Personalized Cancer Treatment Selection using Computational Signaling Pathway Models

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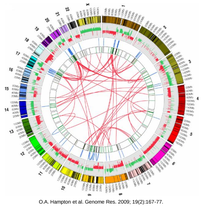
Introduction

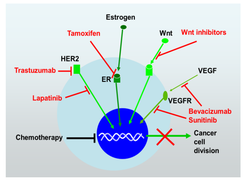
Current developments in clinical oncology, with breast cancer in the front line:

1. cancer genome sequencing is entering clinical diagnostics
2. novel targeted drugs target signaling pathways that drive tumor growth
3. metastasized cancer is expected to change into a chronic disease, requiring repeated personalized choice of targeted therapy and therapy response monitoring

Hence, there is a need to clinically interpret available genomic data in order to diagnose – on an individual basis – which signaling pathway is driving tumor growth in a patient, including the causative mutation, such that appropriate targeted drugs can be chosen. Currently available pathway analysis tools and databases are not suitable for this.



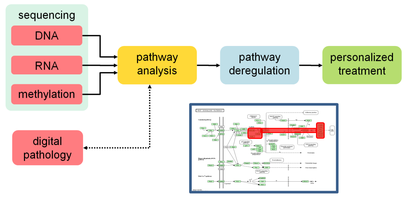
1. An overload of sequencing data



2. Novel cancer drugs target specific signaling pathways

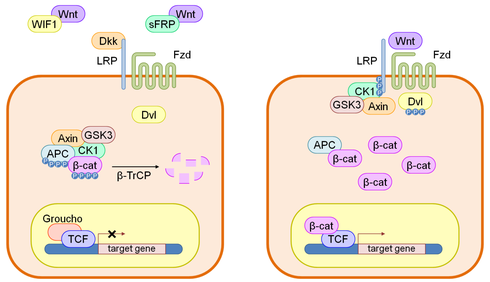
Objective: companion diagnostics

To address the above need, we are developing computational models of signaling pathways, which can be used as companion diagnostic tools to translate complex genomic data into meaningful clinical information to enable selection of targeted drug therapy. The aim is to develop such models for the ~10 major oncogenic pathways, and use them to predict which one is most likely to drive tumor growth in an individual patient, including the probable underlying genomic defect.

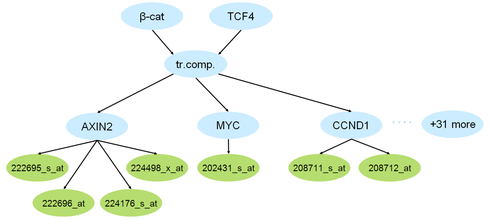


Method: modeling the Wnt pathway

As a proof of concept, we have built a computational model of the Wnt pathway [1], which is active in colon adenoma and a main player in colon cancer, but also relevant in other cancers, among which breast cancer [2].



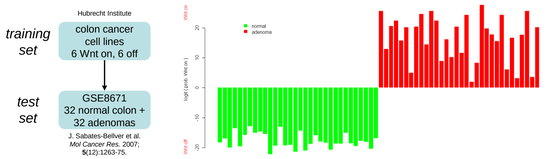
Our first generation model of the Wnt pathway covers its transcriptional program, for which we carefully selected a list of Wnt target genes. We have modeled this pathway by a Bayesian network, which interprets the expression levels of the target genes (from Affymetrix U133Plus2.0 arrays), and infers a probability that the Wnt pathway is active in a certain individual patient tumor sample. The parameters of the model are partly derived from literature and partly fitted on experimental data.



