

A novel Rac1/PAK1/BCL6/STAT5 pathway modulates the expression of cell-cycle-associated genes in colorectal cancer cells



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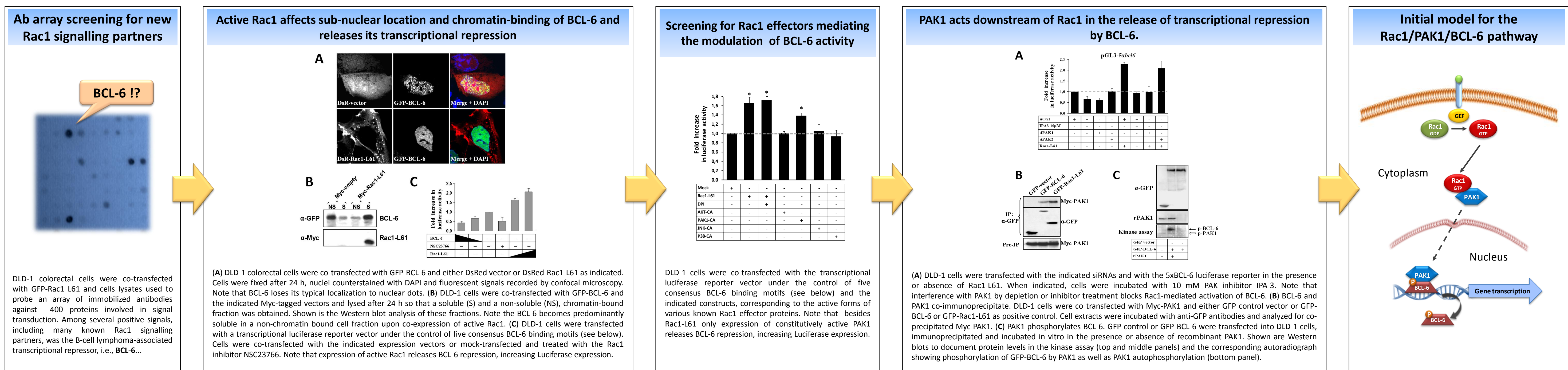
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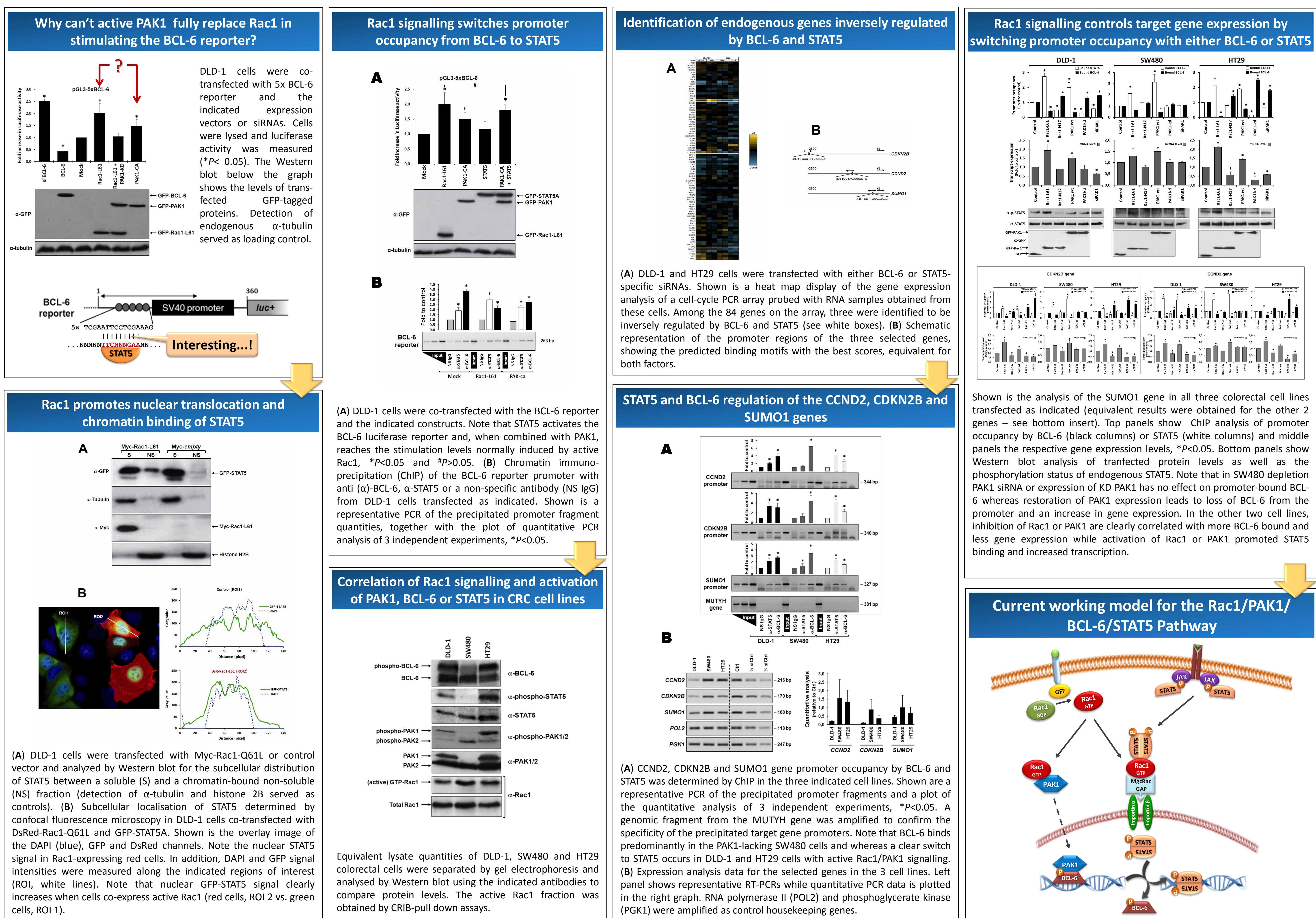
Summary

