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Functionally distinct gene classes as bigger or smaller transcription factor traps: A possible stochastic component to sequential gene expression programs in cancer

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ABSTRACT

In cancer biology, most molecular regulatory mechanisms are casually treated as on/off switches for specific cancer hallmarks, despite the lack of compelling evidence that cancer hallmarks can be exclusively attributed to specific regulatory proteins. To consider a novel paradigm for the basis of regulating a set of effector genes for proliferation, versus apoptosis-effector genes, we used a bioinformatics approach to ascertain differences between the transcription factor binding site occurrences in the two sets of genes. Results indicated that there are more binding sites per gene, for transcription factors that regulate both proliferation and apoptosis, among the proliferation-effector genes than among the apoptosis-effector genes. Proliferation-effector genes also had more open chromatin regions. We also applied this paradigm to the question of why p53 and interferon regulatory factor-1 (IRF-1) first activate cell cycle arrest genes followed by apoptosis genes, with results indicating the cycle arrest genes are bigger p53 and IRF-1 traps. These data support the idea that, as a set of transcription factors becomes active, there is a stochastic component leading to the accumulation of these transcription factors on genes that effect an initial phenotype before their accumulation on genes that effect a subsequent phenotype.

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1. Introduction

Cancer development is a process whereby cells eventually obtain a phenotype that leads to uncontrollable metastasis and clinical pathology. The cancer phenotype is divisible into hallmarks, for example, increased cell division, decreased apoptosis, and tumor cell colonization of distant sites. Furthermore, it has been proposed, and indeed widely accepted, that the acquisition of each hallmark represents a mutation that is specifically associated with individual hallmarks. However, there is little or no specificity to the underlying molecular changes in cancer that connects these changes to one hallmark versus another (Korzus et al., 1997; Long et al., 2011; Luo et al., 2009; Montesano et al., 1999). For example, the transcription factor E2F-1 is deregulated in cancer, is indisputably important for activating pro-proliferative genes, such as histone and dihydrofolate reductase genes (Bandara et al., 1993; Oswald et al., 1996). However, lack of E2F-1 leads to tumors (Yamasaki et al., 1996), almost certainly because E2F-1 is also important in stimulating the transcription of apoptosis genes (Adams and Kaelin, 1996; Phillips and Vousden, 2001). NF-kappaB is also pro-proliferative (Jain et al., 1995) and pro-apoptotic (Ridder and Schwaninger, 2009).

Gene inactivation or oncogene activation has been reported to occur in sequence, which can correlate with the sequence of cancer hallmark acquisition (Fearon and Vogelstein, 1990). However, it is not clear that the sequence of gene inactivation is due to anything other than the greater probability of a larger gene being inactivated before a smaller gene (Long et al., 2011). Meanwhile, large tumor suppressor genes have about the same set of literature relationships to regulatory pathways as do the smaller tumor suppressor genes (Long et al., 2011). These results again call into question the idea that, once gene inactivation occurs, a specific regulatory pathway is affected in a way that leads to the acquisition of a specific cancer hallmark.

The above considerations leave the question, how are different hallmarks established? One possibility, that would employ non-exclusive sets of regulatory proteins, would be that the level of regulatory protein activation, rather than presence or absence of an activated protein, would lead to distinct cancer hallmarks. Indeed, the levels of transactivator concentration and signaling pathway activation have been shown to be crucial to many aspects of developmental hallmark acquisition (Ashe and Briscoe, 2006; Grimm et al., 2010).

The bioinformatics and data mining analyses described below suggest a possible mechanism whereby proliferation and apoptosis could be governed by the level of transcription factor availability rather than by the absolute availability of particular transcription factors that are exclusive to one process or the other (Fig. 1).

Abbreviations: IRF-1, interferon regulatory factor-1; TF, transcription factor; TFBS, transcription factor binding site; YY1, Ying-Yang 1; STAT, signal transducer and activator of transcription; HS, hypersensitive; CIITA, class II transactivator; MHC, major histocompatibility; NFAT, nuclear factor, activated transcription; SAHA, suberanilohydroxamic acid.

