Journal of Immunological Methods xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Immunological Methods

journal homepage: www.elsevier.com/locate/jim

Technical note

Standardization of a human organ culture model of intestinal inflammation and its application for drug testing

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ARTICLE INFO

Article history:
Received 16 October 2014
Received in revised form 20 December 2014
Accepted 23 December 2014
Available online xxxx

Keywords:
Intestinal inflammation
Human organ culture
Standardization
Drug testing

ABSTRACT

Targeting early molecular events in intestinal inflammation may represent a useful therapeutic strategy for maintaining remission in inflammatory bowel disease. Recently, we established an intestinal organ culture model (LEL model), which allows to study the initiation of an intestinal inflammatory response in human tissue. In this model, EDTA-mediated depletion of epithelial cells of colonic mucosa results in an instantaneous inflammatory response in resident lamina propria cells, which shows features of intestinal inflammation *in vivo*. Furthermore, activated immune cells emigrate from the lamina propria onto the luminal side of the basement membrane. Here, we standardize the LEL model and explore its suitability for drug testing. To this end, human mucosal punches of defined surface area were prepared, depleted of epithelial cells, and cultured at an optimized ratio of medium volume/punch area. The intra-assay variability of measurements of inflammatory parameters ranged from 13% for cell migration to 19% for secretion and 30% for tissue gene expression, respectively, of the inflammatory mediators IL-8 and IL-6. Importantly, known suppressive effects of dexamethasone, a drug employed for the treatment of inflammatory bowel diseases, on leucocyte migration, IL8, IL6, and TNF-α production as well as CD86 surface expression by myeloid cells were observed in this model.

In conclusion, the present results suggest that the LEL model may represent a useful human experimental system not only for studying initial activation mechanisms in intestinal inflammation but also for evaluating drug compounds for the treatment of mucosal inflammation.

Abbreviations: LEL, Loss of the epithelial layer; LEL-M, "Loss of the epithelial layer" mucosa; LPL, Lamina propria leukocytes; WO-LPL, "Walk-out" lamina propria leukocytes; LPMO, Lamina propria myeloid cells; WO-LPMO, "Walk-out" lamina propria myeloid cells; TM, Total mucosa; CV, Coefficient of variation.

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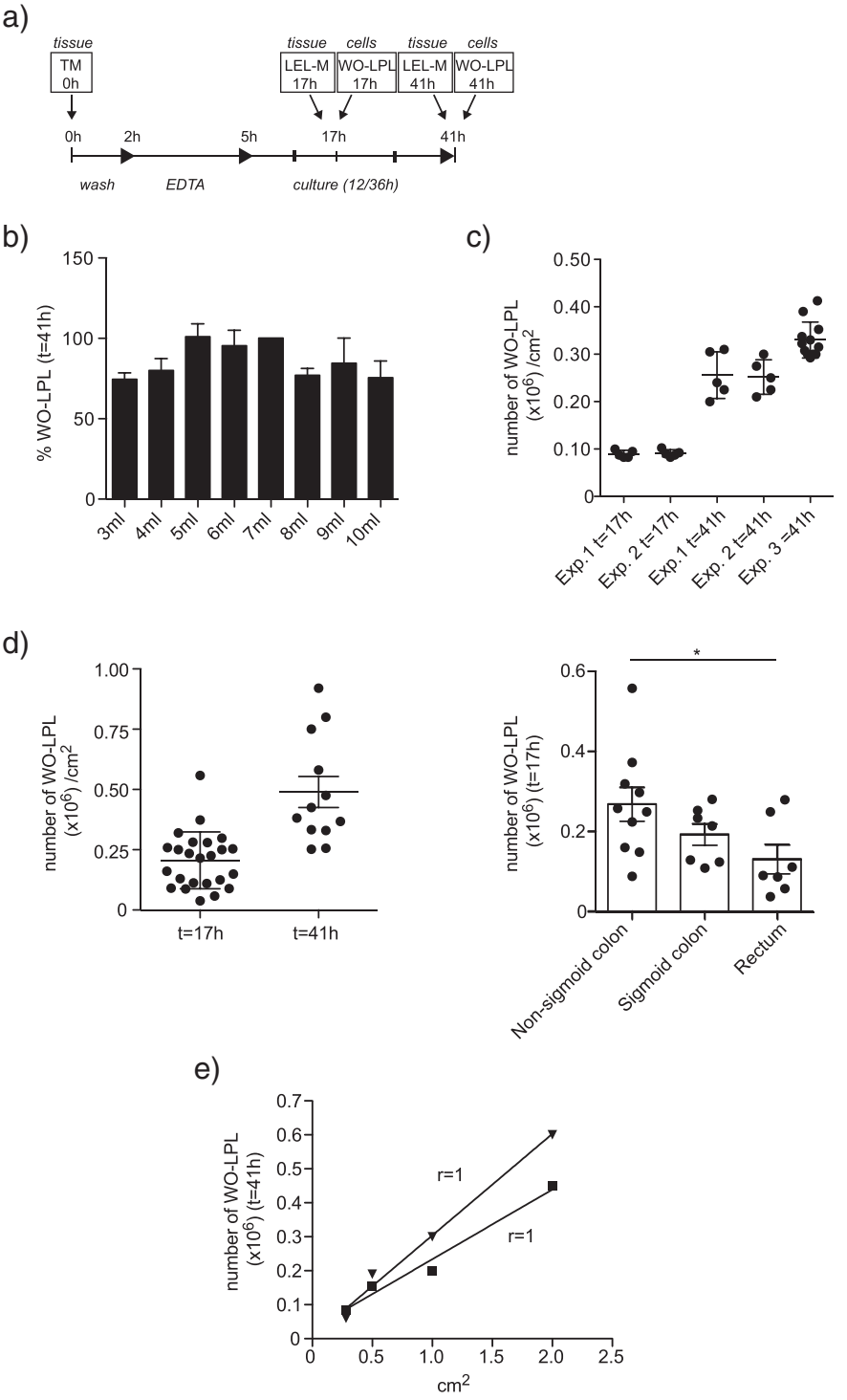
http://dx.doi.org/10.1016/j.jim.2014.12.014
0022-1759/

1. Introduction

Under homeostatic conditions, resident intestinal immune cells exist in a specialized differentiation state, which is characterized by low responsiveness to, respectively, bacterial antigens and antigen receptor triggering. Knowledge regarding molecular mechanisms driving the initial switch from a hyporesponsive to an inflammatory state in these immune cells is limited, which contrasts with the wealth of information gathered on molecular features of symptomatic intestinal inflammation. Insight into early inflammatory events under "regular" (self-limiting) and pathologic (chronic) conditions



Please cite this article as: Szikszai, T., et al., Standardization of a human organ culture model of intestinal inflammation and its application for drug testing, J. Immunol. Methods (2015), http://dx.doi.org/10.1016/j.jim.2014.12.014