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PARP1 Links Transcription of a Subset of RBL2-Dependent Genes with Cell Cycle Progression

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Abstract : Apart from protecting genome, PARP1 has been documented to regulate many intracellular processes inter alia gene transcription by physically interacting with chromatin bound proteins and by their ADP-ribosylation. Our recent findings indicate that expression of PARP1 decreases during the differentiation of human CD34+ hematopoietic stem cells to monocytes as a consequence of differentiation-associated cell growth arrest and formation of E2F4-RBL2-HDAC1-SWI/SNF repressive complex at the promoter of this gene. Since the RBL2 complexes repress genes in a E2F-dependent manner and are widespread in the genome in G0 arrested cells, we asked (a) if RBL2 directly contributes to defining monocyte phenotype and function by targeting gene promoters and (b) if RBL2 controls gene transcription indirectly by repressing PARP1. For identification of genes controlled by RBL2 and/or PARP1,we used primer libraries for surface receptors and TLR signaling mediators, genes were silenced by siRNA or shRNA, analysis of gene promoter occupation by selected proteins was carried out by ChIP-qPCR, while statistical analysis in GraphPad Prism 5 and STATISTICA, ChIP-Seq data were analysed in Galaxy 2.5.0.0. On the list of 28 genes regulated by RBL2, we identified only four solely repressed by RBL2-E2F4-HDAC1-BRM complex. Surprisingly, 24 out of 28 emerged genes controlled by RBL2 were co-regulated by PARP1 in six different manners. In one mode of RBL2/PARP1 co-operation, represented by MAP2K6 and MAPK3, PARP1 was found to associate with gene promoters upon RBL2 silencing, which was previously shown to restore PARP1 expression in monocytes. PARP1 effect on gene transcription was observed only in the presence of active EP300, which acetylated gene promoters and activated transcription. Further analysis revealed that PARP1 binding to MA2K6 and MAPK3 promoters enabled recruitment of EP300 in monocytes, while in proliferating cancer cell lines, which actively transcribe PARP1, this protein maintained EP300 at the promoters of MA2K6 and MAPK3. Genome-wide analysis revealed a similar distribution of PARP1 and EP300 around transcription start sites and the co-occupancy of some gene promoters by PARP1 and EP300 in cancer cells. Here, we described a new RBL2/PARP1/EP300 axis which controls gene transcription regardless of the cell type. In this model cell, cycle-dependent transcription of PARP1 regulates expression of some genes repressed by RBL2 upon cell cycle limitation. Thus, RBL2 may indirectly regulate transcription of some genes by controlling the expression of EP300-recruiting PARP1. Acknowledgement: This work was financed by Polish National Science Centre grants nr DEC-2013/11/D/NZ2/00033 and DEC-2015/19/N/NZ2/01735. L.V. is funded by the National Research, Development and Innovation Office grants GINOP-2.3.2-15-2016-00020 TUMORDNS, GINOP-2.3.2-15-2016-00048-STAYALIVE and OTKA K112336. AR is supported by Polish Ministry of Science and Higher Education 776/STYP/11/2016.

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