IN SITU SUSTAINED DELIVERY OF DEXAMETHASONE TO ENHANCE FUNCTIONALITY OF SUBCUTANEOUS CELL-BASED BIOSCAFFOLDS

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INTRODUCTION

A major problem upon implantation of medical devices and other bioscaffolds is tissue injury which triggers a cascade of inflammatory responses that may compromise their functionality in a short period of time (1,2). This fibrotic capsule (FC) hinders the release of cellular therapeutics, and the entry of nutrients and oxygen to the interior, leaving the functionality of the system compromised. The creation of an inmunoprivileged microenvironment around the implant may help to control the formation of the FC and thus improving the viability of the cell-based system.

In the present work, the effect of a temporary release of an anti-inflammatory agent on co-administered encapsulated allogeneic cells was investigated. The multiple delivery system developed here is based on the co-administration of PLGA microspheres (PLGA MS) containing dexamethasone (DXM) and C_2C_{12} myoblasts secreting erythropoietin (Epo) encapsulated in alginate-poly-L-lysyne-alginate microcapsules (APA MC), with the aim of studying the benefits of the combined system in vivo in terms of decreased foreign body reaction.

MATERIAL AND METHODS

PLGA microspheres. Development and characterization

PLGA microspheres loaded with DXM were prepared by an oil-in water (O/W) emulsion/solvent evaporation technique, by modification of a previously described procedure (3).

APA microcapsules. Development and characterization

C_2C_{12} myoblasts genetically modified to deliver murine Epo (mEpo) were encapsulated in APA microcapsules using an electrostatic droplet generator (4).

Subcutaneous implantation of bioscaffolds

The composite drug delivery system was implanted in female Balb/c mice (Figure 1).

Hematocrit levels in mice

Blood samples were collected weekly from the submandibular vein and hematocrit levels were measured.

Removal of implanted bioscaffolds

60 days after implantation, animals were sacrificed and microcapsules were removed for subsequent histological analysis.

