CV of Samit Chattopadhyay, TWAS, FNA, FASc, FNASc

-- Highlights --

1. 30 years of research experience in wide fields of biology including;

Understanding Epigenetics in Cancers and other diseases; Molecular biology work on HIV transcription and latency; Immune responses upon Mycobacterial infection; Role of Nuclear matrix proteins in DNA damage repair, Splicing etc; Structure function relation of MAR binding proteins; miRNA in cancer and other diseases. Plant genetics, plant molecular biology; Chromosome Techniques, Karyotyping and Cytogentics, Handling Cholera Bacteriphages and their physical mapping; Role of RNA-protein interaction in Viral transcription; Immunobiology and T helper Cell Differentiation.

2. Trained/ guided more than 100 students:

Guided more than 30 Ph D students of which 15 got Ph D degree from this lab
Taught courses at NCCS, Pune University, Calcutta University, Vidyasagar University
Trained university students and students from Indian Academy of science (IAS).
Given lectures in more than 200 conferences in India and abroad
Arranged symposiums in Developmental Biology and Transcription
Guided students from many Institutes and Universities as a part of collaborative work

3. Members/ Fellow of Academies:

The World Academy of Sciences (TWAS), 2016
Sir J C Bose National Fellow, DST, 2013
Fellow of Indian National Science Academy (FNA), Delhi, 2013
Fellow of Academy of Science (FASc), Bangalore, 2011
Fellow of National Academy of Science (FNASc), Allahabad, 2006
Fellow of Maharashtra Academy of Science (FMASc), 2000

4. Publications:

Published several book chapters and more than 70 papers mostly in international Journals:

Immunity, Cell Press; EMBO Journal, Nature Publication; Mucosal Immunology, NPG; Proceedings of National Academy of Sciences (PNAS); Molecular and Cellular Biology (MCB), Nucleic Acids Research (NAR), Journal of Immunology (JI), Journal of Biochemistry (JBC); Journal of Molecular Biology (JMB), International Journal of Biochemistry and Cell Biology (IJBCB); Virology, PLoS One, BBRC, BBA Acta Review

5. Reviewer of several specialized journals like:

Virology, Journal of Biomedicine and Biotechnology, Cell Biology International, Elsevier, International Journal of Cancer, Journal Bioscience, International Journal of Biochemistry and Cell Biology, Cellular and Molecular Life Sciences, FEBS Journal, PlOS ONE etc.

6. Administrative role:

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Associate Dean of NCCS; Teaching several courses; Council member of DY Patil Medical College; Chairman and member of various selection committees at NCCS and other Institutes and Universities; Task Force member of Cancer Research, DBT; Animal Science and Biotechnology, CSIR; Chairman Stores and Purchase, NCCS for last 10 years, Earlier in-charge of making Annual Report, NCCS, Writing Patents, Expert consultant scientist of Pharmaceuticals like Piramal Life Sceince, Mumbai; Amrita Therapeutics, Gujarat. Convener, Guha Research Conference, 2014.

Updated Biodata

1. Broad Subject Area	Life Sciences
2. Area of specialization	Molecular Biology, Cancer Biology and Immunology and Developmental Biology
3. Name of the candidate	Dr. Samit Chattopadhyay, FNA, FASc, FNASc
4. Current position:	Director CSIR-Indian Institute of Chemical Bioloy
5. Mailing Address	CSIR-Indian Institute of Chemical Biology 4, Raja S. C. Mullick Road Kolkata-700 032 Ph: 033 24171157; 033 2473 5368 Mob: 09823409155/ 09422031057 Fax: 033 2473 5197 Email: samit@iicb.res.in/director@iicb.res.in
6. Date of birth	25th December, 1959

