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Modulation of nuclear PI-PLCbeta1 during cell differentiation

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ABSTRACT

PI-PLCbeta1 plays an important role in cell differentiation, and particularly in myogenesis, osteogenesis and hematopoiesis. Indeed, the increase of PI-PLCbeta1, along with Cyclin D3, has been detected in C2C12 mouse myoblasts induced to differentiate, as well as in human cells obtained from myotonic dystrophy. Also in the case of osteogenic differentiation there is a specific induction of PI-PLCbeta1, but in this case the role of PI-PLCbeta1 seems to be independent from Cyclin D3, so that a different mechanism could be involved. As for the hematopoietic system, PI-PLCbeta1 has a peculiar behavior: it increases during myeloid differentiation and decreases during erythroid differentiation, thus confirming the role of PI-PLCbeta1 as a modulator of hematopoiesis.

Contents

1. Introduction

Phosphoinositide-specific phospholipase C (PI-PLC) beta1 is a key enzyme that uses phosphatidylinositol 4,5-bisphosphate (PIP2) as a substrate to catalyze the production of inositol 1,4,5-trisphosphate (IP3) and dyacylglycerol (DAG), that in turn can act as second messengers and regulate cell proliferation and differentiation (Yang et al., 2013). Several

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studies showed the importance of PI-PLCbeta1 in inducing a normal differentiation in a number of experimental models, such as myoblasts and hematopoietic cells. Interestingly, mouse myoblasts can be induced to osteogenic differentiation, and also in this case PI-PLCbeta1 was involved. Therefore, this review will discuss the role of PI-PLCbeta1 during myogenesis, osteogenesis and hematopoietic differentiation.

2. Myogenic differentiation

Phosphoinositides (PIs) are the target of kinases and phosphatases that regulate the inositide phosphorylation, thus producing higher or lower PIs. Recent data showed that nuclear PIs are specifically regulated by the basal transcriptional complex protein TAF3 in C2C12 mouse myoblasts, thus affecting myogenic differentiation (Stijf-Bultsma et al., 2015). This study showed that the enzyme responsible for modulating C2C12 differentiation, along with muscle-specific gene expression, was phosphatidylinositol-5-phosphate 4-kinase type-2 beta (PIP4K2B), that is important for the regulation of cell function (Bulley et al., 2015, Keune et al., 2013a). In particular, C2C12 cells showed at least four different groups of genes that could be regulated by the interaction between PI and TAF3: group 1, that increases in case of PIP4K2B depletion, is suppressed by the loss of the TAF3 PI interaction site and is represented by myogenin; group 2, which is downregulated by PIP4K2B depletion, increases if there is loss of the PI interaction site and is represented by Tetraspanin-7; group 3, that is partly decreased by PIP4K2B depletion, is more strongly suppressed when the PI interaction site is lost and is represented by Insulin-like growth factor-binding protein 4; and group 4, which is not directly regulated by PIP4K2B depletion but by PI interaction. All in all, it is conceivable to hypothesize that group 1 and 2 can be regulated by one of the higher PIs, i.e. phosphatidylinositol 5-phosphate (PI5P), that is the substrate of PIP4K2B, whereas group 3 is positively regulated by PIP2, which is the product of PIP4K2B activity (Stijf-Bultsma et al., 2015).

PIs are degraded by phospholipases, i.e. a family of enzymes whose role in physiology and pathology has been extensively investigated (Dusaban and Brown, 2015; Gomez-Cambronero, 2014). Among the others, PI-PLCbeta1 is a key enzyme that has been implicated in brain function (Garcia del Cano et al., 2014) and in other experimental systems. For instance, PI-PLCbeta1 plays an essential role in myogenic differentiation (Fig. 1), given that in vitro and ex vivo studies showed a specific increase of PI-PLCbeta1 during the formation of myotubes. At first, this was evidenced in C2C12 mouse myoblasts induced to differentiate by the Insulin-like growth factor-1 (IGF-1) stimulus, and this PI-PLCbeta1 increase was also correlated to an activation of Cyclin D3 (Faenza et al., 2007). Indeed, it has been demonstrated that Cyclin D3 promoter possesses a binding sequence for PI-PLCbeta1, and this link might be responsible for the activation of Cyclin D3 following PI-PLCbeta1 intervention (Faenza et al., 2007).

More recently, the importance of PI-PLCbeta1 and Cyclin D3 in myogenesis was also confirmed in human cells (Fig. 1), and particularly in myogenic primary cells obtained from patients affected by myotonic dystrophy (Faenza et al., 2012). Myotonic dystrophy is a disease that is characterized by the lack of skeletal muscle differentiation (Schara and Schoser, 2006; Timchenko et al., 2001) and is caused by a genetic mutation affecting a region that is transcribed into RNA but is not

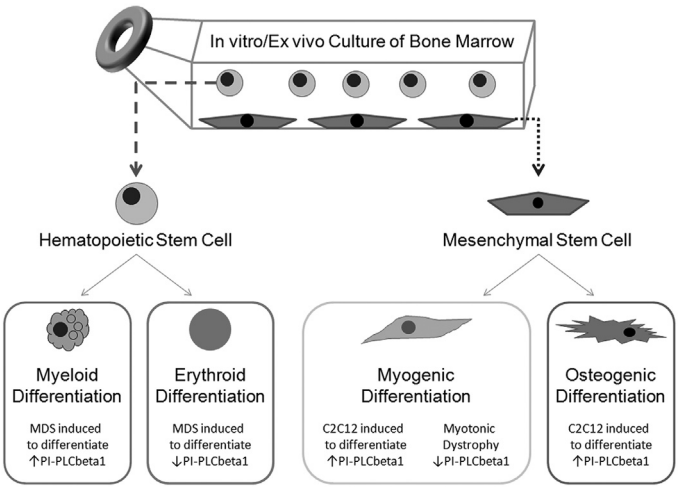

Fig. 1. Role of PI-PLCbeta1 in Cell Differentiation. Bone marrow stem cells undergo several lineages, mainly producing hematopoietic and mesenchymal stem cells that, in turn, can differentiate along a number of lineages. Nuclear PI-PLCbeta1 seems to act as a modulator of differentiation, in that its increase can stimulate the myeloid differentiation of the hematopoietic progenitors in normal cells and in patients affected by Myelodysplastic Syndromes (MDS) that show a favorable response to the demethylating therapy, thus resulting in an activation of normal myeloid differentiation. On the contrary, PI-PLCbeta1 is a negative regulator of the first stages of erythroid differentiation, as detected in MDS samples treated with erythropoietin and showing a positive outcome. As for the role of nuclear PI-PLCbeta1 in myogenic and osteogenic differentiation, also in this case there is an induction of both processes in C2C12-induced differentiation, that mimics the normal processes of differentiation, whilst patients affected by myotonic dystrophy, who are characterized by an impaired myogenic differentiation, show a strong decrease in nuclear PI-PLCbeta1.