Several studies have demonstrated the existence of pluripotent bone marrow–derived stem cells capable of homing to injured cardiac and skeletal muscle; however, there has been little evidence demonstrating the induction of tissue-specific endogenous genes in donor stem cells following engraftment. A new study in this issue reports an intriguing finding that raises additional concerns relating to stem cell plasticity and stem cell therapy in an already heated and controversial field. The study demonstrates that wild-type bone marrow–derived side population stem cells are indeed readily incorporated into both skeletal and cardiac muscle when transplanted into mice that lack δ-sarcoglycan — a model of cardiomyopathy and muscular dystrophy. However, these cells fail to express sarcoglycan and thus to repair the tissue, which suggests that this stem cell population has limited potential for cardiac and skeletal muscle regeneration (see the related article beginning on page 1577).

Bone marrow–derived side population (BM-SP) stem cells have the ability to repopulate the hematopoietic system (1) and to colonize, at low frequencies, many different tissues, including skeletal (2) and cardiac muscle (3). The δ-sarcoglycan–null mouse is a model of cardiomyopathy and muscular dystrophy (corresponding to a human limb-girdle myopathy) and develops microinfarcts in heart and skeletal muscle (4). Muscle cell death in this model is related to the lack of δ-sarcoglycan, which causes loss of the other sarcoglycans (α, β, and γ) and in turn disassembly of the dystroglycan complex (Figure 1), which is composed of several proteins that link the cytoskeleton to the basal lamina and reduce membrane stress during contraction. Absence or reduction of the dystroglycan complex results in increased fragility of the membrane and increased chance of damage to the muscle cell. Resident cells capable of repairing injured skeletal muscle (satellite cells) are well characterized (5), and despite the long-held belief that heart cells cannot regenerate, evidence for the existence of cells with a similar reparative function in the heart has only begun to accumulate during the last 2 years (6, 7). This observation suggests that injured δ-sarcoglycan–deficient tissues should recruit both local and blood-borne stem cells that may contribute to regeneration.

In this issue of the JCI, Lapidos et al. (8) transplanted BM-SP stem cells from wild-type male mice into female δ-sarcoglycan–null mice, and their results, consistent with those from previous studies of stem cell–mediated skeletal and cardiac muscle regeneration, demonstrated the presence of these donor cells, determined by the presence of a Y chromosome inside cardiac and skeletal muscle at the expected frequency. A fraction of the nuclei of these Y chromosome–positive donor cells was unequivocally shown to be present inside the cytoplasm of several differentiated car-
A number of transmembrane proteins, including dystroglycan (DG), sarcospan (SP), and sarcoglycans (α, β, γ, and δ), connect the actin cytoskeleton to the basal lamina by binding dystrophin (in turn linked to actin) on the cytoplasmic side and laminin on the extracellular side of the muscle plasma membrane. Other functionally important proteins such as nicotinamide adenine dinucleotide phosphate oxidase synthetase (NOS) are maintained at the cytoplasmic side of the membrane by a different protein complex also bound to dystrophin.

**Figure 1**
Schematic representation of the dystroglycan complex at the membrane of the muscle cell. A number of transmembrane proteins, including dystroglycan (DG), sarcospan (SP), and sarcoglycans (α, β, γ, and δ), connect the actin cytoskeleton to the basal lamina by binding dystrophin (in turn linked to actin) on the cytoplasmic side and laminin on the extracellular side of the muscle plasma membrane. Other functionally important proteins such as nicotinamide adenine dinucleotide phosphate oxidase synthetase (NOS) are maintained at the cytoplasmic side of the membrane by a different protein complex also bound to dystrophin.
of muscle-specific genes (12). However the genes encoding adult isoforms of sarcomeric proteins as well as other “late” genes characteristic of mature muscle fibers in vivo are not expressed in vitro in the absence of nerve and hormones (13). δ-Sarcoglycan is only expressed during the formation of the dystroglycan complex (Figure 1) and thus may represent a “late” muscle gene (14) that could not be expressed by BM-SP stem cell nuclei (Figure 2), possibly due to a failure to reprogram gene expression. From the experimental design of the Lapidos study (8), it was not possible to know to what degree the donor-derived nuclei have entered into the myogenic pathway (all muscle genes other than δ-sarcoglycan may in fact derive from host nuclei) and whether δ-sarcoglycan may be detectable at a later developmental stage, even though a longer time interval after transplantation was not sufficient to detect its expression.

In this context it would be interesting to repeat the experiments conducted by Lapidos et al., obtaining BM-SP stem cells from mice that express a LacZ reporter gene under the control of a myogenic determination gene (i.e., Myf5 or MyoD) or of a muscle gene expressed early after differentiation, such as MLC1/3F (11). I would predict that LacZ would be expressed at variance with δ-sarcoglycan. If this proves to be the case, then previous conflicting reports could be reconciled.