7. Educational Qualification

Degree/ Diploma/ Certificate	University/Institute	Year	Subjects
Post Doctoral Research	Massachusetts Institute of Technology (MIT), Boston	1995-1998	Chromatin remodeling at TCRβ locus during T development. Role of *cis* elements in V(D)J recombination and allelic exclusion using knock-out mouse model
Post Doctoral Research	University of Connecticut, Farmington, USA	1989-1995	Viral transcription, Transcription elongation through RNA-protein interaction
Doctorate	Jadavpur University, Kolkata, WB	1989	Ph D in Biochemistry, Jadavpur University, Calcutta (Physical mapping of *Vibrio. Cholera* bacteriophage *eltor-4* genome and characterization of phage encoded tRNAs).
Master's Degree or Equivalent	University of Calcutta, WB	1984	Botany with Cytogenetics as special subject

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Bachelor's degree	University of Calcutta, WB	1981	Botany Honours with Cytogenetics as special subject, Zoology, Human Physiology

8. Details of professional training and research experience, specifying period

Major field of the highest degree	• Ph D in Molecular Biology, mapping and characterization of novel tRNA genes from Cholera phages
Highest degree, Specialization and Subjects	• Ph D in Biochemistry, Jadavpur University, Kolkata (Physical mapping of *V. Cholera* bacteriophage *eltor-4* genome and characterization phage encoded tRNAs)
Next lower degree	• M Sc in Botany from Calcutta University, Specialization in Cytogenetics and Molecular Biology

Additional qualification/ Training	• 1989-1995, Post doctoral fellow at University of Connecticut Health Center (UCONN), Farmington, USA, working on the molecular mechanism of viral transcription and role of RNA-protein interaction in modification of RNAP resulting transcriptional processivity (Chattopadhyay et al., PNAS, 1998a; PNAS 1998b). • 1995-1998, Post-doctoral fellow at MIT, Boston, USA working on the chromatin changes in the TCRβ locus during T cell development. Special training in generating knock-out mice to see role of *cis* elements in the regulation of TCRβ enhancer. Role of specific *cis* elements in the regulation of V(D)J recombination. Specialized in generating knock-out mice where specific cis elements were knocked out and demonstrated for the first time how the local chromatin remodeling and accessibility changes the pattern of V(D)J recombination through specific Vβ and Dβ. We have now generated T cell specific conditional knock-out mice for SMAR1 gene and observed that SMAR1 plays a critical role in Th1-Th2-Th17 differentiation (Immunity, Cell Press, JBC, Journal of Immunology)
Training and research experience in last 13 years at NCCS	• 14 students received Ph D under the guidance of PI working on T cell biology, Cancer Biology and epigenetics. More than 100 students were trained as a part of summer project and six months project. Teaching M Sc students at Departments of Biotechnology, Zoology, Department of Bioinformatics, University of Pune etc.
Research experience on neurobiology	• University of Robert Dubre Hospital, Paris as a part of collaborative work (ICMR-INSERM) with Dr. Pierre Gressens. Worked on the regulation of MAR binding proteins during neuronal differentiation in rat model system. Expression of alternatively spliced form of SMAR1 in the neuronal stem cells during embryonic development. We now find that there are a few of miRNAs that are targets of SMAR1 and plays important role in neuronal and erythrocyte differentiation.

