Prof Benu Brata Das; IACS, Kolkata

Research Achievements:

Research Focus:

Prof. Benu Brata Das's group investigates the critical role of DNA topoisomerase 1 (Top1) in replication and transcription, with a focus on cellular responses to Top1-DNA covalent complexes (Top1cc) induced by anticancer drugs like Camptothecin and its derivatives. The lab identifies novel therapeutic targets and post-translational modifications of repair proteins, such as TDP1 and PARP1, crucial for genome maintenance (***The EMBO Journal*; 2009)**. Their ultimate goal is to develop Top1-targeted anticancer drugs for precision medicine. This research significantly advances the understanding of genomic alterations in carcinogenesis and holds promise for novel cancer therapies.

Mechanistic Insights into Mitotic Catastrophe: In a fundamental study, Prof. Das's team discovered CDK1-dependent phosphorylation of TDP1 at residue S61 during mitosis. A phosphorylation-defective TDP1 variant (TDP1-S61A) accumulates on mitotic chromosomes, leading to DNA damage and mitotic defects. They revealed that Top1cc repair during mitosis is mediated by a MUS81-dependent pathway. Replication stress induced by camptothecin or aphidicolin causes TDP1-S61A to accumulate at fragile sites, resulting in chromatid breaks, anaphase bridges, and micronuclei, ultimately leading to 53BP1 nuclear bodies in G1 phase. This study, published in ***The EMBO Journal* (2024),** elucidates the critical role of TDP1 phosphorylation in regulating mitotic activity and preventing genomic instability and presented at the **EMBO Conference** (2024).

Mitochondrial Dysfunction and Disease Pathogenesis: Prof. Benu Brata Das's groundbreaking research has significantly advanced the understanding of mitochondrial dysfunction in neurodegenerative diseases. His pioneering discovery that nuclear-encoded TDP1 is imported into mitochondria (***Proc Natl Acad Sci U S A, 2010***) laid the foundation for further explorations into mitochondrial DNA repair mechanisms. Prof. Das's subsequent research revealed that the SCAN1-mutant TDP1 protein selectively traps on mitochondrial DNA, leading to damage, increased fission rates, and impaired mitochondrial function, ultimately triggering mitophagy in neurons. This seminal study, published in ***Science Advances* (2019)**, has been highly influential, offering new insights into mitochondrial DNA damage in neurological disorders. The impact of this work is underscored by its high citation rate and recognition in top-tier reviews, including ***Nature Reviews Neurology* (2022)** and ***Mitochondrion* (2022),** making it a cornerstone in the field of neurodegenerative research. Prof. Das's contributions have been pivotal in opening new avenues for potential therapeutic targets in neurodegenerative diseases, earning him well-deserved recognition in the scientific community.

Molecular Mechanisms and Cancer Therapy: Prof. Benu Brata Das's research has significantly advanced our understanding of DNA repair mechanisms and their implications for cancer therapy. His lab identified PRMT5 as a key therapeutic target for repairing DNA breaks associated with Top1-DNA trapped complexes. **This discovery highlights PRMT5's role** in enhancing TDP1's repair activity and overcoming resistance to Top1 inhibitors like camptothecin, with findings published in ***Nature Reviews Molecular Cell Biology* (2019)** and presented at the Gordon Research Conference (2018).

Prof. Das's group also uncovered that PRMT5-mediated arginine methylation of TDP1 is essential for maintaining genome stability. Their study, published in ***Cell Reports*** **(2022) and** ***Nucleic Acids Research*** **(2018),** demonstrated that loss of TDP1 methylation leads to defective repair and increased sensitivity to Top1 poisons, suggesting that combining PRMT5 inhibitors with Top1-targeted drugs could improve cancer treatments.

Leishmania donovani DNA repair Research**:** Prof. Das's research on *Leishmania donovani* revealed a novel role for TDP1 in protecting the parasite from oxidative stress and drug resistance. TDP1 knockout *L. donovani* promastigotes showed hypersensitivity to Top1 poisons and antileishmanial drugs, with altered membrane morphology and increased oxidative stress. This study, published in *The* ***FASEB Journal*** **(2022)**, suggests that LdTDP1 plays a critical role in safeguarding against DNA damage and enhancing drug resistance.

