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Cover Story

Xenogeneic delivery of therapeutic products using transient immunosuppression

The modern concept of cell microencapsulation is more than four decades old. Cell microencapsulation has been an important research area, because it holds a great promise for the sustained and controlled delivery of therapeutic proteins such as erythropoietin (Epo). Clinical applications of microencapsulated cells, however, have been severely hampered by the lack of long-term survival of the encapsulated cells. Of the many reasons, immunorejection of encapsulated cells by the body is most difficult to overcome. The study by Murua et al. in this issue [1] deals with a new approach of overcoming such immunorejection.

Microencapsulated cells (e.g., C_2C_{12} myoblasts) can survive for long periods of time when transplanted subcutaneously in syngeneic and allogeneic recipients. After xenotransplantation, however, survival of the encapsulated cells is only short-term because of rejection by the host, requiring immunosuppression. The results by Murua et al. [1] have shown that immunorejection of the microencapsulated xenogeneic cells can be effectively prevented by transient immunosuppression. C_2C_{12} myoblasts, which were genetically engineered to secrete murine Epo (mEpo), were encapsulated in alginate-poly-L-lysine-alginate microcapsules and implanted subcutaneously in Fischer rats. A transient immunosuppressive FK-506 therapy (2 or 4 weeks) was used to ameliorate immunoprotection of microencapsulated cells. Rats receiving short-term immunosuppression with FK-506 maintained high hematocrit levels for a longer period of time (14 weeks) in comparison with the non-immunosuppressed group. In addition, a significant difference in hematocrit levels was detected by day 65 among rats immunosuppressed for 2 or 4 weeks, corroborating the need of a minimum period of immunosuppression (4 weeks) for this purpose. Both macroscopic and histological analyses of the explanted microcapsules revealed formation of blood capillaries surrounding the microcapsule aggregates, mainly observed in the immunosuppressed individuals. The authors hypothesized this could be due to the angiogenic effects reported for Epo. The vascular outgrowth leads to a more suitable microenvironment, where the delivery of oxygen and nutrients to the entrapped cells can be improved. The described findings provide a means of transplanting genetically modified xenogeneic myoblasts in a peripheral immunoreactive site while ensuring their long-term survival. Fischer rats rendered unresponsive during 94 days to encapsulated C_2C_{12} mEpo cells by transient immunosuppression with FK-506 (4 weeks).

The finding by Murua et al. [1] is highly significant for a few reasons. First, immunorejection of microencapsulated cells can be effectively prevented by transient immunosuppression, as opposed to chronic treatment. Second, the initial immunosuppression of only 4 weeks is enough for the survival of cells within the implant for a much longer period of time. These observations are expected to allow active development of various microencapsulated cell systems for effective applications in the pharmaceutical and biomedical fields.

Reference

[1] A. Murua, G. Orive, R.M. Hernández, J.L. Pedraz, Xenogeneic transplantation of erythropoietin-secreting cells immobilized in microcapsules using transient immunosuppression, J. Control. Release 137 (2009) 174–178.

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