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The functional properties of nephronectin: An adhesion molecule for cardiac tissue engineering

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ABSTRACT

Despite significant advances in preventive cardiovascular medicine and therapy for acute and chronic heart failure, cardiovascular diseases remain among the leading causes of death worldwide. In recent years cardiac tissue engineering has been established as a possible future treatment option for cardiac disease. However, the quality of engineered myocardial tissues remains poor. In tissue engineering it is important that the scaffold allows cells to attach, spread, maintain their differentiation status or differentiate into functional cells in order to exhibit their physiological function. Here, we have investigated the suitability of the natural cardiac extracellular matrix component nephronectin as an adhesive material for cardiac tissue engineering. Primary neonatal rat cardiomyocytes were seeded on collagen-, fibronectin- or nephronectin-coated glass coverslips and analyzed for cell adhesion, cellular metabolic activity, response to extracellular stimuli, cell-to-cell communication, differentiation and contractility. Our data demonstrate that most neonatal cardiomyocytes attached in an RGD domain-dependent manner within 18 h to nephronectin. The cells exhibited high metabolic activity, responded to growth factor stimuli and maintained their differentiation status. Moreover, nephronectin promoted sarcomere maturation and alignment, cell-to-cell communication and synchronous contractions. In conclusion, our findings demonstrate that nephronectin has excellent properties for cardiomyocyte adhesion and function and thus has the potential to improve current cardiac tissue engineering approaches.

1. Introduction

Cardiovascular diseases (CVDs) represent a major socio-economic burden. They are responsible for around 30% of death worldwide claiming as many lives as cancer, chronic lower respiratory diseases, accidents and diabetes combined. The estimated cost of CVD in 2008 was US$ 297.7 billion in the US alone accounting for around 16% of the total health expenditures and the future burden of heart disease is expected to further increase [1].

The primary cause of most CVDs is reduced heart function due to the irreversible loss of heart muscle cells, the cardiomyocytes [2–4]. The mammalian heart cannot regenerate and a possible endogenous regenerative capacity can so far not be enhanced to generate enough cardiomyocytes to improve heart function after injury [5]. The only available therapy to effectively replace damaged hearts is at the moment heart transplantation. Unfortunately, there are not enough donor hearts to match the demand [6,7]. Therefore, it is critically important to develop technologies aimed at providing new cardiomyocytes to diseased hearts.

One approach to reverse heart disease is the application of stem cells. In the past it has been proven that transplanted fetal and neonatal cardiomyocytes could functionally integrate and enhance recipient cardiac function. Thus, multiple stem cell types have been tested for re-population of the injured myocardium. However, there appears little or no differentiation of the engrafted cells into cardiomyocytes *in vivo* [8–10]. In addition, injection of stem cells in the heart muscle causes severe cell loss due to shear stress. Injection in the blood circulation requires a homing signal to the damaged tissue, which is still elusive. One solution to this problem might be the integration of tissue engineering and stem cell biology towards creating functional heart muscle *in vitro* [11,12]. The engineered tissue can be adjusted according to the needs of a patient before implantation and materials used as scaffolds might enhance cardiomyocyte differentiation. Importantly, it has been shown that engineered cardiac tissue based on type I collagen gel, Matrigel and primary rat postnatal cardiomyocytes improves LV function after myocardial infarction [13]. However, the used material appears in its present form not suitable for clinical

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