Drug Discovery and Development: Prof. Das's lab has developed new Top1 inhibitors to address camptothecin's limitations. They discovered hydantoin and thiohydantoin derivatives as potent Top1 poisons and identified a class of neutral porphyrin derivatives, such as compound 8, which inhibits Top1 at nanomolar concentrations and overcomes CPT resistance, as detailed in the ***Journal of Medicinal Chemistry*** **(2023; 2018).** Additionally, compound 28, a quinoline-based Top1 inhibitor, demonstrated high potency and stability, showing promise for overcoming CPT-related limitations, with results published in ***Nucleic Acids Research*** **(2016)** and **Journal of Medicinal Chemistry** ***(2019).***

Molecular Mechanisms of Drug Action: Prof. Das explored the role of Poly(ADP-ribose) polymerase (PARP1) in regulating Top1 nuclear mobility through Top1-PARylation. His work revealed that inhibiting Top1-PARylation leads to increased Top1 trapping and compromised DNA repair, highlighting the relevance of combining PARP and Top1 inhibitors in cancer therapy. This work was published in ***Nucleic Acids Research (2014)***

Top 10 best papers of the applicant: ** Corresponding authors*

1. Paul Chowdhuri S and ***Das, B. B***.* TDP1 phosphorylation by CDK1 in mitosis promotes MUS81-dependent repair of trapped Top1-DNA covalent complexes, ***EMBO Journal*** ; 2024 Jul 16. doi: 10.1038/s44318-024-00169-3. **(IF: 9.4)**

2. Ghosh, A., Bhattacharjee, S., Paul Chowdhuri, S., Mallick, A, Rehman, I., Basu, S., and ***Das, B.B**. 2019**. SCAN1-TDP1 trapping on mitochondrial DNA promotes mitochondrial dysfunction and mitophagy. ***SCIENCE ADVANCES***, ***5, eaax9778***. **(IP: 14.1)**

3. ***Das, B.B.***, Dexheimer TS, Maddali K and Pommier Y. Role of Tyrosyl DNA Phosphodiesterase (TDP1) in mitochondria. ***Proc Natl Acad Sci U S A***. 16;107(46):19790-19795. 2010. (**IF: 10.23)**

4. Bhattacharjee S, Rehman I, Basu, S., Nandy S, Richardson J., ***Das, B.B****. **2022**. The interplay between symmetric arginine dimethylation and ubiquitylation regulates TDP1 proteostasis for the repair of topoisomerase I-DNA adducts. ***Cell Reports***, 39, 110940 **(IF: 9:43)**

5. Rehman, I.; Basu, S.; Das, S.K.; Bhattacharjee, S.; Ghosh, A.; Pommier, Y.; and ***Das,***

B.B*. **2018.** PRMT5-mediated arginine methylation of TDP1 for the repair of topoisomerase I covalent complexes. ***Nucleic. Acids Research***., **46**: 5601-5617. **(IP: 16.97)**

6. Roy Chowdhury S., Das SK., Banerjee B., Paul Chowdhuri S., Majumder H.K., and ***Das, B.B****. **2022.** TDP1 knockout *Leishmania donovani* accumulate Topoisomerase1-linked DNA damage and are hypersensitive to clinically used antileishmanial drugs. ***The FASEB Journal***, 36(4): e22265**.(IP: 5.1)**

7. Chowdhuri SP, Dhiman S, Das SK, Meena N, Das S, Kumar A, ***Das, B.B.****. Novel Pyrido[2',1':2,3]imidazo[4,5- c]quinoline Derivative Selectively Poisons *Leishmania donovani* Bisubunit Topoisomerase 1 to Inhibit the Antimony-Resistant Leishmania Infection *in vivo*. ***J. Med. Chem,*** 2023, 66(5):3411-3430. **(IF: 8.01)**

8. ***Das, BB,*** Antony S, Gupta, S, Dexheimer TS, Redon CE, Garfield S, Shiloh Y and Pommier Y. Optimal function of the DNA repair enzyme TDP1 requires its phosphorylation by ATM and/or DNA-PK**.** ***EMBO Journal*****. 28, 3667-3680. 2009.** (**IF: 10.12**)

9. Das, S.K., Rehman, I., Ghosh, A., Sengupta, S., Majumder, P., Jana, B and ***Das BB****[*]***.** Poly(ADP-ribose) polymers regulate DNA topoisomerase I (Top1) nuclear dynamics and camptothecin sensitivity in living cells. **2016**. ***Nucleic. Acids Res.*** 44, 8363-75. **(IP: 16.60)**

10. ***Das, B.B****, Huang S.N., Murai J., *Rehman I[@]*., Amé J.-C., *Sengupta S[@]*., *Das S.K.[@]*.,*Majumdar, P[@]*., Zhang H., Biard D., Majumder H.K., Schreiber V., Pommier Y.*, **2014.** PARP1-TDP1 coupling for the repair of topoisomerase I-induced DNA damage, ***Nucleic. Acids Res***., 42:4435-49. **(IP: 16.60)**

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