TRANSCRIPTIONAL REGULATION THROUGH LONG-RANGE CHROMATIN INTERACTIONS IN MUSCLE CELLS: THE CDKN1C-KCNQ1 LOCUS

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Abstract

The muscle regulatory factor MyoD, the master regulator of myogenesis, induces the expression of the cdk inhibitor p57, a critical regulator in many developmental and pathological processes. p57 is an imprinted gene and its expression, restricted to specific cell types, is subject to a complex epigenetic control not yet completely understood. We found that, during differentiation, MyoD induces the coordinate activation of p57 and of the co-imprinted gene kcnq1. Moreover, we demonstrated that the induction of p57 requires MyoD binding to a long-distance element located within the imprinting control region KvDMR1 and the consequent release of a repressive chromatin loop involving p57 promoter. The present project has two main objectives. The first is the identification of the molecular mechanisms by which KvDMR1 controls the restriction and the induction of p57 during skeletal myogenesis. Specific tasks will be: 1) the analysis of the functional interaction between MyoD and CTCF at KvDMR1, in regulating the dynamics of the chromatin loop. 2) the analysis of the role of the long noncoding RNA Knq1ot1 in the differentiation-dependent regulation of p57. 3) the analysis of the epigenetic determinants of KvDMR1 accessibility to MyoD binding.

The second objective is the elucidation of the epigenetic regulation of kcnq1, a gene coding for a subunit of a voltage-dependent potassium channel and playing an important role in the physiology of skeletal and especially cardiac muscle. This analysis will be performed in an in vitro cell system of cardiac differentiation based on the direct reprogramming of fibroblasts into cardiomyocytes. We plan the following approaches: i) analysis of kcnq1 expression during differentiation ii) analysis of kcnq1 promoter function iii) analysis of the functional interaction of cardiogenic bHLH proteins with KvDMR1 iv) mapping of the long-range chromatin interactions of kcnq1 promoter.
GROUP COMPONENTS

Anna Busanello, Postdoctoral fellow.
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Relevant publications 2006-2012

Busanello, A. Battistelli, C. Carbone, M. Mostocotto, C., Maione R.
MyoD regulates p57kip2 expression by interacting with a distant cis-element and modifying a higher-order chromatin structure
*Nucleic Acids Research.* 2012 40 (17): 8266-75 I.F. 8.03

Mitochondrial localization of PARP-1 requires interaction with mitofilin and is involved in the maintenance of mitochondrial DNA integrity.

Carbone M, Rossi MN, Cavaldesi M, Notari A, Amati P, Maione R.
Poly(ADP-ribosyl)ation is implicated in the G0-G1 transition of resting cells.
*Oncogene.* 2008; 27(47):6083-92. I.F. 7.41

Figliola R, Busanello A, Vaccarello G, Maione R.
Regulation of p57(KIP2) during muscle differentiation: role of Egr1, Sp1 and DNA hypomethylation.
*J Mol Biol.* 2008;380(2):265-77. I.F. 4.01

PARP-1 interaction with VP1 capsid protein regulates polyomavirus early gene expression.
*J Mol Biol.* 2006; 363(4):773-85. I.F. 4.01

Vaccarello G, Figliola R, Cramerotti S, Novelli F, Maione R.
p57Kip2 is induced by MyoD through a p73-dependent pathway.
*J Mol Biol.* 2006; 356(3):578-88. I.F. 4.01