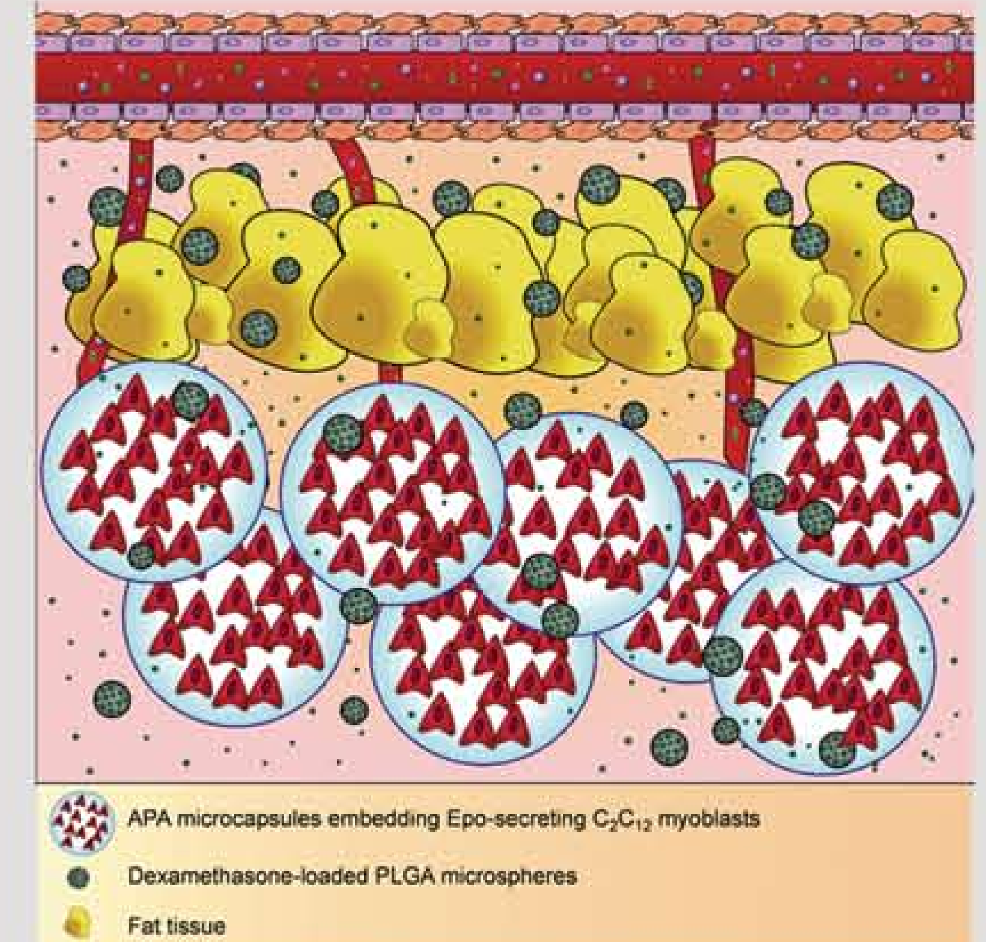

Figure 1. Immunomodulatory environment created in the subcutaneous space of implanted mice

RESULTS AND DISCUSSION

DXM-PLGA microspheres and APA cell-loaded microcapsules had a uniform morphology with a smooth surface devoid of irregularities (Fig.2).

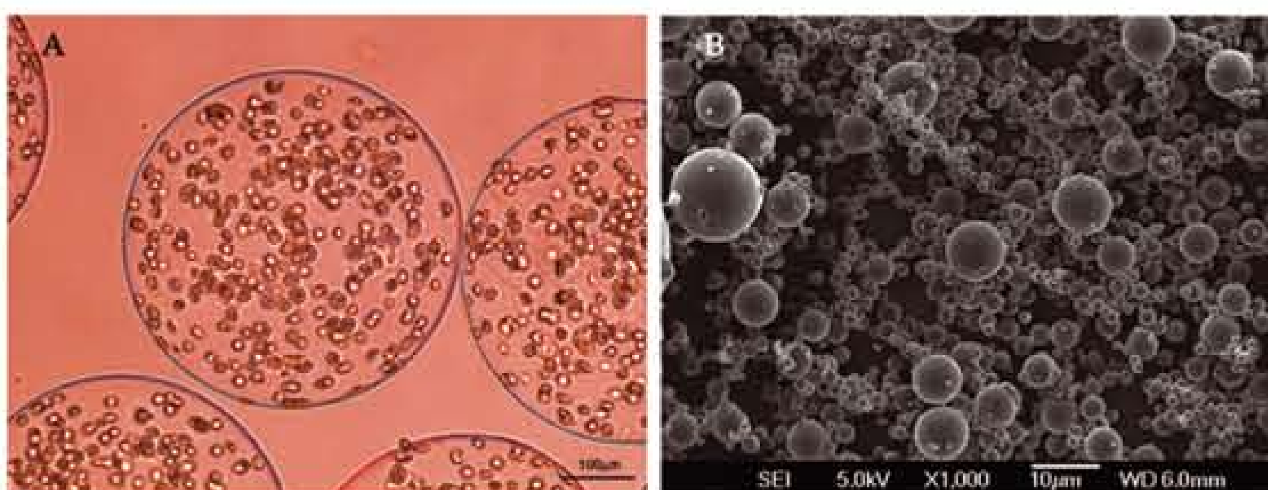

Figure 2. A. APA cell-MC. B. DXM-PLGA MS.

Regarding the potential of DXM to prevent fibrotic reaction around the cellular systems, Figure 3 shows that the use of DXM-PLGA MS causes, from day 20 to the end of the study, a significantly higher hematocrit increase than the group non treated with DXM, especially when the higher cell doses were employed (100 μL APA cell-MC; $p<0.05$)

