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Cell-Surface Protein Profiling Identifies Distinctive Markers of Progenitor Cells in Human Skeletal Muscle

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SUMMARY

Skeletal muscle contains two distinct stem/progenitor populations. One is the satellite cell, which acts as a muscle stem cell, and the other is the mesenchymal progenitor, which contributes to muscle pathogeneses such as fat infiltration and fibrosis. Detailed and accurate characterization of these progenitors in humans remains elusive. Here, we performed comprehensive cell-surface protein profiling of the two progenitor populations residing in human skeletal muscle and identified three previously unrecognized markers: CD82 and CD318 for satellite cells and CD201 for mesenchymal progenitors. These markers distinguish myogenic and mesenchymal progenitors, and enable efficient isolation of the two types of progenitors. Functional study revealed that CD82 ensures expansion and preservation of myogenic progenitors by suppressing excessive differentiation, and CD201 signaling favors adipogenesis of mesenchymal progenitors. Thus, cell-surface proteins identified here are not only useful markers but also functionally important molecules, and provide valuable insight into human muscle biology and diseases.

INTRODUCTION

Skeletal muscle is an organ responsible for movement or physical activity, and therefore is vital for healthy life. Skeletal muscle is mainly composed of multinucleated cylindrical myofibers. Myofibers are terminally differentiated cells, and the cell cycle of their nuclei is irreversibly arrested. However, skeletal muscle regenerates well if myofibers are damaged and undergo necrosis. Skeletal muscle regeneration is attributable to the function of satellite cells that reside between the basal lamina and plasma membrane of myofibers. Satellite cells are normally quiescent, but rapidly become activated after muscle damage and proliferate extensively to produce myoblasts. Myoblasts then differentiate and fuse with each other or damaged myofibers to regenerate muscle. Some myoblasts remain undifferentiated and return to the quiescent state to maintain the satellite cell pool. Thus, satellite cells play a central role in muscle regeneration by acting as muscle stem cells (Bischof, 2004).

Skeletal muscle is also a site where pathological development of ectopic tissues occurs. Adipose tissue, fibrous connective tissue, or even bone can be ectopically formed within muscle not only in muscular disorders but also in other pathological conditions (Uezumi et al., 2014b). Because myofibers are terminally differentiated cells, they cannot be the source of these ectopic tissues. Hence, how these ectopic tissues emerge from skeletal muscle was a long-standing mystery. The identification of mesenchymal progenitors solved this mystery. We and others have identified mesenchymal progenitors distinct from satellite cells in mouse skeletal muscle and have shown that these mesenchymal progenitors contribute to ectopic adipose tissue (Joe et al., 2010; Uezumi et al., 2010), fibrous connective tissue (Uezumi et al., 2011), and heterotopic ossification (Wosczyna et al., 2012). Therefore, satellite cells and mesenchymal progenitors are indispensable cell types for studying skeletal muscle regeneration and pathogenesis, respectively.

Given that satellite cells and mesenchymal progenitors are strongly associated with muscle regeneration and pathogenesis, identifying, distinguishing, and isolating these two progenitor populations in human skeletal muscle are of considerable clinical significance. Compared with

