NLRP3 Activation Induced by Neutrophil Extracellular Traps Sustains Inflammatory Response in the Diabetic Wound

Conclusion

NLRP3 inflammasome expression and activation induced by NETs attribute to the infiltration of innate immune cell and sustains inflammatory response in diabetic wound.

Method

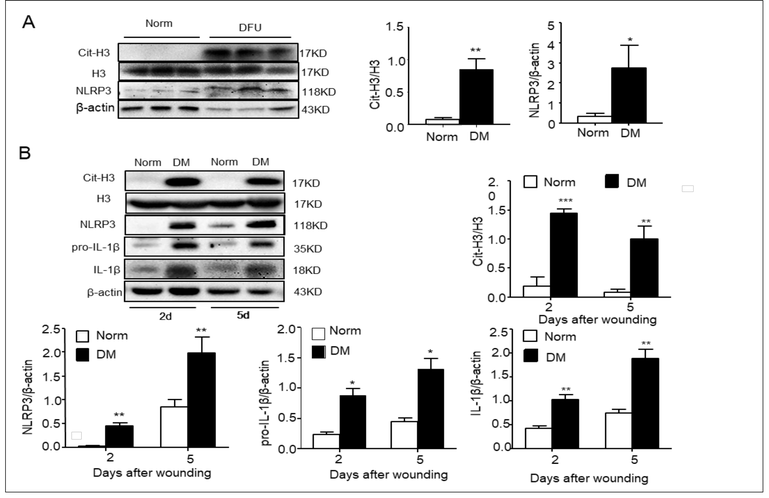
WB, IF and co-IP were used to detect NETs, the level of NLRP3 inflammasome in diabetic foot ulcer patients. After intervention of NETs by Dnase I , the activation of NLRP3 inflammasome were detected, and mechanism was explored. Type I diabetic rats were induced by STZ. Dnase I was given to observe the effect of NETs on NLRP3 inflammsome, inflammatory cell infiltration and wound healing. Statistical analysis was performed using the Student's t-test or ANOVA. Data were analysed by using SPSS 19. All statistical analysis was performed using the GraphPad Prism. The value of $p < 0.05$ was considered statistically significant. Results are expressed as the mean ± SD.

Introduction

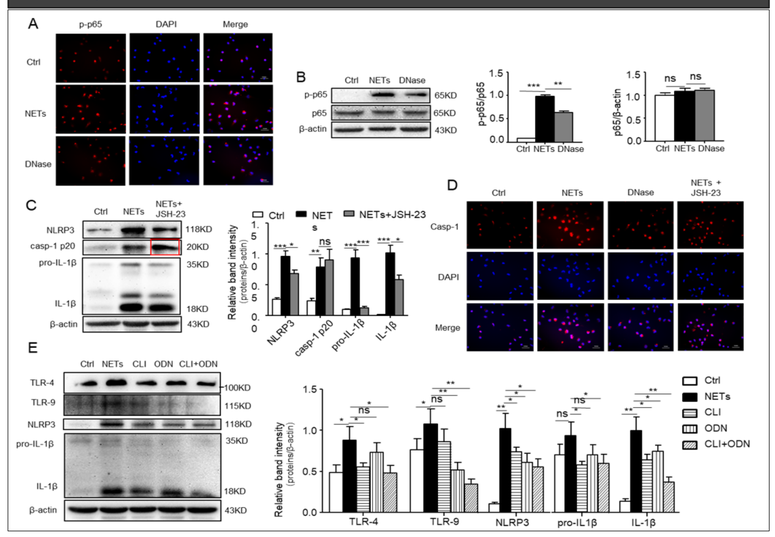
Persistent inflammatory response in the diabetic wound impairs the healing process, resulting in signifcant morbidity and mortality. Mounting evidence indicate that the activation of NLRP3 inflammasome in macrophages contributes to the sustained inflammatory response and impaired wound healing associated with diabetes. However, the main trigger of NLRP3 inflammasome in the wounds is not known. Neutrophils, as sentinels of the innate immune system and key stimulators of macrophage, are immune cells that play the main role in the early phase of healing. Neutrophils release extracellular traps (NETs)as defense against pathogens. On the other hand, NETs induce tissue damage. NETs have been detected in the diabetic wound and implicated in the impaired healing process, but the mechanism of NETs suspend wound healing and its role in fostering inflammatory dysregulation are elusive. Here, we report that NLRP3 and NETs production are elevated in diabetic wounds. NETs overproduced in the diabetic wounds triggered NLRP3 inflammasome expression and activation.