9. Professional recognitions, awards, fellowships received

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- Sir J C Bose National Fellow, Department of Science and Technology, 2013
- Fellow of Indian National Science Academy (FNA), Delhi, 2013
- Fellow of Academy of Science (FASc), Bangalore, 2011
- Fellow of National Academy of Science (FNASc), Allahabad, 2006
- Fellow of Maharastra Academy of Science (FMASc), 2000
- Associate Dean, Academic Cell, NCCS, Pune
- Convener, Guha Research Conference (GRC), 2014
- Member, Molecular Immunology Forum (MIF), 2002
- Member, American Society for Biochemistry and Molecular Biology (ASBMB), USA. 2004
- Member , Society of Indian Cell Biology, 2006
- Co-Convener, Indian Society for Development Biologists (ISDB), 2004
- Member and examiner Thesis Committee, ACTREC, Navi Mumbai, 2007
- Member of Research Advisory Board at Dr. D Y Patil Vidyapeeth, Pune
- Member, Asian Transcription and Chromatin Biology , ChromatinAsia
- Member, Indian Association for Cancer Research (ICAR)
- Research Committee Member, CSIR, Animal Sciences and Biotechnology
- Task Force Member, CSIR, Inter-agency project IAP001, IICB, Kolkata
- Task Force Member, DST-PAC, Delhi
- Task Force Member: Cancer Biology, Department of Biotechnology, Delhi
- Chairman/ Member, Ph D and project student selection committee at NCCS
- Opted Member, DBT-JRF Fellowship, Government of India
- Member of BIRAC, CRS, DBT, 2010 onwards

10. Member of Other Committees (Administrative)

- NCCS Purchase committee member, 2001-2009
- Chairman, NCCS Purchase committee, 2010 till date
- Associate Coordinator of Scientific Advisory Committee, DBT-JRF Exam
- In-Charge for designing and planning of NCCS Annual Report, 2003 to 2007
- Chairman, Biosafety and Ethical Committee, NCCS (2006-2010)
- DBT Nominated Chairman of Biosafety Committee, D Y Patil Medical Institute, Pune

11. Reviewer of several specialized journals like:

A. Virology, B. Journal of Biomedicine and Biotechnology C. Cell Biology International, Elsevier, D International Journal of Cancer, E. Journal Bioscience, F. International Journal of Biochemistry and Cell Biology, G. Cellular and Molecular Life Sciences, H. FEBS Journal,

12. Thesis work for Ph D under my supervision:

1. Dr. Ruchika Kaul was awarded Ph D degree from Pune University. Thesis title "*SMAR-1, a novel T cell specific MAR binding protein: Possible role in V(D)J recombination and chromatin structure modulation during cellular transformation*". 2004.

2. Dr. Asavari Kulkarni was awarded Ph D degree from Pune University. Thesis title "*Role of extracellular HIV transactivator Tat in T cell activation and HIV pathogenesis*". 2004.

3. Dr. Shravanti Rampalli was awarded Ph D degree from Pune University. Thesis title "*Regulation of Retroviral and Eukaryotic Transcription through MAR sequences and MAR binding protein SMAR1*". 2005.

4. Dr. Archana Jalota Bhadwar was awarded Ph D degree from Pune University. Thesis title "*Role of SMAR1 in tumor suppression and p53 meduated cel cycle regulation".* 2007.

5. Dr. Kamini Singh awarded Ph D degree from Pune University. Thesis title "*P53 mediated regulation of SMAR1 and their co-operated role in tumorigenesis through modulation of NFκB and TGFβ target gene expression*", 2007.

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6. Dr. Pavithra Laxminarashiman was awarded Ph D degree from Pune University. Thesis title "*Regulation of MAR binding protein SMAR1 under stress: Implications in cell cycle by modulation of ATM-p53-MDM2 pathways*". 2009, February.

7. Dr. Surajit Sinha was awarded Ph D degree from Pune University, Thesis title "*Role of MAR binding protein SMAR1 in apoptosis*". 2010.

8. Dr. Sreenath K was awarded Ph D degree from Pune University, Thesis title "*Regulation of viral transcription and signal transduction by a MAR binding protein*". 2011.

9. Dr. Sandeep Singh was awarded Ph D degree from Pune University, Thesis title "*To study SMAR1 interacting proteins and role of SMAR1 in cellular differentiation and tumorigenesis*". 2011.

10. Dr. Sunil K Malonia was awarded Ph D degree from Pune University, *Role of MAR binding proteins in the regulation of cytokine genes*. 2011.

11. Dr. Sulabh C Kharbanda was awarded Ph D degree from Pune University, *Identification of SMAR1 binding regions in the human genome and to study its transcription control by epidermal growth factor signaling pathway in context to breast cancer.* 2011.

