Aim and Objectives
Hyaluronic Acid Binding Protein 1, an important hyaladherin which is distinct from other HA binding proteins, was purified using HA affinity chromatography and identified as a glycoprotein containing sialic acid by D'Souza and Datta in 1985. Over the period of time, many documents have been acquainted to understand molecular physiological nature of HABP1. Sequence analysis of HABP1 cDNA divulged its identity with the cDNA sequence of a human splicing factor associated protein, p32 [Krainer et al., 1991; Honore et al. 1993; Genbank accession no. L04636 and M69039] along with its homology with the receptor for the globular head of complement component 1q, gC1qR [Ghebrehiwet et al., 1994; Genbank accession no. X75913], Mam33p, a mitochondrial matrix protein associated with oxidative phosphorylation in S. cerevisiae [Seytter et al. 1998] and YL2, an HIV-Rev binding murine homologue [Luo et al. 1994].

Human HABP1 is a multifunctional, multicompartmental and multifaceted ubiquitous and highly conserved protein. Differential cellular localization of gC1qR may dictate its compartment specific functional role. HABP1/p32 is synthesized with an N-terminal mitochondrial targeting sequence which is cleaved following import into mitochondria [Muta et al., 1997; Matthews and Russell, 1998]. There is only a single mRNA for this protein [Ghebrehiwet and Peerschke, 1998] and there are no known mechanisms for the export of proteins from mitochondria. However, it is distributed in several other cellular compartments, including the ER, the nucleus, golgi and on the cell surface [Ghebrehiwet et al., 1994; Braun et al., 2000; Kittleson et al., 2000; Mahdi et al., 2001; Mahdi et al., 2002, Sengupta et al., 2005]. The multi-compartmentalization of HABP1 has made this protein to interact with wide variety of regulatory protein of different compartments. Its interacting proteins include splicing factors ASF/SF2 [Krainer et al., 1991], complement component C1q, [Ghebrehiwet et al., 1994], lamin B
receptor protein (p58) [Simos and Georgatos 1994], transcription factor TFIIB [Yu et al. 1995a], HIV Tat and Rev proteins [Yu et al. 1995b; Tange et al., 1996], adenovirus protein V [Matthews and Russell, 1998], kininogen [Herwald et al. 1996], vitronectin [Lim et al., 1996] and recently an isoform of small alternating reading frame smARF [Reef et al.], mitochondrial apoptosis inducing protein Hrk [Sunayama et al., 2004] and cell cycle regulatory protein in Schizoscharromyces pombe cdc25 [Mallick and Datta, 2005]. The interaction between p32 and HIV-1 Tat [Yu et al., 1995], Epstein-Barr virus EBNA-1 [Van Scoy et al., 2000], and herpes simplex virus orf73 [Hall et al., 2002] has been shown to stimulate transcription in model reporter constructs, whereas p32 interaction with the cellular transcription factor CBF/NF-Y [Chattopadhyay et al., 2004] or the gamma herpes virus 68 M2 protein [Liang et al., 2004] has been shown to result in an repression of transcription. These examples serve to demonstrate the potential regulatory role of intracellular and cell surface gC1qR, and collectively support the postulate that the differential cellular localization of this molecule may dictate or contribute to its compartment-specific function as a regulator of cellular and microbial proteins. All these various aspects of the mammalian HABP1/p32 like its multifunctionality, structural plasticity, dynamic distribution pattern and localization in every subcellular compartment including the surfaces of different cells [though devoid of any transmembrane domain or GPI anchor], raises the question as to how the expression profile of this protein is getting regulated?

HABP1 protein is ubiquitously found in different tissues and different cell lines, stage specific expression of HABP1 is observed during spermatocyte interaction [Ghosh et al., 2003] and spermatogenesis [Ranganathan et al., 1995] where the expression of HABP1 begins from mid pachytene stage [Bharadwaj et al., 2002]. The mRNA level of HABP1
significantly increases in adult testis. It known to us that it has a role in cell adhesion, cell migration, cellular invasion and proliferation. Over expression of HABP1 in mammalian cell lines [Meenakshi et al., 2003] as well as in lower eukaryotes like yeast [Mallick and Datta, 2005] results in growth retardation and alteration in cellular morphology. Enhanced phosphorylation of HABP1 on HA and PMA stimulation [Rao et al., 1997] and its identification as an endogenous MAP Kinase substrate [Majumdar et al., 2002] suggests its critical role in cellular signaling, maintaining the delicate balance between cell growth and apoptosis. Various cellular processes like cell adhesion, tumor formation [Gupta and Datta, 1991] have already been reported.

The gene encoding HABP1 has been mapped to chromosome 17p12-q13 [Majumder and Datta, 1998]. The genomic sequence “Blast” also revealed the presence of pseudogenes of HABP1 spread over chromosomes 21, 15, 11 and 4 with a varying length and similarity to the parental cDNA sequence. All these pseudogenes sequence lack a 5' promoter sequences lack and possess multiple mutations with the insertion of premature stop codons. 5' upstream sequence analysis of human HABP1 gene revealing multiple transcription sites with no TATA or CCAAT box in the near proximity signifies the importance of transcription factors in HABP1 expression. This finding prompted us to find out more about the transcriptional regulation of HABP1.

HABP1 is a ligand of ECM component, hyaluronan. It is well known that hyaluronan and its ligands have tremendous role in morphogenesis, cell signaling, aging and angiogenesis. There are several reports about HA and its ligands' differential expression in diseased conditions. Hyaluronan is also present at elevated levels in many malignant tumors and, in some cases, is an accurate predictor of patient morbidity. Numerous studies have demonstrated that hyaluronan may play an important role in tumor malignancy. Perturbation of endogenous hyaluronan-tumor cell interactions by overexpression of soluble
hyaluronan-binding proteins inhibits tumor growth, invasion, or metastasis in several tumor types in vivo. Thus, keeping all the abovementioned facts in mind, in order to identify the physiological function of HABP1 we planned to

- Examine the expression of HABP1 in skin papilloma tissues.
- Identify the mechanism of apoptosis induction in HABP1 overexpressed cell lines.
- Determine the transcriptional modulation of HABP1 under stress conditions.
- Finally, the built up functional evidences based on highthroughput and proteomic approach to analyse the overall signal mapping that is perturbed due to HABP1 overexpression.

The purpose of this work is to get an understanding of HABP1 in the cellular milieu, which is like a molecule sitting on the edge of order and chaos like its ligand Hyaluronan, a megadalton macromolecule which serves as a hot spot for a number of biological processes.