Results

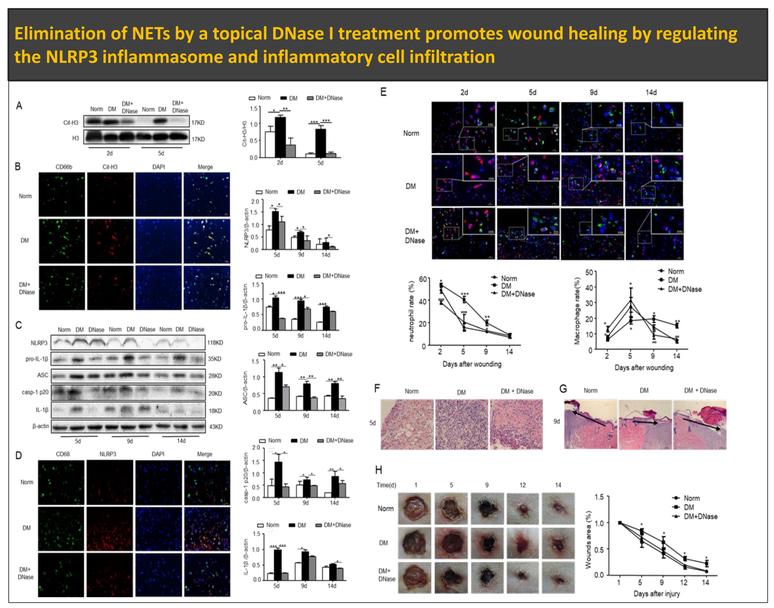
Diabetes primes human and rat NET formation, and NLRP3 inflammasome activation in the wound



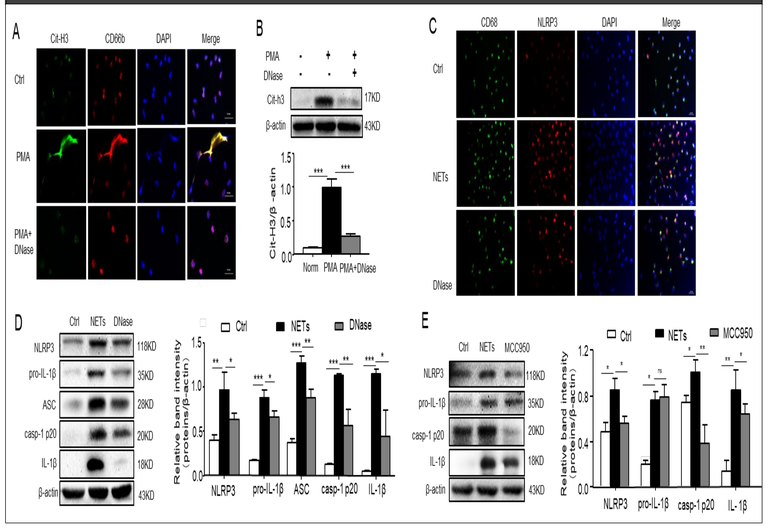
TLR/NF-κB signaling pathway contributes to the up-regulation of NLRP3 and pro-IL-1β induced by NETs



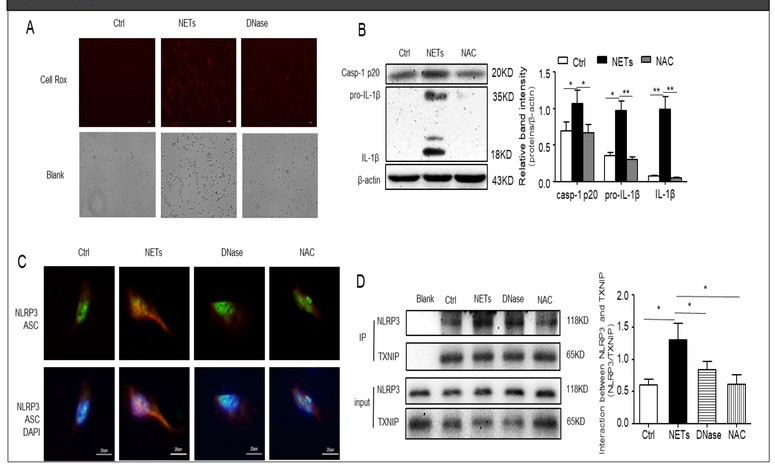
Elimination of NETs by a topical DNase I treatment promotes wound healing by regulating the NLRP3 inflammasome and inflammatory cell infiltration

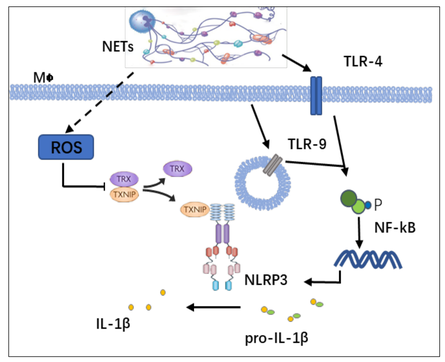


NETs stimulate NLRP3 production and IL-1β release in MΦ



NETs maintain NLRP3 inflammasome activation by the reactive oxygen species (ROS)/TXNIP signaling pathway





summary

- NETs, primed by diabetes, can trigger NLRP3 expression and activation of macrophage
- NETs through the TLR/NF-κB induce NLRP3 and pro-IL-1β expression in Macrophage
- Reactive oxygen species (ROS)/thioredoxin-interacting protein (TXNIP) pathways,
- NETs may be degraded by DNase I, which might regulate the inflammatory statement and constitutes a possible treatment for diabetic wound healing

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