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Cloning and Characterization of Strong Promoters for the Endothelial Cell-Specific Expression of Membrane Complement Regulatory Proteins (mCRPs) in Transgenic Pigs

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The complement system is composed of a complex group of soluble proteins that are part of the immune response against foreign cells such as xenografted cells and some of the cell surface regulators known as membrane complement regulatory proteins (mCRPs) prevent the formation of the membrane attack complex (MAC). The major obstacles to xeno-transplantation of vascularized organs in discordant species combinations, such as pig to human, are found to be hyperacute rejection (HAR) and acute vascular rejection (AVR). To prevent HAR, we need to block the formation of MAC in the xenotransplated cells by overexpressing mCRPs in the endothelial cells. For this purpose, we, at first, prepared strong endo-thelium-specific promoters such as the promoters for Flk-1 (fetal liver kinase-1), ICAM-2 (intercellular adhesion molecule-2), thrombomodulin, MCP (membrane cofactor protein, CD46) and DAF (decay-accelarating factor, CD55). From the luciferase assays, we could find that the 1.1 kb DAF promoter is the strongest followed by the Flk-1 promoter. On the 1.1 kb DAF promoter region, we could find several conserved necleotide sequences interacting with the specific transcription factors. Next, we constructed several transgenic plasmids for the expression of mCRPs such as DAF, CD59, and MCP. In the further study, we will finely characterize the 1.1 kb DAF promoter and try to produce donor pigs for xenotransplatation, which are transgenic for mCRPs.