

The phosphoinositide 3-kinase role in IL-6 induction to differentiation of rat embryonic cardiomyocytes

Maria Angela D'Amico¹, Pascal Izzicupo¹, Alessia Di Fonso¹, Adriana Bascelli¹, Sabina Gallina², Angela Di Baldassarre¹

¹G. d'Annunzio University of Chieti-Pescara, Department of Medicine and Aging Science, Chieti, Italy

²G. d'Annunzio University of Chieti-Pescara, Department of Human Movement Science, Chieti, Italy

Purpose. Cardiomyocytes express IL-6 and its signal transducer, 130-kDa glycoprotein (gp130) that influence cell growth, apoptosis, differentiation and survival by an autocrine pathway. High levels of circulating IL-6 have been reported in patients with congestive heart failure (HF) and after myocardial infarction and IL-6-gp130-signaling participates in HF prevention and compensatory hypertrophy, influencing remodeling processes and inducing Protein kinase C (PKC)-dependent apoptosis. Recent studies demonstrated the presence of precursor cells able to differentiate into cardiomyocytes in the adult heart through signaling pathways similar to those in the embryonic heart thus participating to the physiologic repair of the injured heart. In this line, the study of the embryonic signaling may represent an important cue to understand the molecular bases of the regenerative capacity myocardial progenitors. Aim of this study was to investigate the signal transduction pathways evoked by IL-6 treatment on cardiomyoblasts and its possible differentiating effects.

Methods. H9c2 cells cultured in medium supplemented with 1% FBS (differentiation-promoting medium) in presence of IL-6 (10 ng/ml) up to three days.

Results. Western Blot and Immunofluorescence analysis demonstrated that IL-6 after 3 days of treatment induced a marked increase of the expression of α -myosin heavy chain (α -MHC; terminal cardiac differentiation marker) together with a microfilament reorganization and morphological modifications, that included mono-nucleated cells elongation and fusion into multinucleated tubes. This process was accompanied by an evident nuclear translocation of Nkx2.5 (early myocardial development transcription factor), and by a sub-cellular redistribution of gp130.

Results suggest that the biological effects evoked by IL6 were at least partially mediated by PI3K through Akt and PKCzeta pathways modulation, as confirmed by the varied phosphorylated PI3K level observed after 30 min of IL-6 treatment and PI3K induction of downstream PKCzeta phosphorylation, but not PKCalpha and PKCdelta, whereas Akt de-phosphorylation was detected.

Conclusions. Our observations evidenced that PI3K is a key regulator of IL-6-induction of embryonic cardiomyocytes differentiation by PKCzeta and Akt-signaling pathways. These data suggest a possible role of IL-6 dependent pathways in regenerative capacity of myocardial cells following injuries.

Keywords: Cardiomyocytes differentiation, IL-6, PI3K-signaling pathway