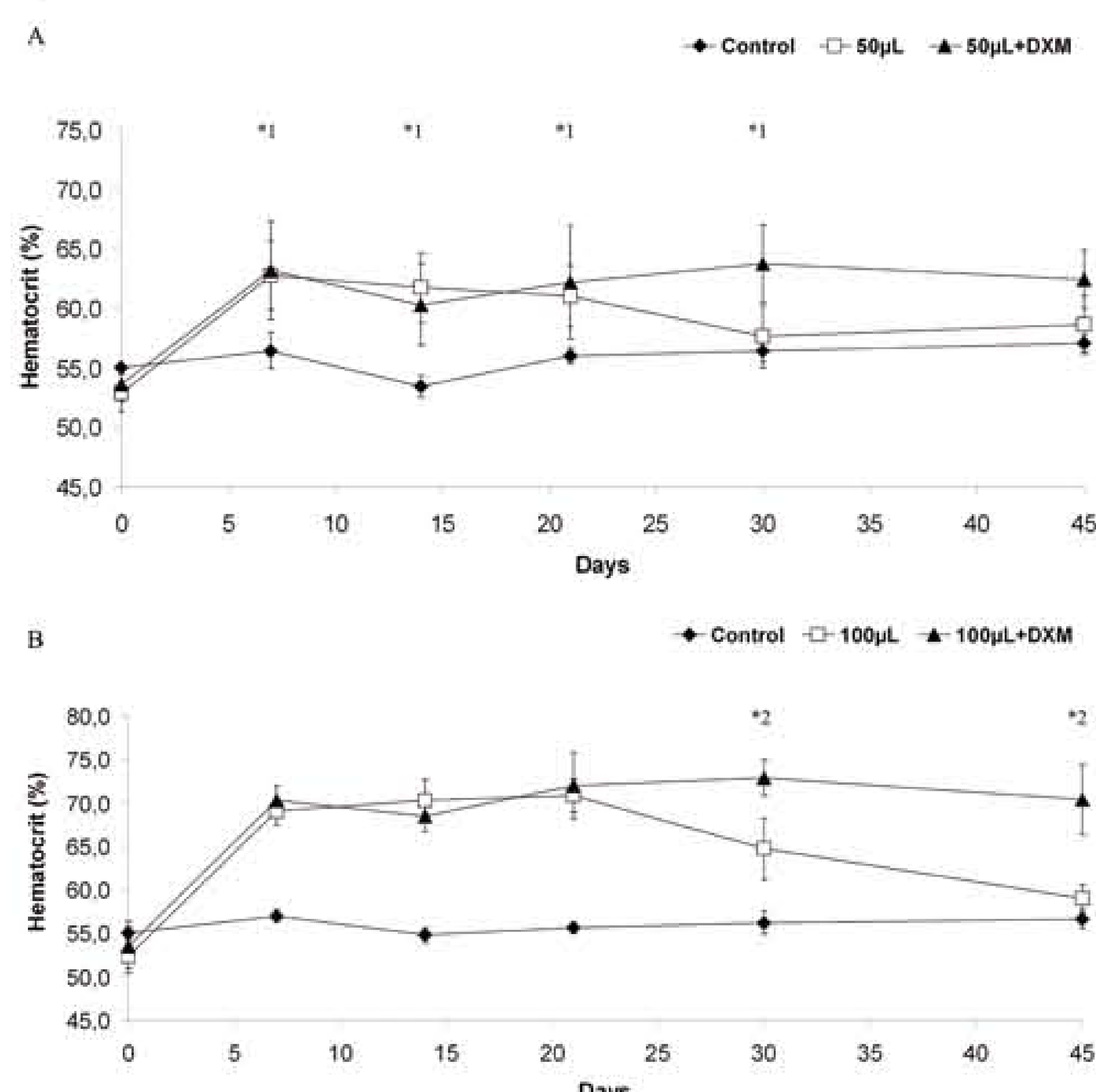

Figure 3. Hematocrit levels of Balb/c mice after implantation of 50/100 μL of microencapsulated cells and DXM-loaded PLGA microspheres. $P<0.05$; *1: control vs. cells; *2: No DXM vs. DXM group. Results are expressed as mean +/- SD.

Histological analysis (Figure 4) of the explanted micocapsules revealed the formation of blood capillaries around the implant, being more pronounced in the groups treated with DXM-PLGA MS. In addition, in these groups, a weaker fibrotic overgrowth is detected surrounding the implants, as stated by higher hematocrit levels, resulting in longer functionality of the cell-based implants.