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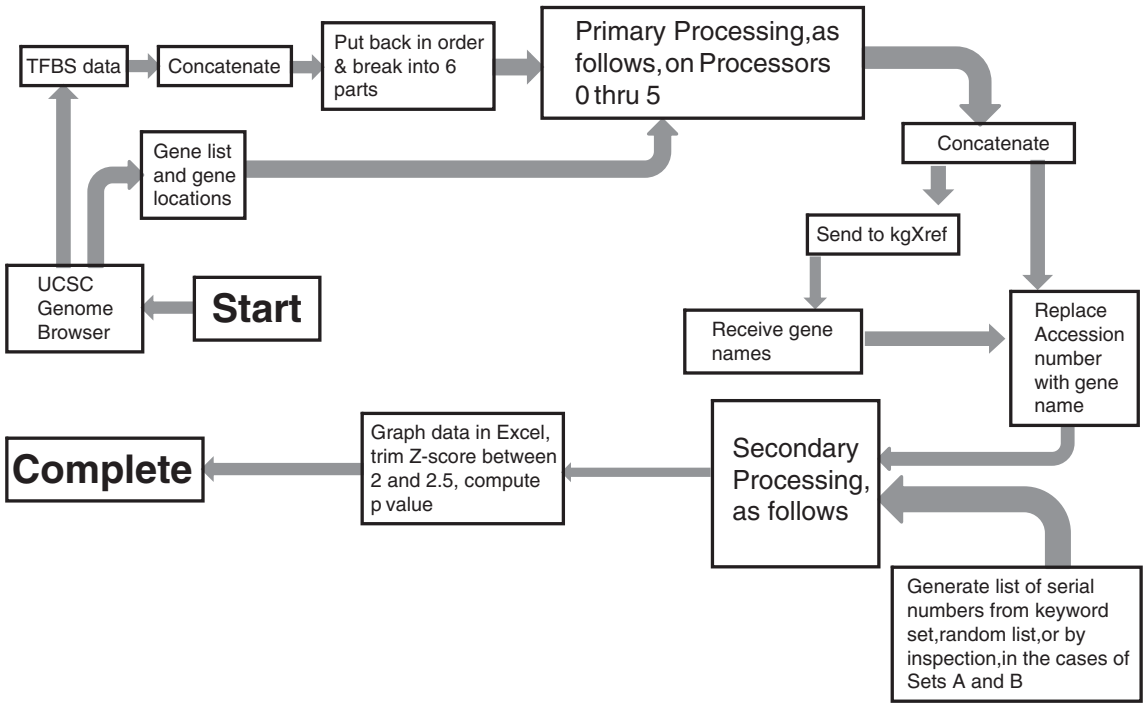

Fig. 1. Summary of data processing. TFBS data and gene lists were ordered from genome database and effectively overlaid, to link TFBS with genes. Genes were then isolated with Keywords, random number generators, or according to Sets A and B, as described in the Methods and Results sections. Plots for figures were generated in MS Excel.

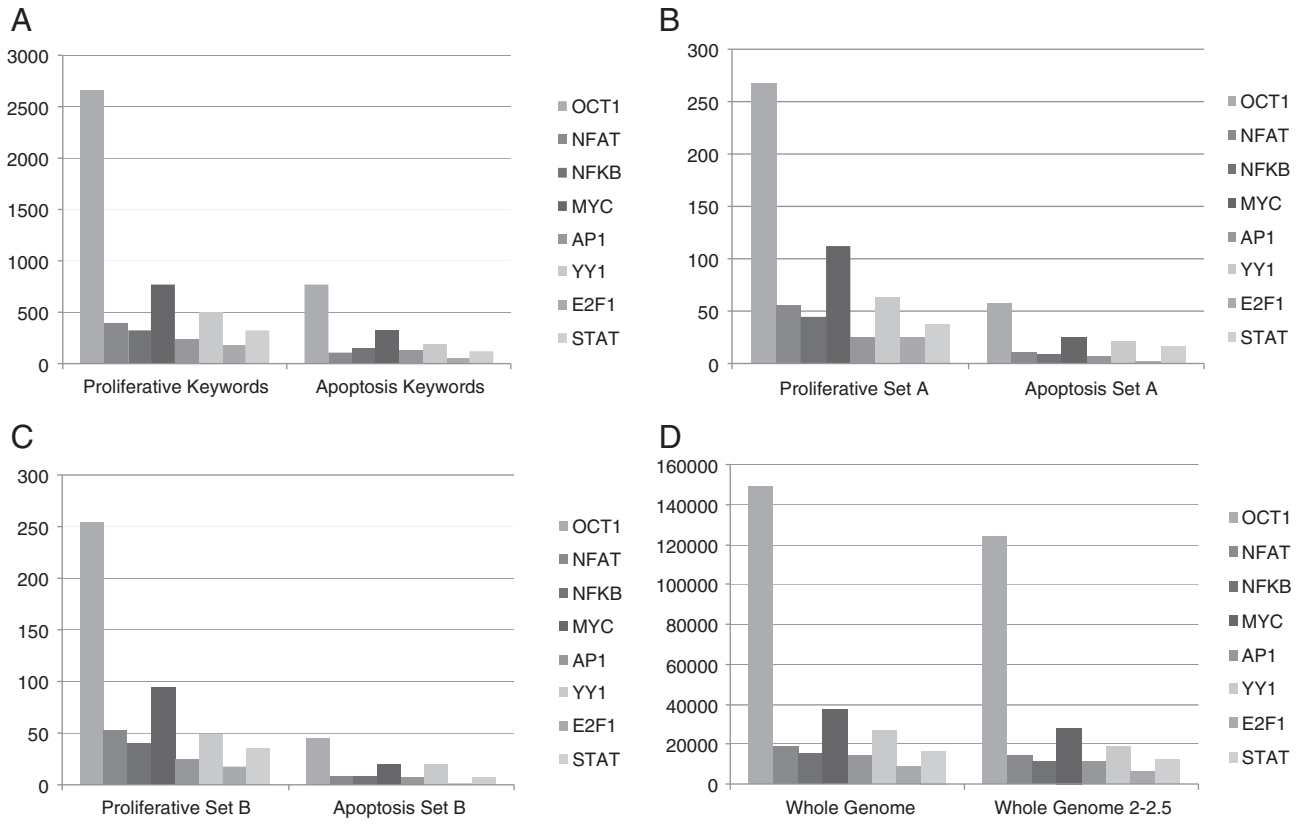

Fig. 2. Number of TFBS for the indicated TFs in the set of proliferation-effector and apoptosis-effector genes. TFBS are within 5000 base pairs on either side of each gene included. The number of TFBS for the Keyword set, Set A and Set B are indicated.

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