12. Dr. Kiran K. Nakka was awarded Ph D degree in from Pune University. Role of SMAR1 protein in Pre-mRNA processing. December, 2012

13. Dr. Nidhi Chaudhary was awarded Ph D degree on from Pune University. Regulation of DNA damage repair by nuclear matrix protein SMAR1. January, 2014

14. Dr. Sijo Varghese Chemmannur, was awarded Ph D from Pune University. Regulation of T cell Differentiation by MAR binding protein SMAR1. June, 2014.

15. Dr. Rahul Mirlekar was awarded Ph D degree from DY Patil Deemed University, SMAR! Mediated regulation of Treg cell differentiation during development of Inflammatory Bowl Disease (IBD). June, 2015

13. Positions holding by the Ph D students from the lab:

1. Dr. Ruchika Kaul-Ghanekar; Senior Scientist, Bharati Vidyapeeth, Pune, Since 2009.
2. Dr. Shravanti Rampalli; Senior Scientist and Wellcome Trust Fellow, NCBS, InStem, Bangalore
3. Dr. Asavari Kulkarni; Postdoctoral Fellow, USA; Working on HIV transcription control
4. Dr. Archana Jalota-Badhwar; Senior Scientist, Piramal Life Sciences, Mumbai
5. Dr. Kamini Singh; Post-doctoral Fellow, Lerner Research Institute, Cleveland, USA
6. Dr. Pavithra Sampath; Postdoctoral Fellow, University of Cambridge, England
7. Dr. Surajit Sinha, PDF, Memorial Sloan Kettering Cancer Centre, New York, USA
8. Dr. Varseish Raina, Research Scientist, NII, New Delhi
9. Dr. Sreenath K, Senior Project leader at Dr. Reddy's Laboratories, Hyderabad
10. Dr. Sandeep Singh, Assistant Professor, Punjab University
11. Dr. Sunil Kumar Malonia, PDF, University of Massachusetts Medical School, USA
12. Dr. Kiran K Nakka, PDF, Canada

14. Awards Received by the Students:

1. Kiran K Nakka SRF, ICMR and Chattopadhyay S. Dr. Nakka was selected for Oral Presentation at RNA – 2011, International Conference on Sixteenth Annual meeting of the RNA Society, Japan, 14th June-18th June, 2011, Abstract title: Regulation of pre-mRNA Splicing by Nuclear Matrix Protein SMAR1. He received Travel Award from the Organizers to attend this prestigious meeting.

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2. INSA Young Scientist Award by Dr Pavithra L Chavali (2013), PhD, Department of Oncology, University of Cambridge, Cancer Research UK-CRI, Li Ka Shing Center, Robinson Way, Cambridge, CB2 0RE, UK. She identified that the tumor suppressorprotein, SMARI is dysregulated in breast cancer and that its over expression arrests the cells at G1-/S phase.

3. Dr. Shavanti Rampalli, Scientist, In-Stem, Bangalore received prestigious Intermediate Wellcome Trust Award, 2012.

16. MEMBERS/ CHAIRMAN/ STUDENT'S ADVISORY BORAD MEMBER etc:

- Student Advisory Committee, NCCS, 2003-2011
- Student Advisory Committee ACTREC, Navi Mumbai, 2009-2010
- Student Advisory Committee, Indian Institute of Science, Bangalore
- Thesis Reviewer, University of Delhi, North Campus, IISc, Pune University
- Student advisory committee, Biotechnology Department, Pune University
- Session Chairperson, Cell Biology Conference, Delhi University, 2006
- Session Chairperson, Transcription meeting 2009
- Session Chairperson, Chromatin-Asia, JNCASR, December 4-6, 2010
- Co-convener, National Symposium on Indian Society for Developmental Biology (ISDB), 2001
- Member: GRC, MIF, SBC, ISDB, IACR, RNA, Asian Transcription Biology, Chromatin-Asia
- Task Force Research Committee, Animal Science and Biotechnology, CSIR, 2011
- Chairman, International Conference, carcinogenesis at Dr Ram Manohar Lohia Hospital, Post Graduate Institute Medical Education and Research, New Delhi, November 19-21, 2012.
- Chairman, 4th International Conference on Stem Cells and Cancer (ICSCC-2013): Proliferation, Differentiation and Apoptosis", 19-22 October 2013, Mumbai, India
- Chairman, DBT Cancer biology Task Force for Selection of UOE projects

