Editorial

Do we have a new early marker of chronic transplant dysfunction now?

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See article by Subramanian et al. [9] (pages 539–548) in this issue.

The development of chronic transplant dysfunction (CTD) has become a limiting factor for long-term graft survival, and it is today’s most important problem in clinical organ transplantation after the first perioperative year. To date, CTD cannot be prevented by current immunosuppressive protocols [1,2]. Depending on the type of organ transplanted (liver, kidney, heart, lung), the incidence of CTD 3 years after engraftment varies from 4 to >50% [3–5]. Irrespective of the organ grafted, graft vessels eventually develop so-called transplant vascular sclerosis (TVS), which is, however, most prominent in cardiac allografts [6,7]. This vascular remodeling process, also called chronic vascular rejection or graft vascular disease, is the main cause of morbidity and mortality in long term survivors of many types of organ transplants. The standard etiology of TVS following organ transplantation is thought to be the local migration and proliferation of medial vascular smooth muscle (VSM) cells in response to inflammatory signals and/or growth factor expression with consequent thickening of the intima. Although this etiology of TVS has never been demonstrated in its entirety, several steps have been documented in vessels with ongoing neointimal formation, including the expression of inflammatory cytokines and growth factors in both the media and neointima, as well as the proliferation of VSM cells in the media [8]. The pathogenesis of TVS seems to be multifactorial, but precise mechanisms involved in the development of this remodeling process still remain obscure. Risk factors appear to include cold ischemia time and reperfusion injury, disparity of the major histocompatibility complex between donor and recipient, number of rejection episodes, and infection (especially by cytomegalovirus) [2,6].

In the current issue of Cardiovascular Research, Subramanian et al. [9] investigated the regulation of the expression of VSM \( \alpha \)-actin in mouse heterotopic heart transplantation. Recently, the authors showed, that after transplantation the VSM \( \alpha \)-actin gene was activated in adult donor cardiomyocytes [10]. The expression of VSM \( \alpha \)-actin was detected 30 days after transplantation and localized predominantly in sarcomeres. The expression of VSM \( \alpha \)-actin in adult cardiomyocytes might be interpreted as a sign for the induction of an embryonic gene program. This re-expression is a well known feature of cardiac hypertrophy, including genes for natriuretic peptides and embryonic contractile proteins [11]. The natriuretic peptide genes are induced in the hypertrophied myocardium in all mammalian species, and especially the induction of the atrial natriuretic peptide is a prognostic indicator of clinical severity [12]. Besides VSM \( \alpha \)-actin [13], other important markers of the embryonic gene program of contractile proteins are \( \beta \)-myosin heavy chain (MHC) [14] and skeletal \( \alpha \)-actin [15]. However, the induction of both \( \beta \)MHC and skeletal \( \alpha \)-actin genes during hypertrophy is predominantly a feature of rodent species [16]. Ventricular hypertrophy in larger animals (canine, pig, etc, including humans) is not associated with the induction of either \( \beta \)MHC or skeletal \( \alpha \)-actin genes, which are constitutively expressed in larger species [16]. Therefore, only VSM \( \alpha \)-actin from the contractile protein markers might be used as an indicator of dysfunctional remodeling following heart transplantation in humans, which Subramanian et al. [9] postulated.

The induction signal for the re-expression of VSM \( \alpha \)-actin in myocytes of cardiac allografts has not been elucidated until now. Subramanian et al. [9] deduced the
VSM α-actin expression from the mechanical stretch on adjacent cardiomyocytes, which was a result of accumulation of myofibroblasts and the resulting production of more extracellular matrix proteins [17]. Another reason can be found in a pathologically imbalanced inflammatory–fibroproliferative response of the surrounding tissue to the allografts [18–20]. The imbalance of proinflammatory cytokine expression plays a key role in the etiology of pathologic cardiac remodeling in different forms of cardiac hypertrophy [21–23] and after myocardial infarction [24,25]. These processes are accompanied by an induction of the embryonic gene program and a disproportional accumulation of proteins of the extracellular matrix, which leads to fibrosis [26]. The common receptor component of the interleukin-6 family of cytokines, gp130, is part of a key signaling pathway for cytokine-dependent regulation of pathologic remodeling of the myocardium leading to cardiac hypertrophy and heart failure [27,28]. This pathway is an example for the sensitive tuning possibilities of the organism [29]. The delicate balance between the activation of gp130-JAK signaling and the induction of its negative feedback regulator, the suppressor of cytokine signaling 3 (SOCS3), might be important in the transition between compensatory cardiac hypertrophy and an irreversible decompensation in cardiac function in heart failure. The activation of the gp130-JAK is accompanied with the organization of sarcomeres, induction of the embryonic gene program and cell survival. The SOCS3 induction leads to the inhibition of the organization of sarcomeres, inhibition of the embryonic gene program and apoptosis. Therefore, we can speculate that the re-expression of VSM α-actin might be a marker of physiological allografts remodeling.

Subramanian et al. [9] hypothesized that a shift in VSM α-actin expression away from smooth muscle cells to fibroblasts and cardiomyocytes is an early and fundamental process involved in cardiac transplant rejection. They analyzed the key transcription proteins regulating VSM α-actin expression: the transcription enhancer factor-1 (TEF-1), the mouse Y box protein 1 (MSY1), the Puro and Purβ, which interact with purine-rich single-stranded DNA. The DNA binding activity of these proteins was increased in cardiac homogenates in transplant vs. donor hearts. This might be an early indication of an elevation of VSM α-actin expression. However, the transcriptional regulation of the VSM α-actin gene represents a complex interaction of above mentioned transcriptional factors as was recently described [30].

We can conclude that the reprogramming of VSM α-actin gene expression might be an early indicator for the remodeling of the allografts, especially since the transcriptional reprogramming proteins are analyzed. However, we do not know whether this remodeling is dysfunctional, since re-expression of the embryonic gene program might also be a sign for a physiologic remodeling, as it was postulated for the development of cardiac hypertrophy [29].

References

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