INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY

www.ijabpt.com Volume-4, Issue-4, Oct-Dec-2013 Coden : IJABPT Copyrights@2013

ISSN : 0976-4550

*Received: 29th August-2013* *Revised: 08th Sept-2013* *Accepted: 28th Sept-2013*

***Review article***

# ABL TYROSINE KINASES AND DNA METHYLATION MAY MEDIATE IN HIGH GLUCOSE INDUCED HYPEROSMOLALITY; ROLE OF TARGET PROTEINS

Manoj G Tyagi and Vishakha Tyagi

Department of Pharmacology, Christian Medical College, Vellore 632002, Tamilnadu

*Author for Correspondence: E-mail: tyagi239@yahoo.co.in*

**ABSTRACT:** Phosphorylation of proteins on their threonine, serine, and tyrosine residues is one of the most commonly occurring posttranslational modifications in eukaryotic cells. Cellular phosphorylation cascades facilitates the amplification of extracellular signals following changes in environmental conditions via the ability of phosphorylated activators to modulate the expression of numerous genes. Because these reactions are rapidly reversible, they are important for the regulation of many cellular functions including signal transduction, cell division, and proliferation. Hyperosmolality can induce tyrosine phosphorylation of TonEBP/OREBP. Tyrosine phosphorylation by Abl kinases of several target proteins is a key mechanism for modulating signal transduction in hyperosmolar conditions. In this review article we discuss the role of Abl tyrosine kinases and DNA methylation during glucose induced hyperosmolality.

## INTRODUCTION

Abl (Abelson murine leukemia) protein tyrosine kinases have been extensively studied and reviewed (Smith & Mayer, 2002, Gu *et al* 2009) because of their many important roles, including those in cancer and stress-induced apoptosis. c-Abl (ABL1) tyrosine kinase was originally identified as the normal cellular homologue of the constitutively active v-Abl oncogene product of Abelson murine leukemia virus. Another constitutively active form, BRC-ABL, is responsible for causing human leukemia. In contrast to the constitutive activity of the oncogenic forms of Abl, the activity of normal c-Abl is tightly restricted in unstimulated cells. The differences between the tight restriction of normal c-Abl kinase activity and the elevated constitutive activity of the oncogenic forms are complex and are not well understood.

On the other hand, Diabetic or hyperglycaemic neuropathy is a major complication of diabetes, estimated to develop in approximately 50% of diabetic patients, and is the main cause of nontraumatic amputations in the U.S. Hyperglycaemic neuropathy reflects decreased nerve conduction velocity, which indicates a prominent role for Schwann cells because they ensheath peripheral nerves and provide support for nerve conduction and axon regeneration (Lehmann and Hoke, 2010, Thompson *et al* 2010). Moreover, high glucose induces oxidative damage in Schwann cells (Pop-Busui *et al* 2006), considered a major factor in diabetic complications (Russell *et al* 1999). A major challenge in treating diabetic complications is that molecular and pathological features of high glucose are maintained despite excellent control of blood glucose, a phenomenon referred to as metabolic memory ( Ihnat *et al* 2007). For example, elevated glucose increases fibronectin and inflammatory mediators, such as IL-1 beta, NF-kappa B, VEGF, TNF-alpha, TGF-beta and ICAM-1, and these effects are sustained following normalization of glucose levels in the window of days to weeks, however these may contribute to the neuropathy in these patients (Roy *et al* 1990, Kowluru *et al* 2010). TonEBP has been shown to affect the activity of aldose reductase an enzyme which causes conversion of glucose to sorbitol. In this article we review the actions of Abl kinase and DNA methylation in modulating signaling elements during high glucose induced hyperosmolality.