17. SCIENTIFIC SERVICES PROVIDED AS SUPPORT:

- Number of projects served (may also include services such as statistical and economic analysis): Working with Piramal Life Sciences on identification of anti cancer and anti-HIV compounds by screening of compound library.
- Teaching at various institutes and Departments within and outside Pune
- Guiding project students from all over India
- Guiding project students from Indian Academy of Science, KVPY etc.
- Task Force Research Committee, Animal Science and Biotechnology, CSIR, 2011

Inter-disciplinary, inter-institutional and intra-institutional activities

18. SCIENTIFIC COLLABORATORS:

- Dr. Pierre Gressens, Hospital Robert Debre, Paris, France
- Dr. Olivier Cases, Hospital Robert Debre, Paris, France
- Dr. Nilanjana Maulik, UCHC, Farmington, USA
- Dr. Siddhartha Roy, Director, IICB, Kolkata
- Dr. Tapas K Kundu, JNCASR, Bangalore
- Dr. Subeer Majumdar, NII, New Delhi
- Dr. H. K Prasad, AIIMS, New Delhi
- Dr. U. D Gupta, NJIL & OMD, Agra
- Dr. Uday Kumar Ranga, JNCASR, Bangalore
- Dr. Debasish Mitra, NCCS, Pune
- Dr. Tanya Das, Bose Institute, kolkata
- Dr. Kishore Paknikar, ARI, Pune
- Dr. Mahendra Sonawane, NCRA, Pune
- Dr. J. K. Pal, Pune University
- Dr. B. G. Hajra, NCL, Pune

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- Dr. Indrani Datta, Manipal University, Bangalore
- Dr. Pankaj Poddar, NCL, Pune
- Dr. Gaurisankar Sa, Bose Institute, Kolkata
- Dr. K M Paknikar, ARI, Pune
- Dr. Saumitra Das, IISc, Bangalore
- Dr. Elora sen, NBRC, Gurgon
- Dr. Chandrasekhar, IICT, Hyderabad
- Dr. Tapas K Hazra, Galveston, USA
- Dr. Amitava Das, NCL, Pune
- Dr. Subhrangsu Chatterjee, Bose Institute, Kolkata

*** There are several DBT and DST funded projects in which Dr. Chattopadhyay was a principal investigator along with other scientists as Co-PI. In these projects scientists from all over India and abroad were involved as a part of joint co-investigators.

19. Membership in Institutional Committees:

- Associate Dean, Academic Cell, NCCS, Pune, India
- Member/ Chairman, Stores and Purchase Section
- Coordinator and Faculty In-charge; Scientific Advisory Committee (NCCS-SAC)
- Selection of six month project and JRF students for doing Ph D at NCCS

20. Organizing Seminars and Symposia:

- In-charge of arranging seminars and symposiums at NCCS. Organizes more than 20 talks from Indian and scientists from abroad.
- Co-convener, National symposium on Indian Society for Developmental Biology (ISDB), 2001.
- Advisory Committee member, society for Biological Scientists (SBC), NCCS, 2010.
- Arranged more than 30 seminars at NCCS in last few years and formal in-charge for the same.
- Convener, GRC-2014 To be held at Khajuraho, MP, December 6-10, 2014

OUTLINES OF ONGOING PROJECTS:

The eukaryotic interphase chromatin is a highly organized structure. Specific scaffolding proteins form complexes with DNA and play pivotal role in DNA packaging. An important feature of DNA packaging involves folding of the chromatin into loop domains, which are periodically attached to the nuclear matrix through binding to specialized DNA sequences called Matrix Attachment Region or MARs. We study how proteins that specifically bind to MARs regulate genomic DNA organization and nuclear functions such as transcription, recombination, splicing, repair etc.

