CHAPTER 12

INFLAMMATION IN SKELETAL MUSCLE REGENERATION

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1. INTRODUCTION

Functional interactions between the immune system and skeletal muscle have been little explored. Until recently, most investigations of muscle inflammation consisted of histological assessments of acute muscle injury or diagnoses of inflammatory myopathies. However, few experimental studies addressed the mechanisms through which immune cells and skeletal muscle affect one another’s differentiation, growth, function or viability. Nevertheless, hints have been provided in the scientific literature for decades to suggest that immune cells may play regulatory roles in muscle development, repair or regeneration. For example, 50 years ago, the sequential invasion of skeletal muscle by morphologically-distinct leukocyte populations was identified as a consequence of muscle injury (Godman, 1957). Furthermore, the elevated numbers of distinct leukocyte populations during muscle repair and regeneration suggested that leukocytes could play a role in those processes (Godman, 1957). Several investigators also noted the presence of leukocytes in elevated numbers and close proximity to skeletal muscle fibers during embryonic development (Abood and Jones, 1991; Nishikawa et al., 1998). Perhaps the unexplored regulatory roles of leukocytes in myogenesis are also reflected in their roles in muscle repair and regeneration.

This chapter focuses on evaluating recent discoveries concerning the functions of leukocytes that invade muscle following injury or modified muscle use, or during muscle disease. Emphases are put on leukocyte populations that can affect muscle repair and regeneration, and on the specific molecules that mediate interactions between muscle cells and leukocytes that affect muscle regeneration. These recent
findings provide the basis for a model that is presented to represent potential functions and interactions between inflammatory cells that can affect repair and regeneration of skeletal muscle.

2. FUNCTIONS OF LEUKOCYTES IN MUSCLE REPAIR AND REGENERATION THAT FOLLOW ACUTE TRAUMA OR MODIFIED MUSCLE USE

Acute muscle trauma or modified muscle use results in a stereotypic inflammatory response that is characterized by the sequential invasion of muscle by specific myeloid cell populations, comprised almost entirely of neutrophils and specific subpopulations of macrophages (Fig. 1). This sequential response suggests that leukocytes may play multiple roles in regulating repair and regeneration of muscle, but they may also promote muscle damage through their capacity as cytolytic cells. The sequential invasion by myeloid cell populations also suggests that each successive stage of the invasion process may depend on interactions between the injured muscle and myeloid cells that invaded previously.

2.1 Do Neutrophils Influence Skeletal Muscle Regeneration?

Neutrophils are rapid and early invaders of skeletal muscle following muscle injury, with their concentrations in muscle becoming tremendously elevated within hours of muscle damage. Neutrophil activation in response to injury is highly-structured, and dominated by the respiratory burst, in which neutrophils rapidly release high concentrations of free radicals that can target cellular debris for removal by phagocytosis. Neutrophils also release proteases that can degrade tissue debris or extracellular matrix (ECM), and secrete pro-inflammatory cytokines that may further promote tissue inflammation (Wiedow and Meyer-Hoffert, 2005). Thus, neutrophils have the capacity to ready injured muscle for regeneration by removing damaged tissue,