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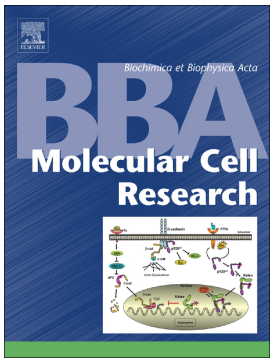


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# c-Abl Phosphorylation of Yin Yang 1's Conserved Tyrosine 254 in the Spacer Region Modulates its Transcriptional Activity

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## ABSTRACT

Yin Yang 1 (YY1) is a multifunctional transcription factor that can activate or repress transcription depending on the promotor and/or the co-factors recruited. YY1 is phosphorylated in various signaling pathways and is critical for different biological functions including embryogenesis, apoptosis, proliferation, cell-cycle regulation and tumorigenesis. Here we report that YY1 is a substrate for c-Abl kinase phosphorylation at conserved residue Y254 in the spacer region. Pharmacological inhibition of c-Abl kinase by imatinib, nilotinib and GZD824, knock-down of c-Abl using siRNA, and the use of c-Abl kinase-dead drastically reduces tyrosine phosphorylation of YY1. Both radioactive and non-radioactive *in vitro* kinase assays, as well as co-immunoprecipitation in different cell lines, show that the target of c-Abl phosphorylation is tyrosine residue 254. c-Abl phosphorylation has little effect on YY1 DNA binding ability or cellular localization in asynchronous cells. However, functional studies reveal that c-Abl mediated phosphorylation of YY1 regulates YY1's transcriptional ability *in vivo*. In conclusion, we demonstrate the novel role of c-Abl kinase in regulation of YY1's transcriptional activity, linking YY1 regulation with c-Abl tyrosine kinase signaling pathways.

## 1. Introduction

Protein kinase signaling pathways transduce extracellular signals that are integrated at gene promotors, transcription factors, co-regulators and chromatin proteins [1]. Therefore, transcription factors are critical for signal transduction pathways that relay information from the cell surface to the nucleus [2]. Tyrosine phosphorylation is an important mechanism for modulating biological processes such as differentiation and growth [3]. Also, aberrant regulation of signaling pathways that are controlled by tyrosine phosphorylation has been associated with various types of cancers. Many protein tyrosine kinases (PTKs) have been identified as the products of proto-oncogenes [4].

Transcription factors may harbor multiple phosphorylation sites that serve as points of convergence of signaling pathways that initiate at the plasma membrane [5]. Adding to the complexity of regulation is the finding that transcription factors can be the target of several posttranslational

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