Sudeshna Kar. Ph.D

Chromatin dynamics and cellular plasticity in chronic diseases

Profile: Dr. Kar is a Team Lead Scientist working at JH-IMM at Jamia Hamdard, New Delhi with more than 18 years of experience in studies related to dynamics, mechanical basis and functional consequences of chromosome remodeling in both eukaryotes and prokaryotes. She received her doctoral degree from Indian Institute of Chemical Biology, Kolkata and received the Fogarty Visiting Fellow award for her post-doctoral studies in Dr. Sankar Adhya's lab at the National Cancer Institute, NIH, USA. She worked on the structure-function of bacterial chromosome and chromosome-remodeling proteins in determining gene expression patterns and cellular behavior, leading to a discovery of a major paradigm shift in commensal microbial behavior through nucleoid remodeling. In her current position at JH-IMM, she has continued to further her research on chromatin re-modeling, transcription reprogramming and cell fate transitions involving differentiation and malignant transformation, in both bacteria and mammalian cells. She is the recipient of Howard Hughes Institute Award of Excellence for NIH Internship program for 2004-2005 and 2005-2006 as well as Technology Transfer Award of National Cancer Institute, NIH – 2003. Her work is funded by research grants from various national granting agencies and she participates in the peer-review process of several international journals and research grant proposals.

Research Interest: Signaling networks that define cell identity are tightly controlled during normal cellular homeostasis. Reprogramming or dysregulation of either the genetic, epigenetic or transcription component of this intricate network, through either extrinsic or intrinsic factors, leads to gain or loss of cell-specific function and acquisition of alternative cell fate. The principal focus of Dr Kar's research is to understand how the same genetic content can specify diverse patterns of gene expression in different contexts related to processes involving cell fate decisions like differentiation and oncogenesis.

Her research to date has led to the specific hypothesis that cells can be induced to undergo physiological reprogramming through manipulation of the chromatin environment by extrinsic or endogenous chromatin-reconfiguring proteins**. She works with bacterial histones as chromatin remodelling tools to identify and decipher the molecular mechanisms and signalling pathways during cell fate transitions, in both bacteria and mammalian cells.** Her studies use molecular, biochemical and cellular analyses to study defined physiological phenomena related to cellular plasticity in conditional, reversible, genetically-malleable and/or biochemically-controllable model systems.

Current Projects:

The current research of Kar-lab is focused on studying the cell fate transitions pertinent to two specific pathological conditions. Both these projects involve reconfiguring the natural chromatin state by bacterial histones to guide the cellular plasticity program towards a definite functional end, specifically as follows:

- Oncogenic transformation in colorectal cancer
- Neuronal regeneration in Parkinson's disease

Project 1: Colorectal tumorigenesis driven by dysregulation of normal host-gut microbe equilibrium. Aberrant gut microbial behaviour is now viewed as a critical contributor to the development of colorectal cancer (CRC). We are using genetically-engineered E.coli to develop an in vitro model system to investigate microbiota-mediated neoplastic transformation of intestinal cells as well as to use as a prototype to study the initiation/promotion of colorectal neoplasia arising out of a specific etiological factor (microbial dysbiosis) in clinical samples. Establishment of an etiological, functional and mechanistic relationship between aberrant commensals and genesis of CRC will help our understanding of malignant cellular transformation and ultimately, for designing effective strategies for CRC diagnosis and treatment.

Project 2: Neuronal regeneration in dopaminergic neurons by a histone-mimic bacterial protein through re-modelling of host epigenome. Using naturally-occurring and engineered bacterial histone-mimic proteins, we have developed biological molecules which act as neuroprotective and neuritogenic agent against neuronal dystrophy relevant to neurological disorder pathologies like Parkinson's disease. The neurotrophic effects of these molecules include the ability to stimulate axonal regrowth, neurite formation, dendritic sprouting, and modulate intracellular calcium and neurotransmitter synthesis and release. Neurochemical, molecular and behavioral parameters indicate that TmHU these molecules significantly attenuate behavioral deficits, dopaminergic neuronal death and striatal dopamine depletion in the MPTP mouse mouse model of Parkinson's disease. Using these validated biopeptides, we are trying to discover new biomarkers and therapeutic targets that affect the onset, progression, or regression of neurodegeneration and develop cheap, naturally-occurring bacteria-derived protein as a potential disease-modifying molecule in progressive neurodegenerative disease pathologies.

Selected Publications (Top ten)

1. Sahu U, Chaudhuri A, Parvez S, Biswas S and **Kar S**. Induction of intestinal stemness and tumorigenicity by aberrant internalization of commensal non-pathogenic E.coli. **Cell Death Dis**. 2017 Mar 16;8(3):e2667. doi: 10.1038/cddis.2017.27.
2. Chaudhary S, Sahu U, **Kar S**, Parvez S. Phytanic Acid-Induced Neurotoxicological Manifestations and Apoptosis Ameliorated by Mitochondria-Mediated Actions of Melatonin. **Mol Neurobiol**. 2016 Oct 26
3. Sahu U, **Kar S***. Outsider to insider: Resetting the natural host niche of commensal E. coli K-12. **Bioeng Bugs** 2012; 3: 8 5-91.
4. Koli P, Sudan S, Fitzgerald D, Adhya S, **Kar S***. Conversion of commensal Escherichia coli K-12 to an invasive form via expression of a mutant histone-like protein. **mBio** 2011; 2(5):e00182-11. doi:10.1128/mBio.00182-11.
Commentary in ASM blog – "Small Things considered"
http://schaechter.asmblog.org/schaechter/2011/10/the-fa%C3%A7ade-of-e-coli-k-12.html
5. **Kar S**, Choi EJ, Guo F, Dimitriadis EK, Kotova S and Adhya S. Right-handed DNA wrapping by an octameric form of histone-like protein HU modulates cellular transcription. **J Bio Chem**. 281, 40144-41053.
6. Kar S, Edgar R and Adhya S. Nucleoid remodeling by an altered HU protein: reorganization of the transcription program. **Proc Natl Acad Sci U S A.** 2005. 102(45):16397-402.

7. Rao S, Hu S, Mchugh L, Lueders L, Henry, K, Zhao Q, Fekete RA, Kar S, Adhya S and Hamer DH. Toward a live microbial microbicide for HIV: commensal bacteria secreting an HIV fusion inhibitor peptide. **Proc Natl Acad Sci U S A**. 2005 23;102(34):11993-8.
8. Roy S, Dimitriadis E, **Kar S**, Miller M and Adhya S.Gal Repressor-Operator-HU Ternary Complex: Pathway of Repressosome Formation. **Biochemistry**. 2005 April 12; 44(14):5373-80.
9. Adhya S, Guo F and **Kar S**. HU, nucleoid structure and transcription profile. **J Biomol Struct Dyn**. 2005 June, 22 (6).
10. **Kar S** and Adhya S. Recruitment of HU by piggyback: a special role GalR in repressosome assembly. **Genes Dev**. 2001 Sep 1; 15(17): 2273-81.