The GMR Approach of Cancer Gene Therapy

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***Short Abstract* — We prove that cancer nodules and surrounding normal tissue are governed by distinct Gene Master Regulators (GMR) and that smart manipulation of a GMR's expression selectively affects cancer cells. The method, consistent with our Genomic Fabric Paradigm, relies on an original mathematical algorithm that establishes the gene hierarchy from the transcriptomic profiles of tumor biopsies based on their Gene Commanding Height (GCH). GCH is a composite measure of gene expression control and coordination with major functional pathways. We present validation of the approach using microarray data obtained in our NYMC laboratory by profiling human thyroid, kidney and prostate cancer samples.**

***Keywords* — gene master regulators, genomic fabric, transcriptomic topology, microarray, thyroid cancer, kidney cancer, prostate cancer.**

I. Introduction

NUMEROUS groups race to discover the gene biomarkers whose alteration (as sequence or expression) alone is indicative of a particular disease in all humans. However, thousands other genes (whose contribution is neglected but not necessarily negligible) are affected. In each person a similar disease results from a unique, never-repeatable combination of gene alterations. As selected from the most frequently altered genes in large populations (indicating little protection by the homeostatic mechanisms like for low-key players) biomarkers are of little therapeutic value. Instead, our Genomic Fabric Paradigm [1] identifies in the cancer nodules of **each** patient the GMRs whose highly protected expression governs major functional pathways by controlling the expression of numerous other genes. The genomic fabric is defined as the transcriptome associated with the most interconnected and stably expressed network of genes responsible for a particular functional pathway. The fabric exhibits specificity with respect to race/strain, sex, age, tissue/cell type, and lifestyle and environmental factors. It remodels during development, progression of a disease, and in response to external stimuli. GFP is powered by mathematically advanced analytical tools (e.g. [2]) that are presented together with the experimental protocol to collect and profile the cancer nodules from a heterogeneous tumor.

II. Results

Our experimental protocol requires that biopsies from cancer nodules and surrounding normal tissue (best reference for malignancy) are split in four, quarters profiled separately as biological replicas of the same transcriptomic machinery subjected to slightly different local conditions. Thus, we get for every single gene three independent measures: average expression level (L), expression variability (V) and expression coordination (C) with each other gene. "L" is used to determine what gene is up/down-regulated in malign vs normal tissue, "V" to estimate the control of transcript abundance in each condition and "C" how the genes are networked in functional pathways to satisfy a kind of "transcriptomic stoichiometry" [3]. Together, these results are uploaded in an algorithm that constructs the genomic fabrics of major functional pathways [4] and their interplays [5], determines the GCH scores of individual genes and establishes the gene hierarchy in each part of the tumor. We have published recently proves that malign and normal regions of kidney [6] and thyroid [7] tissues are governed by different GMRs. Here, we provide additional evidence for several cases of prostate cancer and validate the therapeutic value of the GMR approach in standard cell lines of human cancers of thyroid, lung and blood.

III. Conclusion

GMR approach identifies for each patient the most legitimate gene targets for cancer gene therapy. Smart manipulation (e.g. up-regulation if pro-apoptotic or silencing if anti-apoptotic) of the personalized GMR would have the best result not for everybody but for that person.

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