Systems Therapeutics for Personalized Medicine: Current Status and Prospects.

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Many progressive diseases involve multiple cellular pathways in different cell types within an organ and often different organs as well. This complexity has made it difficult to develop drugs that can halt the progression of diseases such as aneurysms, heart failure and kidney disease. For these types of diseases systems pharmacology and therapeutics is likely to be better suited to develop combination therapy and for new drug discovery. Systems level reasoning offers the ability to scale across levels of biological organization as well as with respect to time. Cell level regulatory pathways and networks can be inferred from transcriptomic and proteomic studies on tissues and organs in diseased states and utilized to identify potential drugs for therapy. Graph theory models of pathways and networks as well as dynamical models of cellular functions can be used to identify drugs and devise therapeutic regimes. In collaboration with our colleagues who are experts in aneurysms we have integrated transcriptomic data from blood vessels of humans and mice with Marfan syndrome to build networks and identify common subcellular pathways that can be targeted by drugs. Models of cellular networks enabled us to identify baclofen as a potential therapeutic agent. Treatment of mice with aortic aneurysms show improved vessel wall pathology and physiological function and mice show improved survival. In another study in the nervous system we used dynamical models of neurite outgrowth and spatial considerations to treat injured neurons to enable axonal regeneration. We devised a four drug combination with two drugs (cannabinoid receptor agonist and IL6) applied at the cell body along with Taxol and APC (activated protein C) at the site of axonal injury to regenerate axons in injured optic nerves of rats to partially restore visual evoked potentials in the brain. These proof-of-principle studies show that systems level models can be powerful tools for drug discovery and therapeutics. In the future the challenge will be to use such computational models for discovery of new drugs and to devise therapeutic strategy to treat individuals effectively. The integration of network and dynamical models with machine learning algorithms that enable us to track trajectories between the healthy and progressive disease states could be a useful approach to build whole body models of individuals based on their clinical data and molecular details for personalized therapy.