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8th world congress on
Epigenetics and Chromosome

Understanding epigenetic reprogramming by X chromosome reactivation

Irene Cantone

University of Naples Federico II, Italy

Erasure of epigenetic memory is required to convert somatic cells towards pluripotency.

Reactivation of the inactive X chromosome (Xi) has been used to model epigenetic reprogramming in mouse, but human studies are hampered by Xi epigenetic instability and difficulties in tracking partially reprogrammed iPSCs. Recently, I have established a cell fusion reprogramming system that recapitulates features of human naïve pluripotency and enables tracing early chromatin changes. This system revealed that loss of XIST and H3K27me3 from the human Xi precedes and is required for Xi transcriptional reactivation ahead of cell division (Cantone et al., Nature Comm 2016). Interestingly, single-cell RNA-FISH and allele-specific RNA sequencing analyses revealed that reprogramming-mediated human Xi reactivation was partial and selective for a specific subset of genes. Selective Xi reactivation was not limited to gene loci residing within specific chromatin domains (e.g. H3K27me3 or H3K9me3 domains) neither influenced by proximity to XIST locus.

Reactivation was instead associated with stochastic Xi expression ahead of reprogramming, as shown by single cells and isogenic fibroblast clones (Cantone et al., Genome Biology 2017). Notably, stochastic Xi transcription is stabilized in some clonal lineages suggesting that single-cell transcriptional variability might underlie heritable gene reactivation even in heterochromatic contexts. Implications for targeted Xi gene reactivation during human pluripotent reprogramming and in somatic cells will be discussed as a concept for modelling and therapy of human X-linked diseases

Biography

Irene Cantone has completed his PhD at the age of 25 years from Telethon Institute of Genetic and Medicine and postdoctoral studies from MRC London institute of Medical Sciences. She has been awarded Marie-Curie, EMBO and Human Frontiers Science Programme long-term fellowship. She is currently a Professor at the University. She has published more than 15 papers in reputed peerreviewed journals (e.g. Cell, Nature Structural Molecular Biology, Nature Communication and Genome Biology) and has been serving as an editorial board member of PLOS and Nature journals

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Environmental epigenetics in population exposed to chronic arsenic & Cancer

Pritha Bhattacharjee

University of Calcutta, India

Chronic arsenic exposure and its cancer association is already known. Our study explored the epigenetic perspectives of arsenic toxicity. The major investigations we performed include DNA damage response, telomere regulation, arsenic methylation and mitochondrial biogenesis. Our novel findings are to identify signature patterns for arsenic exposure (compared to those who are unexposed) and arsenic-induced characteristic lesion (compared to arsenic exposed No Skin Lesion group). Although arsenic induced skin lesions are hallmarks of arsenic toxicity, it is observed only among15-20% of the exposed population. This clearly indicates environment and gene crosstalk each other with significant variation at population level. We have identified alteration in DNA methylation pattern for the candidate genes, histone post translational modifications and also differential miRNA regulation. Among all different pathways, most critical is the arsenic metabolism pathway. This metabolism depends on the efficiency of arsenic methylation, which is further dependant on methylation donor SAM (S-Adenosyl L-methionine) level and enzyme activity of AS3MT (Arsenite methyltransferase). Our study identified how arsenic depletes SAM level and affect overall metabolism leading to arsenic susceptibility. Mitochondrial biogenesis also play a significant role, where regulatory genes including PGC1α, Tfam, NRF1 and NRF2 were upregulated among arsenic induced cancer patients via promoter hypomethylation. Thus, our study considers a holistic approach to understand the epigenetic interplay in the individuals having prolonged arsenic exposure history.

Biography

Pritha Bhattacharjee is teaching at the Department of Environmental Science, University. of Calcutta, as Assistant Professor for last 8 years. She has completed her PhD from CSIR-Indian Institute of Chemical Biology in 2007 and continued her postdoctoral studies in arsenic research. Her major expertise lies with Environmental epigenetics, Occupational health and Lifestyle disorders. Dr Bhattacharjee has authored/co-authored in 55 International journal publications with 1584 total citations and h-index 19. She wrote several book chapters including text book on Environmental Studies. Dr. Pritha serves as editorial board member for highly acclaimed Frontiers in Genetics and many other journals. She is guiding a number of PhD students in biological research.

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MECOM-regulated distal super-enhancer activates ETS2 transcription and promotes colorectal cancer progression

Xing-sheng Shu

Shenzhen University, China

It has long been documented that abnormal activities of distal cis-regulatory elements such as enhancers contribute to the intitation and progression of cancer. Recently, super-enhancer hijacking was found to be esstential for the activation of certain oncogenes. However, the mechanism of action for most tumor-specific super-enhancers still largely remain elusive. Here, we report that a potential oncogene ETS2 was activated by a super-enhancer located at its 3' distal region in colorectal cancer (CRC). The super-enhancer physcially interacts with ETS2 promoter fragments and is required for transription activation of ETS2. Intriguingly, we found that a eQTL site for ETS2 resides in this super-enhancer and genetic variation at the SNP potentailly abolished the binding of a well-known oncogenic trancritpion factor MECOM. Consistently, the expression of MECOM and ETS2 correlated well with each other in CRC cell lines and multiple CRC datasets and silecning of MECOM induced downregulation of ETS2. Moreover, the expression of enhancer RNA (eRNA) from the ETS2 super-enhancer also correlated with the expression of ETS2 in primary CRC samples. Finally, silencing of both MECOM and ETS2 lead to the inhibition of proliferation, migration and sphere formation of CRC cells. Taken together, we uncovered a novel MECOM-super enhancer-ETS2 regulatory axis that might be crucial for activating oncogenic ETS2 in CRC.

Biography

Xing-sheng Shu received his B.S. degree from the School of Life Sciences, Peking University and his Ph.D. degree from the Department of Clinical Oncology, Faculty of Medicine, The Chinese University of Hong Kong. He is currently an associate professor at School of Medicine, Shenzhen University. Dr. Shu has been focusing on study the aberrant transcriptional and epigenetic regulations in digestive cancers, he has published more than 30 papers with >900 citations and an H-index of 15, including research articles in Oncogene, Journal of Pathology, Theranostics and other high level academic journals.