Coden : IJABPT Copyrights@2013 ISSN : 0976-4550

## DNA Methylation in glucose induced hyperosmolality

According to previous metabolic memory studies, the persistent effects of high glucose suggest a possibility for epigenetic alterations particularly those mediated through methylation of DNA. Both Fbp1 and Fbp2 expression, which were the most inhibited genes in the present study, are regulated by DNA methylation (Esther Kim *et al* 2013). DNA methylation is involved in the control of genomic imprinting, which is an epigenetic form of gene regulation whereby a gene or genomic domain can be biochemically marked with information about its potential origin. Changes in DNA methylation profiles can occur during aging and in pathologic states, such as cancer and metabolic diseases (El-Osta et al 2008, Suzuki et al 2004). Metabolic disorders such as obesity and type 2 diabetes (T2D) have reached epidemic rates in most developed and developing countries but little is known of the role of DNA methylation in diabetes pathogenesis. Several lines of evidence support a role for nongenetic factors in the development of insulin-resistance and indicate that epigenetic factors, possibly through DNA methylation, may play a role in diabetes pathogenesis (Figure 1). Thus, depending on the individual CpG dinucleotide, DNA methylation corresponded either positively or negatively with gene expression. These patterns may be dependent on the specific loci of regulation and transcription factor binding, and are the subject of further examination. Importantly, almost all of the changes in DNA methylation were not reversed by a return to normal glucose levels.

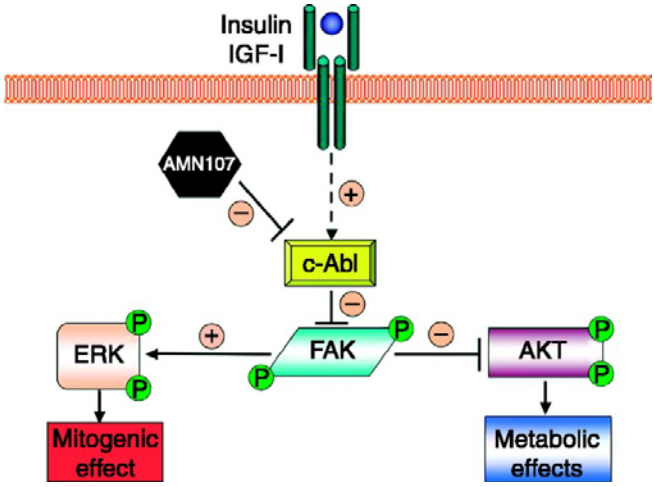


**Figure 1 : Insulin action through c-Abl tyrosine kinase enzyme.**

## c-Abl protein kinase and DNA methylation

The structural configurations and dynamic regulation of the c-Abl tyrosine kinases have been reviewed recently by Panjarian *et al* (2013). The facilitated binding of c-Abl to DNA containing methylcytosine residues may also be due to an indirect influence of the methyl group on the deformability of the double helix consequent upon protein binding. In contrast to HMG proteins, c-Abl does not bend its target sequence but nevertheless is sensitive to the deformability of the DNA. At present it is difficult to explain why the binding of c-Abl to DNA is enhanced when C residues are replaced with M residues. One possible explanation, as yet purely conjectural, is that the C→M substitution exaggerates the propensity of the double helix to denature locally, thus favouring the interaction of c-Abl with M-containing DNA. Moreover, studies have identified DNA binding proteins which interact with a sequence found in an intron of the tyrosine kinase coding portion of the murine c-abl gene and Methylation inhibits the interaction of dna binding proteins with a potential C-ABL intron regulatory element (Hengst-Zhang & Weitzman 1992, Bjornston *et al* 2008). The repression of TopBP1 (Topoisomerase binding protein 1) on c-Abl expression was abolished when DNA methylation was inhibited, suggesting either that TopBP1 repressor function might require DNA methylation or that TopBP1 itself is involved in DNA methylation. Third, it has been reported that HDACs interact with DNA methyltransferases to synergistically repress gene expression. This could be a novel mechanism by which TopBP1 represses gene expression and certainly warrants further investigation. Furthermore, the role for TopBP1 in silencing c-*Abl* may have some therapeutic implications, as silencing of c-*Abl*plays an important role in cell transformation under certain conditions (Zheng *et al* 2005). Whether these interactions between c-Abl and DNA methylation also contribute to hyperglycaemic neuropathy needs further investigation.