Past several years our lab has been engaged in understanding the role of nuclear matrix and associated proteins in pathophysiological processes. We have focused on one such novel matrix associated protein SMAR1 that is down regulated in human breast cancer (Singh et al., PLoS-One, 2007). It acts as a global repressor for many genes including Cyclin D1, IκBα, CK8, Bax and Puma by directly recruiting HDAC1-mSin3a dependent repressor complex (Rampalli et al., MCB, 2005; Singh et al., PLoS One, 2007; Singh et al., JBC, 2009). Our findings reveal that SMAR1 functions in two different ways to regulate global gene expression. First, it acts as a transcriptional repressor and second by modulating the transactivation potential of transcriptional co-activators like NF-κB, p53 and p300. While NF-κB regulates plethora of cytokine and chemokine genes involved in tumor metastasis and angiogenesis, the tumor suppressor p53 on the other hand regulates the fate of tumor cells

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through selective activation of Bcl-2 family proteins. Additionally, p300 acetylates various transcription factors like p65 and c-Myc which are involved in oncogenic transformation. These cofactors globally affect various signaling pathways leading to activation of genes that onset the process of tumorigenesis. Thus, a change in the level of SMAR1 as is seen during cancer progression is inversely correlated to the oncogenic activities of these three cofactors.

Major Work in Progress:

Regulation of CD44 gene: Implication in cancer
DNA damage repair by SMAR1 through Ku70 acetylation
Control of cytokine genes for T_H1-T_H2- T_H17 and T-reg differentiation
SMAR1 mediated regulation of miRNA miR371-373: possible role in metastasis
Understanding cancer cell metabolism: Role of DNMTs and their alternative splicing
Genome wide RNAi screening for SMAR1 target genes in cancer and cancer stem cells
Identification of anticancer compounds that modulate SMAR1 function
Role of BANP in Zebra Fish Embryo Development

Regulation of CD44 gene: Implication in cancer

Transcription and pre-mRNA splicing have emerged as highly coordinated processes. Alternative pre-mRNA splicing is indispensible for post transcriptional gene regulation. We first identified that nuclear matrix protein SMAR1 interacts with splicing co-activator SRm160 which is known to regulate Ras dependent CD44 alternative splicing and also enhances constitutive splicing. Alternative exon usage is dependent on the extracellular stimuli. Inclusion of variable exons in CD44 mRNA is dependent on MAP kinase signaling pathway. CD44 has 10 constant exons and 10 variable exons residing between constant exon 5 and 6. Higher levels of CD44 variants confer strong metastatic potential to tumors. In the context of SRm160, present study deals with the regulation of CD44 alternative splicing by nuclear matrix protein SMAR1 in an ERK dependent manner. Knock down of SMAR1 enhances the inclusion of CD44 variable exons. We found SMAR1 interacts with Sam68 endogenously, another protein of Signal Transducer and Activator of RNA splicing (STAR) family, and MAP kinase mediated activation causes post translational modification of SMAR1 by ERK and mediates the translocation of protein from the nucleus to cytoplasm. In a signal independent manner SMAR1 is found to enhance constitutive splicing of the β-globin pre-mRNA. Over expression of SMAR1 has found to increase the constitute splicing of β-globin pre-mRNA while knock down or immunodepletion of SMAR1 did not affect much of the constitutive splicing. Gel exclusion chromatography based characterization of high molecular weight protein complexes had shown that SMAR1 is part of the splicing complex containing SC35. Studies show that SMAR1 levels are down regulated in advanced stages of cancer. This implies that in these cancers the abnormal alternative splicing of CD44 and the generation of CD44 splice variants will not be prevented due to low levels of SMAR1 and this will cause an increased tumor metastasis and invasion. We are now investigating that whether a dual control of CD44 expression exists; one via upregulation of p53 by certain anticancer drugs, wherein p53 transcriptionally inactivates the expression of CD44 and secondly whether this p53 can bind to the