Gene expression depends on binding of transcriptional regulators to gene promoters, a process controlled by signalling pathways. The transcriptional repressor BCL-6 downregulates genes involved in cell cycle progression and becomes inactivated following phosphorylation by the Rac1 GTPase activated protein kinase PAK1. Interestingly, the DNA motifs recognized by BCL-6 and STAT5 are similar. Because STAT5 stimulation in epithelial cells can also be triggered by Rac1 signalling, we asked whether both factors have opposing roles in transcriptional regulation and whether Rac1 signalling may coordinate a transcription factor switch. We used chromatin immunoprecipitation to show that active Rac1 promotes release of the repressor BCL-6 while increasing binding of STAT5A to a BCL-6-regulated reporter gene. We further show in colorectal cell lines that the endogenous activation status of the Rac1/PAK1 pathway correlated with the phosphorylation status of BCL-6 and STAT5A. Three cellular genes (cyclin D2, p15INK4B, SUMO1) were identified to be inversely regulated by BCL-6 and STAT5A and responded to Rac1 signalling with increased expression and corresponding changes in promoter occupancy. Together, our data show that Rac1 signalling controls a group of target genes that are repressed by BCL-6 and activated by STAT5A, providing novel insights into the modulation of gene transcription by GTPase signalling.

Previous work: Rac1 Signaling Modulates BCL-6-Mediated Repression of Gene Transcription



New Data: The STAT5/BCL-6 transcriptional switch downstream of Rac1



Conclusion & Perspectives:

- We identified a novel pathway through which Rac1 signalling can modulate the expression of a selected group of target genes.
- The next step will be the genome-wide identification of these genes to plot a profile of the impact of this pathway in the regulation of the cells transcriptome.

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