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The mevalonate pathway: An integrated view of apoptosis control to abrogate cancer cell growth

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The mevalonate biochemical pathway leads to the synthesis of cholesterol in every mammalian cell, but also to the production of intermediary fatty acids that drive the activation of small G proteins from the Ras, Rho, Rac etc. families. Collectively, these proteins stimulate cell growth, especially cancer cell growth, when they carry activating mutations. It is, therefore, important to try to circumvent their functional activity. We have published the first bioinformatics model of the cholesterol pathway (BMC Syst Biol. 2008 Nov 24;2:99. *Dynamical modeling of the cholesterol regulatory pathway with Boolean networks*), including the influence of statins on the pathway. Statins inhibit the HMG-CoA reductase enzyme, which converts HMG-CoA into mevalonate, lower cholesterol in humans and efficiently trigger cancer cell apoptosis in experimental models. It is believed that apoptosis induction by statins may be due, in part, to their ability to prevent prenylation - and thus activation - of small G proteins. We have undertaken an integrated analysis aimed at determining the activity of the pathway in response to statins through surveying several endpoints, by analytical, molecular and cellular approaches: Enzyme activities (HMG-CoA reductase, Mevalonate Kinase, Farnesyl Pyrophosphate Synthase and Squalene Synthase) and alternative pre-mRNA splicing of the genes encoding these enzymes, metabolite concentrations (Farnesyl Pyrophosphate, Geranyl Geranyl Pyrophosphate), protein prenylation (Ras, RhoA, Rac1, Cdc42) and apoptosis levels. A bioinformatics model will be built to integrate all these parameters. This approach should lead to a novel systems biology view of the effects of statins in cancer models.

Biography

Laurent CORCOS has completed his PhD in 1988 from Paris VI University and the Pasteur Institute. He obtained a post-doctoral training from the McArdle Institute for Cancer Research (Madison WI). He now directs the ECLA team (see http://www.genetic-brest.fr/index.php?rub=cancerologie_appliquee_a_episage_alternatif_themes_diriges_par_laurent_corcos_2) within the INSERM U613 research Unit.