.71; 1.69±0.66 vs 0.89±0.15 vs 11.58±1.90, P<0.05, low vs high vs vehicle, respectively).

Conclusions: Our findings indicate DARB treatment may decrease G2/M cell phase arrest and attenuate renal fibrosis suggesting a new renoprotective mechanism for DARB.