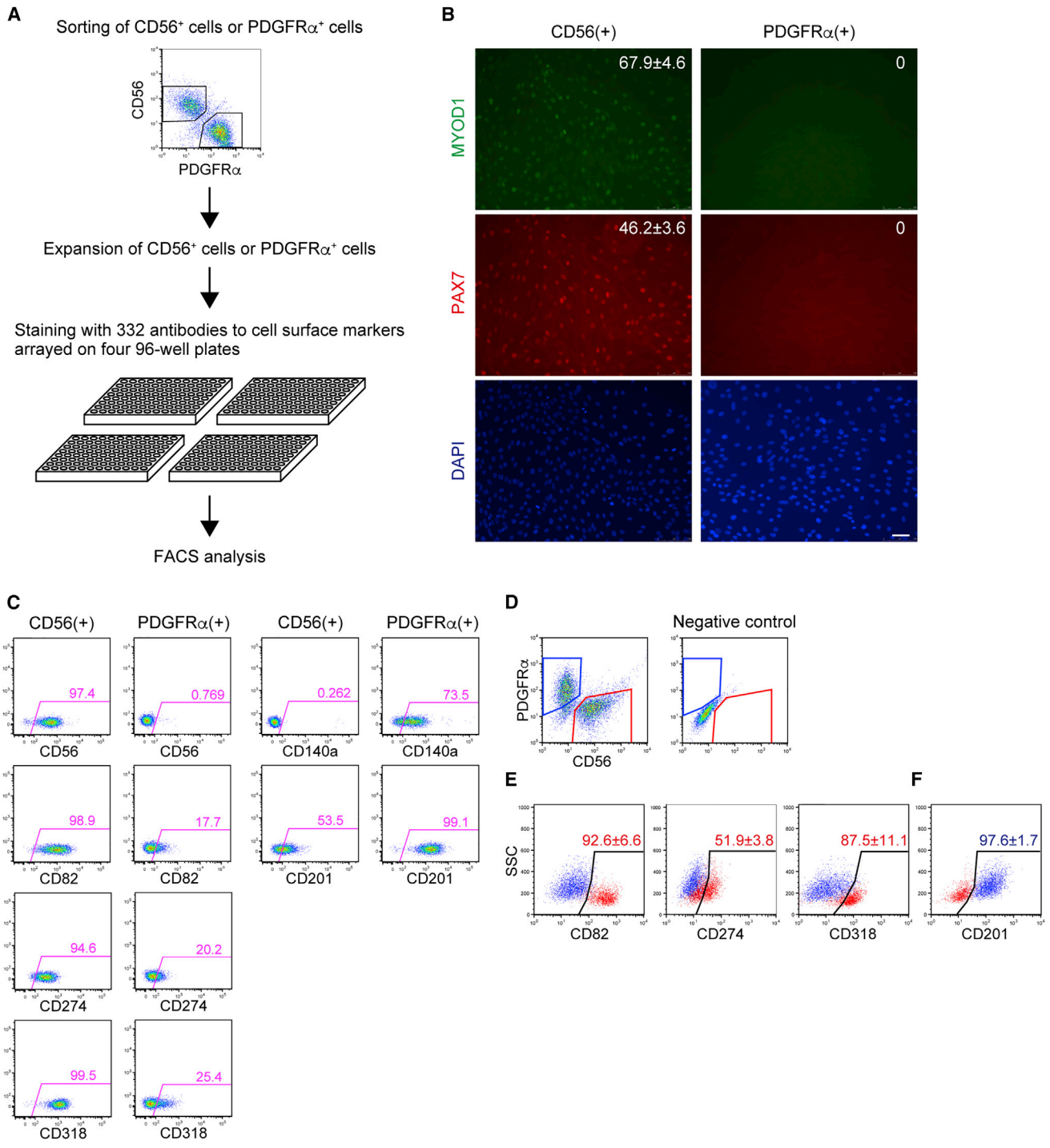

Figure 1. Cell-Surface Protein Profiling of Human Skeletal Muscle-Derived Progenitors by Antibody Screening

(A) Scheme of antibody screening.

(B) Expanded CD56$^+$ cells and PDGFRα$^+$ cells were stained with antibodies against MYOD1 and PAX7. The percentages of positive cells are shown in the panels as means ± SD, n = 5 randomly selected fields. Scale bar, 50 μm.

(C) Distinctive markers identified by antibody screening.

(D) Primary human skeletal muscle-derived cells were stained with antibodies against CD56, PDGFRα, and a newly identified marker. CD56$^+$ (red) and PDGFRα$^+$ (blue) gates were set by analyzing negative control samples stained with an isotype control antibody or secondary reagent only.

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