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SMAR1 promoter, increasing its expression and thereby preventing the abnormal alternative splicing of CD44, in higher grades of cancer (Under Review in PNAS).

SMAR1 mediates DNA damage repair through deacetylation of Ku70

Matrix attachment region-binding proteins (MARBPs) are unique class of proteins that bind to specific non-coding sequences in the genome termed as scaffold/matrix attachment regions (S/MARs), and globally modify the topology of chromatin. Previous studies have established the importance of SMAR1 in helping DSB repair. Further we extended our study and reveal for the first time that NM-associated proteins play a key role in cellular response upon IR-induced DNA damage. SMAR1 imparts a critical role in the cell fate decision upon DNA damage by maintaining Ku70 in a deacetylated state via HDAC6. Deacetylated form of Ku70 is enriched in the damage-associated chromatin fraction for efficient repair and also controls mitochondrial translocation of Bax. Furthermore, SMAR1 is a novel target of ATM kinase upon IR and regulates G2/M checkpoint. Phosphorylation of SMAR1 at Ser 370 residue increases upon IR in an ATM-dependent manner and such post translational modification increases the activity of SMAR1. Recruitment of SMAR1 on chromatin was also studied as chromatin-bound fraction contains all the repair associated proteins. SMAR1 gets recruited to chromatin upon DNA damage and this recruitment is ATM dependent as found by decreased recruitment when cells were pretreated with ATM inhibitor KU55933 and PI3K inhibitor caffeine. Acetylation status of Ku70 decides the cell's fate and it was found that SMAR1 modulates the acetylation of SMAR1 by favoring the deacetylation of Ku70 through its interaction with HDAC6. *In silico* analysis showed that SMAR1 binding interactions with Ku70 are predominantly dependent on several key salt bridge interactions, such as (A) VAL-157(Ku70) : ARG-335(SMAR1), (B) ASP-156(Ku70) : LYS-322(SMAR1), (C) LYS-114(Ku70) : ASP-185(SMAR1), (D) SER-96(Ku70) : ARG-316(SMAR1), and (E) SER-155(Ku70) : ARG-335 (SMAR1). The trimeric model of SMAR1 bound to HDAC6 and Ku70 revealed that 240-350 residues of SMAR1 interact to the N-terminal region of Ku70 through various inter residual salt bridge formation. *In silico* analysis of HDAC6-SMAR1-Ku70 docked model revealed that Ku70 is bound to SMAR1 adjacent to HDAC6-binding site. It was observed that C-terminal domain (CTD; residues 248-371) of SMAR1 is sandwiched between Ku70 and HDAC6. Deacetylated Ku70 interacts with pro-apoptotic protein Bax and inhibits the translocation of Bax from cytoplasm to mitochondria. Interaction studies between Bax and Ku70 were done and it was discovered that SMAR1 inhibits the release of Bax from Ku70. Knockdown of SMAR1 causes weak interaction between Bax and Ku70. Localization of Bax was also studied upon SMAR1 over expression and knockdown. SMAR1 favors the Bax localization in the cytoplasm and thus inhibits apoptosis. By inhibiting apoptosis, SMAR1 regulates the cell survival also. It was found that SMAR1 causes better cell survival, both endogenously and post IR. All such results strongly suggest the crucial role of SMAR1 in DNA damage repair and cell's fate decision making (Cell death and Disease, 2014).

