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Effect of Hormone-Driven Ageing on Inflammatory Cell Clearance of Bacteria under Hyperglycaemic Conditions

Amina Belboul, Mohamed El Mohtadi, Kathryn Whitehead and Jason Ashworth*

* Centre for Bioscience, Manchester Metropolitan University, Manchester, United Kingdom.

Jason Ashworth (J.Ashworth@mmu.ac.uk)

Background:
Diabetic Foot Ulcers (DFUs) typically become colonised by a variety of bacteria, often persisting in protective biofilm arrangements. In most cases the bacterial colonisation is kept in check by host immunity but some DFUs can become infected due to defective phagocyte activity and/or one or more bacterial species evading host responses. With antibiotic resistance now commonplace, there is an urgent need to reduce the reliance on antibiotics and develop novel treatments to combat wound infections. One novel strategy is to stimulate natural innate immune responses through increased phagocyte activity. The endogenous hormone estrogen is reported to be a master regulator of innate inflammatory responses, with declining levels of estrogen with increasing age leading to impaired healing. However, the effect estrogen supplementation might have on innate host responses in infected DFUs remains largely unknown. Thus, the aim of this study was to investigate the potential use of estrogen to promote macrophage-mediated clearance of two problematic wound-associated pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* (PA), under diabetic (hyperglycaemic) conditions using a biofilm model of infected DFUs.
Materials/methods:
In vitro host-pathogen interaction assays were used to determine the effect of estrogen (17β-estradiol) on macrophage-mediated clearance of MRSA and PA biofilms (n=12) under increasing hyperglycaemic (>11mM glucose) conditions. The phagocytic activity of macrophages was visualised by fluorescence microscopy to confirm bacterial uptake.
Results:
Hyperglycaemia significantly ($P<0.05$; n=12) impaired macrophage-mediated clearance of both MRSA and PA biofilms in a concentration-dependent manner, suggesting poorly controlled hyperglycaemia in diabetics may dampen the phagocytic activity of macrophages. Intriguingly, estrogen significantly reversed the detrimental effects of hyperglycaemia on MRSA and PA biofilm clearance. Pronounced uptake of bacteria by estrogen-treated macrophages was visualised by fluorescence microscopy, confirming enhanced bacterial phagocytosis compared with untreated controls.
Conclusions:
The findings show estrogen reverses the detrimental effects of hyperglycaemia on macrophage-mediated phagocytosis of key wound-associated bacteria, even when such bacteria are established within a protective biofilm environment. This highlights the possibility that topical estrogen or localized estrogen receptor activation at the wound site might be effective therapeutic strategies to resolve infected DFUs.