### c-Abl and phosphorylation of TonEBP

In order to maintain biochemical homeostasis under hypertonic stress, cells elicit a genetic program of osmoadaptive responses in which intracellular electrolytes are gradually replaced by uncharged small organic osmolytes including sorbitol, betaine, myo-inositol, taurine and glycerophosphocholine (Burg *et al* 1997). These organic osmolytes play a key role in osmoadaptation because they can be accumulated to a high level without perturbing macromolecular structure and function. Specific enzymes and transporters are responsible for the accumulation of these organic osmolytes: sorbitol and glycerophosphocholine are synthesized by aldose reductase (AR) and neuropathy target esterase (NTE), respectively; whereas betaine, myo-inositol and taurine are taken up into cells via betaine transporter (BGT1), sodium/myo-inositol cotransporter (SMIT), and sodium/chloride-dependent taurine transporter (TAUT), respectively (Rim *et al* 1998, Ferraris 1999). Gene transcription of these enzymes and transporters, collectively known as osmoprotective genes, is markedly upregulated by hypertonic challenge. This is carried out by one or multiple enhancers known as the osmotic-response element (ORE) (Takenaka *et al* 1994) or tonicity-responsive enhancer (TonE) (Ko *et al* 1997) located in the regulatory region of these genes, except for the NTE gene for which the activity of putative OREs has not been functionally confirmed. The identified ORE and TonE share a putative consensus sequence of NGGAAAWDHMC (N). In general, the ORE/TonE exists singly or in tandem at the proximal promoter region of these genes, but OREs/TonEs can also be scattered along an extended upstream region, as demonstrated by the SMIT gene (Miyakawa *et al* 1999). The cognate transcription factor for ORE/TonE was independently identified as TonE-binding protein (TonEBP) and ORE-binding protein (OREBP) through yeast one-hybrid screening and affinity chromatography (Ko *et al* 2000), respectively. TonEBP/OREBP-Y143 is a predicted c-Abl phosphorylation site. c-Abl kinase preferentially phosphorylates peptides with the consensus YXXP, where Y is tyrosine, X is any amino acid, and P is proline. The activity of the enzyme phospholipase C γ 1 affects the TonEBP nuclear localization via the Y 143. It has been proposed that the contribution of c-Abl to the high NaCl induced increase of transactivating activity of TonEBP through a less understood action on the protein kinase ATM (Cujec *et al* 2002, Irarrazabal *et al* 2010).

## Conclusion

Hyperglycemia, similarly to aging, induces chromatin remodeling in mouse hepatocytes, in comparison to normoglycemia and early-age, respectively. Changes in glucose metabolism also affect the action and expression of various proteins and action mediated through the c-Abl kinases, promoting changes in chromatin conformation and dynamics. Because increased hyperplasia and apoptosis have been reported in hepatocytes of diabetic rats, it has been hypothesized that hyperglycemic animals might also suffer from early aging . It is suggested that c-Abl protein mediate cellular changes through the hypertonicity induced DNA damage and DNA methylation could also be key to these effects on cellular integrity.

## REFERENCES

Bjornsson HT, Sigurdsson MI, Fallin MD, (2008). Intra-individual changeover time in DNA methylation with familial clustering. JAMA;299:2877–83.

Burg MB, Kwon ED, Kültz D (1997). Regulation of gene expression by hypertonicity.Annu Rev Physiol 59:437-455.

Cujec.P. Patricia F. Medeiros, Phil Hammond, Cecil Rise, and Brent L. Kreider (2002). Selection of v-Abl Tyrosine Kinase Substrate Sequences from Randomized Peptide and Cellular Proteomic Libraries Using mRNA Display hybrid and its display. Chemistry & Biology, Volume 9, Issue 2, February, Pages 253–264

E S. Kim , Fumiko Isoda , Irwin Kurland and Charles V. Mobbs. (2013). Glucose-Induced Metabolic Memory in Schwann Cells: Prevention by PPAR Agonists. Endocrinology May 24, 1097, 1-14

El-Osta A, Brasacchio D, Yao D, Pocai A, Jones PL, Roeder RG, Cooper ME, Brownlee M.(2008). Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia.J Exp Med. 205(10):2409-2417.

Ferraris JD, Williams CK, Ohtaka A, Garcia-Perez A. (1999). Functional consensus for mammalian osmotic response elements. Am J Physiol, 276:C667-C673.

Gu J. J., Ryu J. R., Pendergast A. M. (2009) Abl tyrosine kinases in T-cell signaling. Immunol. Rev.228, 170– 183.