First generation Bayesian network model of the Wnt pathway. Parameters of the top part (blue) are derived from literature; parameters of the bottom part (green) are fitted on experimental data

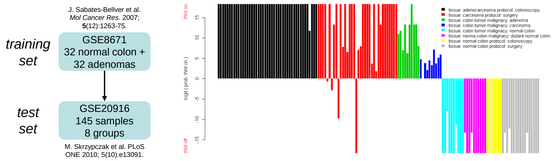
Results

We first fitted a model on data from six pairs of Wnt knock-down experiments on colon cancer cell line LS174T performed at the Hubrecht Institute, and tested it on a public set of 32 normal colon samples plus 32 colon adenomas from patients (GSE8671). This model perfectly predicted no Wnt activation in the normal samples and an active Wnt pathway in the adenomas.

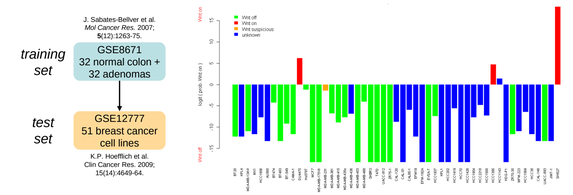


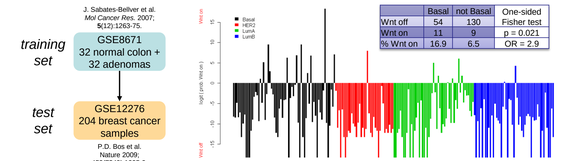
Next, we fitted the model on the 32 normal and 32 adenoma samples, and tested it on a set of 145 normal colon and colon cancer samples from patients (GSE20916). The model again predicted no Wnt activation in all 44 normal samples, and an active Wnt pathway in all cancer samples, except for four of the 36 samples from surgically removed colon carcinomas, which are more heterogeneous than early malignant samples obtained through colonoscopy.

As a reference, only looking at Axin-2 mRNA levels did not give the same discrimination results.

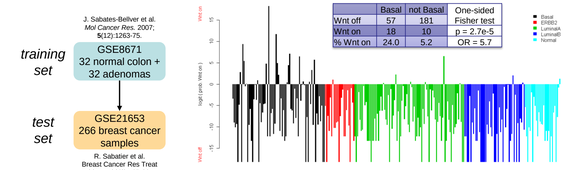


Thirdly, we took the latter model, trained on colon samples, and tested it on three breast cancer data sets, one with 51 breast cancer cell lines (GSE12777) and two sets of breast cancer samples from patients (GSE12276, n = 204; GSE21653, n = 266). Also on this different tissue type, our model correctly predicted Wnt activation for the few breast cancer cell lines that are known to have an active Wnt pathway. For the two patient studies, a significantly higher number of samples of the basal subtype were predicted to have an active Wnt pathway compared to the other subtypes (Fisher's exact test: p = 0.021 for GSE12276; p = 2.7e-5 for GSE21653), in line with increasing evidence for Wnt activation in the basal subtype [3].





	Basal	not Basal	One-sided Fisher test
Wnt off	54	130	
Wnt on	11	9	p = 0.021
% Wnt on	16.9	6.5	OR = 2.9



	Basal	not Basal	One-sided Fisher test
Wnt off	57	181	
Wnt on	18	10	p = 2.7e-5
% Wnt on	24.0	5.2	OR = 5.7

Conclusion

Our first generation computational Wnt model performs well to probabilistically predict Wnt pathway activation in individual tissue samples, based on microarray mRNA analysis of its target genes, and shows significantly more Wnt activation in basal type breast cancer samples.

Experimental validation is in progress, amongst others on the GSE12276 samples and breast cancer cell lines with Erasmus MC, as well as further fine tuning of the model on breast tissue.

References

1. H. Clevers (2006). Wnt/β-catenin signaling in development and disease. *Cell* 127(3):469-80.
2. T.J. King et al. (2011). The Wnt/β-catenin signaling pathway: A potential therapeutic target in the treatment of triple negative breast cancer. *J Cell Biochem* doi:10.1002/jcb.23350 (epub ahead of print).
3. A.I. Khramtsov et al. (2010). Wnt/ β-catenin pathway activation is enriched in basal-like breast cancers and predicts poor outcome. *Am J Pathol* 176(6):2911-20.