Acheron, a novel regulator of myoblast differentiation

Zhaohui Wang, *University of Massachusetts - Amherst*

Abstract

Programmed cell death is essential for normal development and adult tissue homeostasis in almost all multicelluar organisms. Acheron gene was first isolated from the intersegmental muscles (ISMs) in *Manduca sexta* as a death-associated gene. Subsequently, we cloned human and mouse homolog of Acheron. Acheron encodes a novel protein that has not been previously characterized. Protein structure analysis revealed that Acheron proteins are structurally related to La proteins, but define a novel subfamily. Tissue expression analysis showed that mAcheron is widely expressed in most tissues at both the RNA and protein levels, with brain and heart displaying the highest levels. ^ In mouse C_2C_{12} cells, endogenous Acheron is constitutively expressed in cycling myoblasts and myotubes. Despite the presence of a putative nuclear localization site, the protein is localized predominantly in the cytoplasm. Analyses of the different Acheron transfected C_2C_{12} cells suggested that Acheron is implicated in mediating differentiation and apoptosis in C_2C_{12} cells by differentially regulating the expression of MyoD, Myf5 and Bcl-2. Acheron expression allows C_2 C_{12} cells to up-regulate MyoD and differentiate into myotubes when the cells are induced to undergo differentiation. However, it does not support the myoblast self-renewal by specifically inhibiting the expression of Bcl-2, a key survival factor for 'reserve' cells in DM. Inhibition of Acheron activity by tAch (a putative dominant negative regulatory factor of Acheron) or antisense Acheron results in greatly increased 'reserve' cell population and decreased differentiation under differentiation condition. The mediation of differentiation and survival by Acheron may be achieved through its regulation on integrin—FAK signaling. ^ To help determine how Acheron functions, we performed a yeast 2-hybrid screen with Acheron as the bait. A clone that contains partial cDNA of Ariadne was isolated from the screen. Ariadne contains RING finger domain and is known to bind to

ubiquitin E2 conjugase. *In vitro* ubiquitination assay revealed that Ariadne has ubiquitin E3 ligase activity. We speculate that Ariadne may function as an E3 to target Acheron for ubiquitination and subsequent proteasome-dependent degradation. ^

Subject Area

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