Ihnat MA, Thorpe JE, Ceriello A. (2007). Hypothesis: the 'metabolic memory', the new challenge of diabetes. Diabet Med. 24 (6):582- 586.

Hengst-Zhang J A, Sigmund A. Weitzman. (1992). Methylation inhibits the interaction of dna binding proteins with a potential C-ABL intron regulatory element. Biochemical and Biophysical Research Communications, Volume 186, Issue 3, 14 August, Pages 1515–1521

Irarrazabal, C. E., Gallazzini, M., Schnetz, M. P., Kunin, M., Simons, B. L., Williams, C. K., Burg, M. B., and Ferraris, J. D. (2010) PLC- γ1 contributes to signaling high NaCl-dependent activation of the osmoprotective transcription factor TonEBP/ OREBP. Proc. Natl. Acad. Sci. U. S. A. 107**,** 906–911

Ko BC, Ruepp B, Bohren KM, Gabbay KH, Chung SS. (1997). Identification and characterization of multiple osmotic response sequences in the human aldose reductase gene. J Biol Chem, 272:16431-16437.

Ko BC, Turck CW, Lee KW, Yang Y, Chung SS. (2000). Purification, identification, and characterization of an osmotic response element binding protein. Biochem Biophys Res Commun, 270**:**52-61

Kowluru RA, Zhong Q, Kanwar M. (2010). Metabolic memory and diabetic retinopathy: role of inflammatory mediators in retinal pericytes. Exp Eye Res. 90 (5):617-623.

Lehmann HC, Hoke A. (2010). Schwann cells as a therapeutic target for peripheral neuropathies. CNS Neurol Disord Drug Targets. 9(6):801-806.

Miyakawa H, Woo SK, Dahl SC, Handler JS, Kwon HM. (1999). Tonicity-responsive enhancer binding protein, a rel-like protein that stimulates transcription in response to hypertonicity. Proc Natl Acad Sci USA**,** 96**:**2538-2542.

Pop-Busui R, Sima A, Stevens M. (2006). Diabetic neuropathy and oxidative stress. Diabetes/metabolism research and reviews. 22(4):257-273.

Rim JS, Atta MG, Dahl SC, Berry GT, Handler JS, Kwon HM. (1998). Transcription of the sodium/myo-inositol cotransporter gene is regulated by multiple tonicity-responsive enhancers spread over 50 kilobase pairs in the 5'-flanking region.J Biol Chem, 273:20615-20621.

Roy S, Sala R, Cagliero E, Lorenzi M. (1990). Overexpression of fibronectin induced by diabetes or high glucose: phenomenon with a memory. Proc Natl Acad Sci U S A. 87(1):404-408.

Russell JW, Sullivan KA, Windebank AJ, Herrmann DN, Feldman EL.(1996). Neurons undergo apoptosis in animal and cell culture models of diabetes. Neurobiol Dis. 6(5):347-363.

Smith J. M., Mayer B. J. (2002) Abl: mechanisms of regulation and activation. Front. Biosci. 7, d31–d42.

Suzuki, J., Sukezane, T., Akagi, T., Georgescu, M. M., Ohtani, M., Inoue, H., Jat, P. S., Goff, S. P., Hanafusa, H., and Shishido, T. (2004) Oncogene 23,8527-8534

Shogang Panjarian, Roxana E Iacob, Shugui Chen, John R Engen and Thomas E Smithgall. (2013). Structure and Dynamic Regulation of Abl Kinases published in J. Biol. Chem, 288:5443-5450

Takenaka M, Preston AS, Kwon HM, Handler JS. (1994). The tonicity-sensitive element that mediates increased transcription of the betaine transporter gene in response to hypertonic stress. J Biol Chem, 269:29379-29381.

Thompson RF, Atzmon G, Gheorghe C, Liang HQ, Lowes C, Greally JM, Barzilai N. (2010). Tissue-specific dysregulation of DNA methylation in aging. Aging cell. 9(4):506-518

Zeng L, Hu Y, Li B. (2005). Identification of TopBP1 as a c-Abl-interacting protein and a repressor for c-Abl expression. J Biol Chem. Aug 12;280 (32):29374-80.