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Novel approaches towards personalized cancer therapy

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Abstract

Current cancer treatment that includes chemotherapy is only 25% effective. The p53 tumor suppressor is central in cancer development and response to therapy, but has not been frequently used for therapeutic applications due to the complexity of its action reflected in 64,000 papers describing its function. Here we integrate this vast amount of information by constructing a large-scale logical model of the p53 interactome from database and current literature. The model includes 205 nodes representing genes or proteins, DNA damage input and apoptosis output, and 677 logical interactions. Predictions from model analysis including *in silico* knock-outs and steady state analysis were validated through text mining and *in vitro* based experiments. Novel findings included upregulation of individual pathways in p53 negative cells and numerous other changes in pathways resulting from *in silico* mimicking mutations. The comparison of model simulations with genome wide experimentally obtained data from bone and colon cancer cell lines demonstrated a significant rate of successful predictions ranging between 52 % and 71 % depending on the cancer type. Growth factors and receptors were identified as factors contributing selectively to the control of osteosarcoma and colon cancer cell growth. In summary, we show that dynamic models provide predictive power and better understanding of p53 actions. This approach will make possible individual patients' treatment, will define a sub population of “high” responders for design of clinical trials, and identify shifts in signaling pathways that give rise to resistance to therapy.

Biography

Dr Marija Krstic-Demonacos has completed her PhD from University of California San Francisco and postdoctoral studies from Glasgow University. She is the Professor in the University of Salford in England. She has published 37 papers in reputed journals and is serving as an editorial board member of Oncology Reports journal. In addition, commercialization potential of her research is evidenced by the three patents she owns. She has presented at numerous conferences and served as reviewer for various international funding bodies and journals.

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