New Thiazolidinedione Affects Neutrophil Phenotype and Human Neutrophil-T Cell Interactions

Larissa Benvenutti[1,2]*, *Sandali Malandkar*[2], *Andriéli R. Dutra*[1], *Maria E. Vieira*[1], Maria E. Signorini Pereira[1], *Fátima C. Buzzi*[1], *Derek Gilroy*[2], *Nara L. M. Quintão*[1], *José R. Santin*[1]

[1]*Universidade do Vale do Itajaí,UNIVALI, Brasil.*
[2]*University College of London (UCL), Division of Medicine.*
*Larissa.benvenutti@univali.br

INTRODUCTION

Neutrophils are short-lived phagocytes forming the first immune defense and modulating adaptive responses by activating or inhibiting T cells. Functional differences exist between young and senescent neutrophils, and drugs may alter their responses, causing immunotoxicity. Thus, assessing the effects of the new thiazolidinedione (D3) developed at UNIVALI is essential.

OBJECTIVE

This study aimed to evaluate how D3 influences the phenotype of quiescent neutrophils and its effects on T cells activation, to investigate potential immunotoxic effects.

MATERIALS AND METHODS

Approved by the UCL Ethics Committee (1309/006), human neutrophils were isolated from healthy donor blood using negative magnetic selection (EasySep). Cells were incubated with or without D3 (1 μM) for 4 and 6 hours, and surface markers related to activation and senescence were analyzed (CD101, CD64, CD15, CD33, CD47, CD11b, CD54, CD49d, CD38, CD45RA, CXCR4, CD10, CXCR2, Annexin V, HLA-DR, CD62L, CD66b, CD16, and Zombie UV). To assess D3's effect on T cell activation, CD4 T lymphocytes (EasySep-isolated) were incubated alone or with neutrophils and D3 for 96 hours. T cells activation markers were analyzed by flow cytometry. (CD49d, CXCR4, HLA-DR, CCR7, CD25, CD69, CD45RA, CD45RO, CD62L, and Zombie UV). Data was analyzed using multidimensional analysis in RStudio.

RESULTS

The D3 compound increased the population of senescent neutrophils ($CD11b^{high}$, $CD62L^{low}$, $CD101^{high}$, $CD66b^{high}$, $CD47^{high}$, $CXCR2^{low}$), which have reduced chemotactic capacity, increased NET formation, and decreased phagocytosis. Although D3 did not affect the activation of isolated T cells, but inhibited their activation with neutrophils, suggesting it disrupts cell crosstalk. Thus, D3 acts directly on neutrophils, promoting their senescence and suppressing T cell activation.

CONCLUSION

D3 induces a senescent neutrophil phenotype that impairs adaptive immunity by inhibiting T cell activation, indicating that may cause harmful effects under physiological conditions.

KEYWORDS: T cell activation; immunosenescence; Thiazolidinedione; Immunotoxicity