Protein Kinase C activation regulates NDRG1 expression

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N-myc downstream regulated gene 1 (NDRG1) is a member of the NDRG family of intracellular proteins, and plays a central role in a wide range of biological processes including stress response, differentiation, and maintenance of the myelin sheath. The overexpression of NDRG1 is an indicator of poor prognosis in various pathological conditions. Here, we found that NDRG1 is an independent prognostic marker of poor outcome in breast cancer (BC). The relationship with an aggressive phenotype was underlined by the survival analysis, where Kaplan-Meier curves showed a worse clinical outcome in the subgroup of Triple Negative BC (TNBC) with high NDRG1 expression. In vitro, CRISPR-based inactivation of NDRG1 allowed us to demonstrate that this protein is required for breast cancer cell invasion, without affecting viability. NDRG1 expression is regulated by a variety of molecular mechanisms, including transcriptional and post-translational control. We observed that different acute stress conditions converge on protein kinase C (PKC) activation driving enhanced NDRG1 expression through a signaling pathway that involves ROCK/AMPK/Akt kinases. This newly discovered mechanism was specific for

NDRG1 as the expression of other NDRG members was not affected. Together, our results suggest that pathophysiological PKC-mediated activation of NDRG1 may be a response mechanism to metabolic stress and anticancer agents.