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Differential expression of HMGA proteins influence HP1 dynamics and myogenic differentiation

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Introduction:

HMGA proteins are abundant architectural chromatin proteins. They bind to AT-rich DNA and localize preferentially in heterochromatin. Their acidic C-terminal domain is considered to be relevant in interactions between HMGA and other factors. In addition, HMGA proteins are expressed particularly in early embryos and undifferentiated cells. In differentiated cells they are downregulated and high HMGA expression levels in adult cells correlate with tumor progression and malignancy.

Materials and Methods:

We used C2C12 mouse myoblast cells as a model system to investigate the influence of HMGA1 on differentiation and chromatin plasticity. Therefore, we created C2C12 cells stably expressing HMGA1a-EGFP and performed knock down of HMGA1 by siRNA. Using bimolecular fluorescence complementation (BiFC), we examined protein-protein interaction between HMGA and HP1 in living cells.

Results:

We showed for the first time that HMGA1 expression is gradually downregulated after induction of myogenesis. However, persistent HMGA expression inhibited myogenesis. This inhibition can be explained by an HMGA-dependent misexpression of several genes that are required for proper differentiation. RNAi experiments demonstrated that downregulation of HMGA proteins is necessary to restore proper gene expression and to release the myogenic program.

Furthermore, BiFC analyses revealed that the acidic C-terminus of HMGA interacts with the chromodomain of HP1. Photobleaching experiments indicated that the HP1 residence in heterochromatin dependents on the presences of functional HMGA proteins. Moreover, HP1 binding properties during early myogenic differentiation variegate dependent on the expression level of HMGA1.

Discussion and Conclusion:

Together, our data indicate that the differential expression of HMGA proteins and their capacity to interact with HP1 proteins participates in the regulation of heterochromatin maintenance and plasticity during differentiation. We propose that downregulation of HMGA proteins is required to allow chromatin plasticity and remodeling and to enable cells to enter the myogenic differentiation program.