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New approaches to personalised cancer care

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Abstract

Although chemotherapy is commonly used in cancer treatment, it is only 25% effective. The p53 tumor suppressor is crucial for both cancer development and response to therapy, but has been less amenable to therapeutic applications due to the complexity of its action reflected in 63,000 papers describing its function. Here we provide a systematic approach to integrate this vast amount of information by constructing a large-scale logical model of the p53 interactome from database and literature information. The model contains 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 using literature searches and *in vitro* based experiments. Novel findings included upregulation of Chk1, ATM and ATR pathways in p53 negative cells and numerous changes in pathways brought on by knockout tests mimicking mutations. The comparison of model simulations with microarray data 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 a systematic compilation of knowledge into dynamic models provides predictive value and better understanding of p53 actions. This approach will facilitate tailoring of individual patients' treatment, will define a sub population of “high” responders for design and management of clinical trials, and identify shifts in signaling pathways that give rise to resistance to therapy.

Biography

Marija Krstic-Demonacos has completed her PhD from University of California San Francisco and postdoctoral studies from Glasgow University. She is the Principal Investigator and Lecturer in the University of Manchester. She has published more than 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 funding bodies and journals.