Can BM-SP stem cells be used for therapy?

Despite a number of problems such as low abundance, failure to grow extensively in vitro, and low differentiation potency toward nonhematopoietic lineages, BM-SP stem cells have become very popular in experimental stem cell therapy for primary myopathies and heart infarct (reviewed in refs. 15 and 16). However, if their differentiation toward a mature muscle phenotype cannot be achieved, their prospective use in stem cell therapy for the regeneration of both cardiac and skeletal muscle becomes unrealistic. On the other hand, it should be considered that chromatin remodeling agents, which epigenetically modify histones and associated proteins, may contribute to enhancing expression of certain genes such as those associated with muscle maturation. This hypothesis would be easily testable by repeating the experiments in mice treated with histone deacetylase or methyl-transferase inhibitors.

Finally, it would be important to repeat the same experiments described here by Lapidos et al. (8) with other types of stem cells, such as mesenchymal stem cells (17), multipotent adult progenitors (18), or even neural stem cells (19). None of these cell types have been tested in models of muscu-
lar dystrophy, where replacement of specific
gene products such as the sarcoglycans
could easily be detected. Mesoangioblasts,
on the other hand, have been shown to be
efficacious in restoring expression of β-sar
coglycan in the α-sarcoglycan–null mouse as
well as the expression of the whole dys
trophin complex, including δ-sarcoglyc
an (20). All of these cell types are easy to
expand in culture and, once their homing
and muscle differentiation activities can be
optimized, they may represent a better per
spective for the stem cell therapy of striated
muscle diseases than BM-SP stem cells.

Acknowledgments

I would like to thank G.L. Condorelli and
M. Sampaolesi for critical reading of the
manuscript.

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Marfan syndrome and mitral valve prolapse

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Mitrval valve prolapse (MVP), an abnormal displacement into the left atrium of a thickened and redundant mitral valve during systole, is a relatively fre
quent abnormality in humans and may be associated with serious compli
ations. A recent study implicates fibrillin-1, a component of extracellular
matrix microfibrils, in the pathogenesis of a murine model of MVP (see the
related article beginning on page 1586). This investigation represents an
initial step toward understanding the mechanisms involved in human MVP
disease and the development of potential treatments.

Mitrval valve prolapse: scope
of the problem and evolution
of the defining criteria

Mitrval valve prolapse (MVP) is gener
ally understood to be the displacement of
abnormally thickened, redundant mitral
leaflet(s) into the left atrium during sys
tole (Figure 1) (1). One of the possible con
sequences of this condition is that the
 malfunctioning mitral valve allows back
flow of blood in the left atrium (mitral regur
gitation), which, when severe, leads to
left ventricular enlargement and failure.
Besides severe mitral regurgitation, MVP
has been associated with serious compli
ations such as bacterial endocarditis and
sudden death, and primary mitral valve
surgery is currently performed most fre
quently to specifically treat MVP (1, 2).
Since the early 1970s, research has sug
ested that echocardiography is the ideal
noninvasive technique to visualize the
prolapsing mitral leaflets (3–5). However,
continually changing echocardiographic tech
iques and criteria for the diagnosis of
MVP have in many cases further obscured,
rather than clarified, our understanding of
prolapse in its primary form and in asso
ciation with other disorders (6). Over the
past decade, new echocardiographic crite
ria for MVP have been established based
on an understanding of the 3D structure
of the mitral valve (7). Defined according
to these criteria, prolapse is the displace
ment of 1 or both mitral leaflets by more
than 2 mm above the high points of the
mitral annulus as recorded in either the
parasternal or apical long-axis view (Fig
ure 1, detail). This 2 mm displacement
derives from studies showing that smaller
displacements are not associated with in
creased leaflet thickness, mitral regur
gitation, or valve-related complications
(8). In cases where leaflet displacement
is greater than 2 mm, prolapse is further
subdivided into classic and nonclassic
forms based on leaflet thickness (classic,
>5 mm; and nonclassic, ≤5 mm), with com
plications such as endocarditis or severe
mitral regurgitation generally occurring
in patients with classic prolapse (9).
Using these criteria, a recent population
study of 3,491 subjects from the offspring

properties of murine hematopoietic stem cells that
the mdx mouse restored by stem cell transplantation.
extracellular matrix microfibrils, in the pathogenesis of a murine model of MVP (see the
related article beginning on page 1586). This investigation represents an
initial step toward understanding the mechanisms involved in human MVP
disease and the development of potential treatments.

Nonstandard abbreviations used: FBN1, fibrillin-1;
MVP, mitral valve prolapse; TGFB2, TGF-β receptor 2.

Conflict of interest: The authors have declared that no con
flict of interest exists.

Citation for this article: J. Clin. Invest. 114:1543–1546