Control of cytokine genes for T_H1-T_H2- T_H17 and T-reg differentiation

Regulation of T cell lineage commitment is of high importance as it influences the adaptive immune responses. Naïve CD4 T cells can differentiate into distinct effector T cells up on encountering

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antigens. IFNγ secreting Th1 cells and IL4 secreting Th2 cells are the most predominant of T cell subtypes. Specific transcriptional factors and cytokines demarcate these cell types. Expression of Th1 cell-specific transcriptional factor T-bet is induced in Th1 cells by IFNγ signaling in combination with IL12. In the case of Th2, another transcriptional factor GATA3 is induced by the downstream signaling from IL4. Recently, apart from the traditional Th1 and Th2 cells, a novel subset of IL17 secreting Th17 cells were have been identified which have important role in inflammatory responses. In response to TGFβ and IL6 signaling, the naïve T cells differentiate to Th17 pathway. The combination of this signaling leads to the induction of RORγt which is the Th17 specific transcriptional factor. RORγt, along with other signaling molecules activate IL17 gene expression which is the signature cytokine of Th17 cells.

We are working on a matrix attachment region binding protein (MARBP) SMAR1 that globally regulates gene transcription through recruitment of HDAC1-Sin3 complex at various promoters. Previous results from our lab suggested a critical role of SMAR1 in the differentiation of T helper cells to Th1 and Th2 subtypes by the regulation of T-bet promoter (Varghese et al., Mucosal Immunology, 2015). We have studies the role of SMAR1 T ell responses upon *Mycobacterium tuberculosis* infection in animal model and found that while the transgenic mice is more susceptible to the infection, deletion of SMAR1 makes the mice more resistant. Thus, manipulating such masregulators may control infection and further disease progression. SMAR1 mediated regulation of T cell lineage elucidated on yet another function of SMAR1 in regulating Th17 differentiation. The expression level of SMAR1 is downregulated in naïve T cells polarized *in-vitro* towards Th17. Induced expression of SMAR1 inhibits Th17 polarization by binding to the MAR regions on the IL17 locus. Research on SMAR1 further assumes it to be a global regulator of gene transcription having multifarious functions in the regulation of other cytokine genes that drives specific T cell lineages. Th17 cells are the most important candidate for the immune responses against inflammatory conditions. Hence, regulation of Th17 by a cell intrinsic factor can be a potent regulator of inflammatory responses. Understanding the regulation of the inflammatory responses by SMAR1 will be accessed using over-expressed and T cell specific conditional knock-down mice. In this regard, chemically induced colitis and rheumatoid arthritis models are under study to better understand the function of nuclear matrix proteins in T cell differentiation and thus in immunity through T cell polarization (Mirlekar et al., Mocosal Immunology (b), 2015). In future, these studies will be extended in human patients where expression of SMAR1 in both synovial fluid and blood samples will be checked in arthritis patients and find possible correlations.

Genome wide RNAi screening to identify SMAR1 targets in cancer and cancer stem cells

Considering the multifaceted role of SMAR1 in maintaining chromatin structure integrity and global regulation of gene transcription, we are studying the involvement of SMAR1 in regulation of miRNAs. Microarray data from our lab suggests that SMAR1 can regulate many miRNAs including miR-34a, miR-34b, miR-373 and miR-302c. These miRNAs are involved in breast cancer metastasis. Interestingly, genome wide analysis of SMAR1 binding sites by ChIP on Chip has revealed many

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genes involved in cancer metastasis and angiogenesis that could potentially be regulated by SMAR1. Software analysis predicted the possible involvement of miR-320 in regulating SMAR1 expression. Custom synthesized miRNA promoter chips will be made to study the factors that can possibly regulate various miRNA clusters. These studies will be extended in clinical samples to study expression analysis of several miRNAs implicated in disease condition. We aim to generate miRNA database wherein all the miRNAs that are affected in stage specific manner can be placed and can then used as prognostic or diagnostic marker (Nucleic acids Research, Submitted).