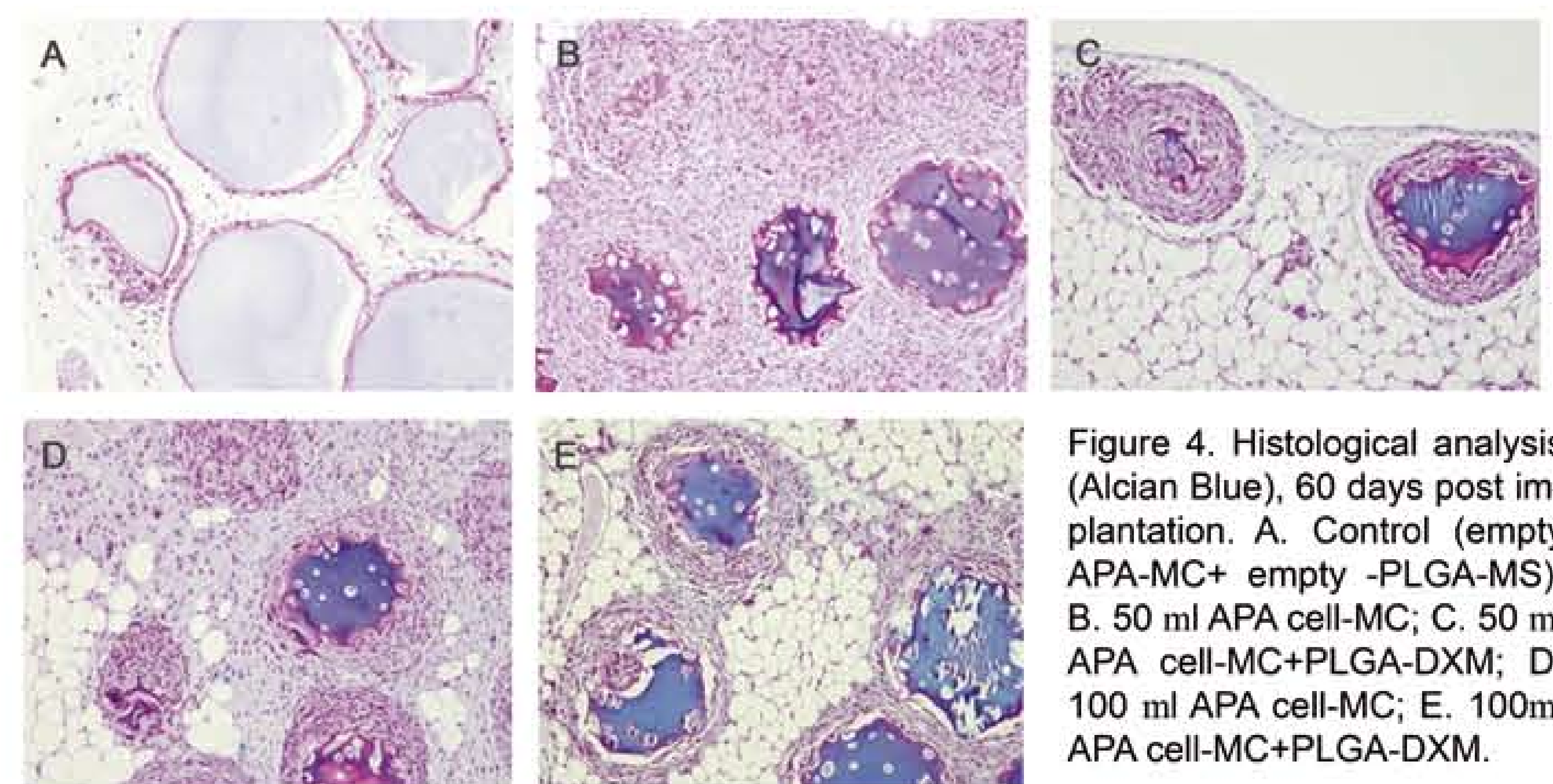

Figure 4. Histological analysis (Alcian Blue), 60 days post implantation. A. Control (empty APA-MC+ empty -PLGA-MS); B. 50 ml APA cell-MC; C. 50 ml APA cell-MC+PLGA-DXM; D. 100 ml APA cell-MC; E. 100ml APA cell-MC+PLGA-DXM.

CONCLUSION

The co-administration of PLGA microspheres loaded with DXM along with encapsulated Epo-secreting myoblasts may improve the functionality of the cell-based implant. The release of DXM from PLGA microspheres can be a useful pharmacological strategy to prevent the acute inflammatory response caused by biomaterials and the surgical procedure itself after implantation of cell-based bioscaffolds.

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