Novel role of HDAC6 in a mouse model of impaired diabetic wounds

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Abstract

We show for the first time that sustained activity of histone deacetylase 6 (HDAC6) in wounds of diabetic mice contributes to delayed wound healing. Topical application of HDAC6 inhibitor; Tubastatin A (TSA) gel promoted the wound healing in diabetic mice compared to blank gel treated mice. TSA topical application reduced the infiltrating neutrophils, macrophages and T cells in the early phase of wounds. Similarly TSA topical application promoted the wound healing by inducing collagen deposition, angiogenesis, re-epithelization and fibrotic factors in the late stages of diabetic wounds. Protein analysis of the diabetic wounds treated with TSA showed increased acetylation of α-tubulin with no effect on the expression of pro-IL1β, pro-caspase-1 and active caspase-1 indicating no influence of TSA treatment on inflammasome activation. Macrophages are crucial for sustained inflammation activation; hence we have explored the effect of TSA on inflammatory factors (IL-1β and IL-10) expression using raw 264.7 cells. Macrophages exhibited upregulation of HDAC6, IL-1β and down regulation of IL-10 upon stimulation with high glucose and LPS. Selective inhibition of HDAC6 with TSA inhibited the IL-1β and promoted IL-10. Detailed probing to determine the effect on IL-1β resulted that TSA inhibit IL-1β release by inhibiting exocytosis while not showing any effect on its maturation. Similarly, inhibition of HDAC6 in macrophages stimulated with high glucose and LPS promoted the acetylation of tubulin. For further confirmation we have used nocodazole (known acetylation inhibitor) and found that nocodazole reversed the tubulin acetylation in high glucose conditions. Our findings indicate that sustained HDAC6 expression in diabetic wounds contributes to impaired early healing responses and HDAC6 may represent a new therapeutic target for diabetic wounds.

Biography:

Kalyani Karnam is pursuing her PhD degree in 4th year from BITS Pilani hyderabad campus in pharmacology. She has done her postgraduation from NIPER guwahati in pharmacology. Se has published 2papers in reputed journals and 3of her publications are under communication in the field of diabetic wounds. She was availed with JRF fellowship from DST-SERB and achieved SRF fellowship from CSIR (Government of India).

Speaker Publications:

1. C16 Accelerates Wound Healing by Inhibiting High Glucose Induced Inflammasome Activation in a Mouse Model of Diabetic Wounds; (February 21, 2020). Available at SSRN.
2. HDAC6 inhibitor accelerates wound healing by inhibiting tubulin mediated IL-1β secretion in diabetic mice; Researchgate- DOI: 10.1016/j.bbadis.2020.165903
3. P0684HDAC5/KLF2 AXIS REGULATES NLRP3 MEDIATED RENAL INFLAMMATION AND FIBROSIS ASSOCIATED WITH NEPHROCALCINOSIS-RELATED CHRONIC KIDNEY DISEASE; Researchgate- DOI: 10.1093/ndt/gfaa142.P0684
4. SAT-091 HISTONE DEACETYLASE 5 (HDAC5)-BMP-7 AXIS REGULATES EPITHELIAL MESENCHYMAL TRANSITION IN RENAL TUBULAR EPITHELIAL CELLS; Research gate- DOI: 10.1016/j.ekir.2020.02.098

11th Tissue Science and Regeneration Congress; April 20-21, 2020- Webinar.

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