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Development of Methods for Covalent Modification of Pancreatic Islets

(Chemistry and Biochemistry / Arts and Sciences)

For the past several years our lab has been examining a variety of chemical approaches to the modification of fresh tissue surfaces. Taking advantage of the fundamental chemical reactivities of the simple chemical building blocks found in bulk tissue (amino acids, carbohydrates, fats), we have developed several general methods for tissue modification. One demonstration of the utility of these methods is our discovery of novel tissue 'glues' that utilize simple cross linking reagents and selective chemical reactions to afford mechanical bonds in complex tissue matrices.

A different application of chemical tissue-modification is the stabilization and 'camouflaging' of Islets of Langerhans. These pancreatic islets are small cell clusters, comprised of several types of hormone-secreting cells, that are found throughout the healthy pancreas. These miniature 'organs' are responsible for blood glucose control, and are non-functional in patients with Type I insulin-dependent diabetes. The transplantation of healthy pancreatic islets into diabetic patients is an area of intense clinical study, and has resulted in 'cures', albeit temporary, in a large number of cases. Several challenges prevent the wide-spread application of islet transplantation, including the limited availability of healthy donor organs, the difficulty in efficiently isolating functional islets, the immune rejection of foreign islets, and the degradation of the transplanted donor islets. Recent studies of chemically modified islets have reported significantly reduced immune rejection and a longer half-life, suggesting that this approach has clinical relevance.

We herein propose a systematic investigation of a series of tissue-modification strategies on murine or porcine pancreatic islets. The extent and stability of the chemical modifications will be determined and compared to previous approaches found in the literature. The biocompatibility of the tissue modification chemistry will also be examined by testing the ability of the modified islets to release insulin in response to glucose stimulation as compared to unmodified islets.