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Mechanistic role of BR-DIM in human prostate cancer: Clinical experience

Prostate cancer (PCa) is treated with androgen deprivation therapy (ADT) but it becomes refractory and leads to metastasis (mCRPC) which is incurable, suggesting that innovative treatment options are urgently needed. We found deregulated expression of microRNAs (miRNAs) such as miR-34a, miR-124, miR-27b, miR-320 and the let-7 family, and it appears to play important roles in regulating androgen receptor (AR) splice variant expression. The miR-320 and let-7 family inhibit the expression of stem cell markers such as Lin28B, EZH2, Nanog, Oct4 and CD44, which are associated with enzalutamide resistance, and thus could be responsible for the development of mCRPC. These dysregulations can be attenuated by treatment of PCa cells with 3,3'-Diindolylmethane (BR-DIM), which led to conduct a clinical trial. In the phase II clinical trial with localized PCa patients were treated with BR-DIM at a dose of 225 mg orally twice daily for a minimum of 14 days. DIM levels and AR activity were measured at the time of prostatectomy. Moreover, we also assessed the level of expression of miRNAs and the expression of AR and its splice variants in the radical prostatectomy specimens and compared it with diagnostic biopsy specimens. We found that BR-DIM treatment caused down regulation in the expression of AR, AR splice variants, Lin28B and EZH2, which appears to be mediated through the re-expression of let-7, miR-27b and miR-320 and miR-34a in human PCa specimens after BR-DIM treatment. In summary, our results provides the scientific basis for a "proof-of-concept" for therapeutic clinical trial for achieving better treatment outcome which will have a significant impact on the management of PCa patients.

Biography

Dr. Sarkar has completed his Ph.D at the age of 26 years from Banaras Hindu University and continued postdoctoral studies at Memorial Sloan-Kettering Cancer Institute in New York. He has published 555 peer-reviewed research articles and review articles, and also published 50 book chapters. He edited four books and he is an Academic Editor for PLoS One, and also serves in the editorial board of 10 cancer journals. His basic science research led to drug discovery and he is an expert in conducting translational research including clinical trials.

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