Tumor necrosis factor-α alters integrins and metalloprotease ADAM12 levels and signaling in differentiating myoblasts

K. Grzelkowska-Kowalczyk, J. Tokarska, K. Grabiec, M. Gajewska, M. Milewska, M. Błaszczyk

Department of Physiological Sciences, Faculty of Veterinary Medicine, Warsaw University of Life Sciences (SGGW), Nowoursynowska 159, 02-776 Warsaw, Poland

Abstract

The extracellular matrix (ECM) is important in the regulation of myogenesis. We hypothesized that tumor necrosis factor-α (TNF-α) modifies ECM during differentiation of mouse C2C12 myoblasts. Exogenous TNF-α (1 ng/ml) stimulated myoblast fusion on the 3rd day (by 160% vs control) but not on the 5th day of myogenesis. The level of integrin α5 was significantly augmented by TNF-α during 5-day differentiation; however, integrin β1 was higher than control only on the 3rd day of cytokine treatment. Both the abundance of integrin α5 bound to actin and the level of integrin β1 complexed with integrin α5 increased in the presence of TNF-α, especially on the 3rd day of differentiation. Similarly, the stimulatory effects of TNF-α on integrin α3, metalloprotease ADAM12 and kinases related to integrins, FAK and ILK, were limited to the 3rd day of differentiation. We concluded that TNF-α-induced changes in ECM components in differentiating myogenic cells, i.e. i) increased expression of integrin α5, β1, α3, and metalloprotease ADAM12, ii) enhanced formation of α5β1 integrin receptors and interaction of integrin α5-cytoskeleton, and iii) increased expression of kinases associated with integrin signaling, FAK and ILK, were temporarily associated with the onset of myocyte fusion.

Key words: ADAM12, FAK, ILK, integrins, myogenesis, TNF-α

Introduction

The proinflammatory cytokine, tumor necrosis factor-α (TNF-α) influences muscle development, growth and metabolism through numerous mechanisms. It has been shown to promote muscle wasting in several pathological conditions (Yeh et al. 2008) and to impair anabolic hormone/factor signaling in mature myotubes in vitro (Grzelkowska-Kowalczyk and Wieteska, 2006, O’Connor et al. 2008, Grzelkowska-Kowalczyk and Wieteska-Skrzeczyńska 2010). TNF-α is important in satellite cell activation (Chen et al. 2007) and, simultaneously, it inhibited myoblast differentiation by alteration of IGF-I bioavailability (Wieteska-Skrzeczyńska et al. 2011 b).

Extracellular matrix (ECM) is involved in the regulation of myoblast proliferation, migration, adhesion and differentiation (Krauss et al. 2005, Bellayr...