# FEATURES

VOLUME 116 • NUMBER 9

## Functional Significance of Nuclear α Spectrin



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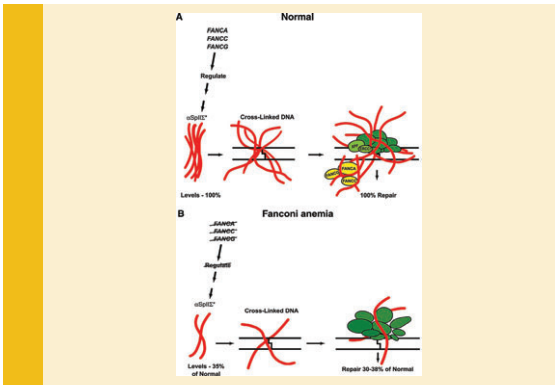
ACCEPTED MANUSCRIPT ONLINE 10 MARCH 2015




Nonerythroid alpha spectrin (αIISp) interacts in the nucleus with an array of different proteins indicating its involvement in a number of diverse functions. However, the significance of these interactions and their functional importance has been a relatively unexplored area. The best documented role of nuclear αIISp is in DNA repair where it is critical for repair of DNA interstrand cross-links (ICLs), acting as a scaffold recruiting proteins to sites of damage in genomic and telomeric DNA. A deficiency in αIISp can importantly impact DNA ICL repair as is seen in cells from patients with the genetic disorder, Fanconi anemia (FA), where loss of αIISp leads to not only defects in repair of both genomic and telomeric DNA but also to telomere dysfunction and chromosome instability. This previously unexplored link between αIISp and telomere function is important in developing an understanding of maintenance of genomic stability after ICL damage. In FA cells, these defects in chromosome instability after ICL damage can be corrected when levels of αIISp are returned to normal by knocking down μ-calpain, a protease which cleaves αIISp. These studies suggest a new direction for correcting a number of the phenotypic defects in FA and could serve as a basis for therapeutic intervention. More in depth, examination of the interactions of αIISp with other proteins in the nucleus is of major importance in development of insights into the interacting key elements involved in the diverse processes occurring in the nucleus and the consequences loss of αIISp has on them.

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## Growth Hormone Induces Transforming Growth Factor-Beta-Induced Protein in Podocytes: Implications for Podocyte Depletion and Proteinuria



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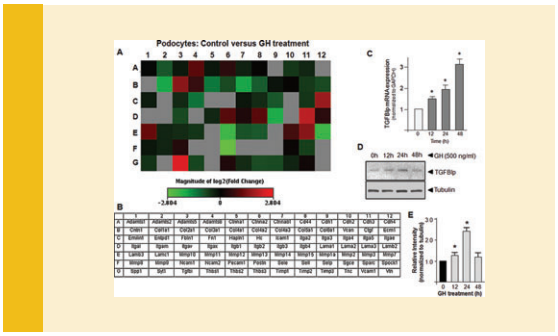
ACCEPTED MANUSCRIPT ONLINE 4 MARCH 2015




The glomerular podocytes form a major size selective barrier for the filtration of serum proteins and reduced podocyte number is a critical event in the pathogenesis of proteinuria during diabetic nephropathy (DN). An elevated level of growth hormone (GH) is implicated as a causative factor in the development of nephropathy in patients with type 1 diabetes mellitus. We have previously shown that podocytes express GH receptor and are a target for GH action. To elucidate the molecular basis for the effects of GH on podocyte depletion, we conducted PCR-array analyses for extracellular matrix and adhesion molecules in podocytes. Our studies reveal that GH increases expression of a gene that encodes transforming growth factor-beta-induced protein (TGFBIp) expression. Similarly, microarray data retrieved from the Nephromine database revealed elevation of TGFBIp in patients with DN. Treatment with GH results in increased secretion of extracellular TGFBIp by podocytes. Both GH and TGFBIp induced apoptosis and epithelial mesenchymal transition (EMT) of podocytes. Exposure of podocytes to GH and TGFBIp resulted in increased migration of cells and altered podocyte permeability to albumin across podocyte monolayer. Administration of GH to rats induced EMT and apoptosis in the glomerular fraction of the kidney. Therefore, we conclude that the GH-dependent increase in TGFBIp in the podocyte is one of the mechanisms responsible for podocyte depletion in DN.

Journal of Cellular Biochemistry

## Gcn5 Modulates the Cellular Response to Oxidative Stress and Histone Deacetylase Inhibition



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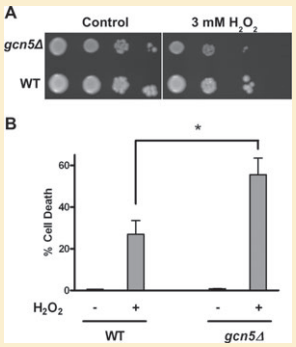
ACCEPTED MANUSCRIPT ONLINE 9 MARCH 2015

To identify chemical genetic interactions underlying the mechanism of action of histone deacetylase inhibitors (HDACi) a yeast deletion library was screened for hypersensitive deletion mutants that confer increased sensitivity to the HDACi, CG-1521. The screen demonstrated that loss of *GCN5* or deletion of components of the Gcn5 histone acetyltransferase (HAT) complex, SAGA, sensitizes yeast to CG-1521-induced cell death. Expression profiling after CG-1521 treatment reveals increased expression of genes involved in metabolism and oxidative stress response, and oxidative stress response mutants are hypersensitive to CG-1521 treatment. Accumulation of reactive oxygen species and increased cell death are enhanced in the *gcn5*Δ deletion mutant, and are abrogated by anti-oxidants, indicating a central role of oxidative stress in CG-1521-induced cell death. In human cell lines, siRNA mediated knockdown of GCN5 or PCAF, or chemical inhibition of GCN5 enzymatic activity, increases the sensitivity to CG-1521 and SAHA. These data suggest that the combination of HDAC and GCN5/PCAF inhibitors can be used for cancer treatment.

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## Regulation of *CYBB* Gene Expression in Human Phagocytes by a Distant Upstream NF-κB Binding Site



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ACCEPTED MANUSCRIPT ONLINE 9 MARCH 2015

The human *CYBB* gene encodes the gp91-*phox* component of the phagocyte oxidase enzyme complex, which is responsible for generating superoxide and other downstream reactive oxygen species essential to microbial killing. In the present study, we have identified by sequence analysis a putative NF-κB binding site in a DNase I hypersensitive site, termed HS-II, located in the distant 5′ flanking region of the *CYBB* gene. Electrophoretic mobility assays showed binding of the sequence element by recombinant NF-κB protein p50 and by proteins in nuclear extract from the HL-60 myeloid leukemia cell line corresponding to p50 and to p50/p65 heterodimers. Chromatin immunoprecipitation demonstrated NF-kB binding to the site in intact HL-60 cells. Chromosome conformation capture (3C) assays demonstrated physical interaction between the NF-κB binding site and the *CYBB* promoter region. Inhibition of NF-κB activity by salicylate reduced *CYBB* expression in peripheral blood neutrophils and differentiated U937 monocytic leukemia cells. U937 cells transfected with a mutant inhibitor of κB "super-repressor" showed markedly diminished *CYBB* expression. Luciferase reporter analysis of the NF-κB site linked to the *CYBB* 5′ flanking promoter region revealed enhanced expression, augmented by treatment with interferon-γ. These studies indicate a role for this distant, 15 kb upstream, binding site in NF-κB regulation of the *CYBB* gene, an essential component of phagocyte-mediated host defense.