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The association between *in vivo* physicochemical changes and inflammatory responses against alginate based microcapsules

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ABSTRACT

Application of alginate-polylysine (PLL) capsules for immunoisolation of living cells are suffering from a varying degree of success and large lab-to-lab variations. In this study we show that these differences in success rates can be attributed to alginate dependent essential physicochemical changes of the properties of capsules *in vivo* that will render the capsules more susceptible to inflammatory responses. Capsule properties were studied before and after implantation by XPS, by immunocytochemistry, and by measuring zeta potentials. We studied a capsule type which provokes for unknown reasons a strong inflammatory response, i.e. high-guluronic (G) alginate capsules and a capsule type with near identical physicochemical properties but which evokes a minimal inflammatory response, i.e. intermediate-G alginate capsules. The cause of the difference in response was a decrease in nitrogen content on high-G capsules due to detachment of PLL *in vivo* and an increase of the zeta-potential. Our data illustrate an important overlooked phenomena; the physicochemical properties are not necessarily the properties after exposure to the *in vivo* microenvironment and might induce undesired inflammatory responses and failure of encapsulated cellular grafts.

1. Introduction

The most commonly applied procedure for immunoprotection is microencapsulation of tissues in alginate-based capsules as originally described by Lim and Sun [1]. Alginate, the main component of the capsule, is composed of chains of guluronic acid (G) and mannuronic acid (M) and can have varying quantities of these two acids. The alginate binds polyaminoacids at the surface of the capsules which provides semi-permeable properties. During recent years, important advances have been made with this technology. Human trials have been started and shows temporary but persistent survival of human microencapsulated tissue after allotransplantation of encapsulated parathyroid cells [2] and islets of Langerhans [3–5]. Also, microencapsulation has been shown to allow for prolonged survival of xenotransplanted islet grafts in both chemically induced and autoimmune diabetic rodents [6], dogs [7,8], and monkeys [9]. Although this illustrates the principle applicability of the alginate-encapsulation technique, a fundamental barrier has to be overcome since graft survival varies considerably from several days to months [10]. This variation in success rate is usually attributed to differences in the tissue responses (*i.e.* biocompatibility) against the applied capsules.

Many report different causes for the tissue responses against alginate-based capsules. Purity of the alginate [11–14], the interaction of the alginate with the polyamino acid [13,15–18], and the mechanical stability [12,19] are all considered to be crucial factors in the responses against the capsules. Also the alginate-type has been subject of studies focusing on identification of factors influencing biocompatibility, but conclusions on which type of alginate is most adequate can still not be drawn [18]. This is caused by the fact that in most of these studies alginate-effects are overshadowed by variations in experimental design which makes comparison and sound interpretation difficult if not impossible. Many studies [18,20] compare alginates with different guluronic acid content in capsules with a different or poorly documented stability. Also the applied alginates lack details on purity or have a documented different degree of purity [12,18,21]. In addition to capsule properties also other factors such as limitations of the transplantation site such as the low oxygen tension in the peritoneal cavity may contribute to failure and enhancement of host responses [22].

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