LARGE DIFFERENCES IN TRANSCRIPTIONAL NETWORKS OF NORMAL AND TUMOR COLON CELLS

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Introduction

• Transcriptional regulatory programs have an essential role in cancer.

• Although specific alterations are well described, studies at the whole genome level are required to obtain more information about the transcriptional programs involved in tumor development.

• This work has been developed in the context of colorectal cancer within the COLONOMICS project (www.colonomics.org).

Objectives

• Characterize the differences between transcriptional programs of normal and tumor colon cells, through a reverse engineering reconstruction of gene regulatory networks.

Materials & Methods

• Gene expression profiles for 196 colon samples (98 tumors and 98 paired normal tissues) were obtained using the Affymetrix HG-U219 array plate.

• Regulatory networks for both normal and tumor samples were built using the ARACNe algorithm. Kernel bandwidth and mutual information null distribution parameters were previously estimated for the dataset. 1000 bootstrap replicates were performed and summarized to obtain accurate consensus networks.

• Additional tools:

- Cytoscape platform: Visualizations and topological network analyses.
- BINGO: Overrepresentation of GO categories in biological networks.
- R statistical environment: Additional analyses and data processing.

Results

• The tumor regulatory network shows a large loss of transcriptional interactions (Figure 1).

The tumor regulatory network contains:

- 37% fewer transcription factors (1185 vs. 755).
- 56% fewer target genes (5471 vs. 2384).
- 80% fewer direct transcriptional interactions (61235 vs. 11940).

This fact suggests that the loss of interactions may not be only due to potential alterations at the DNA level, but also because of failures in the transcriptional machinery of the tumor.

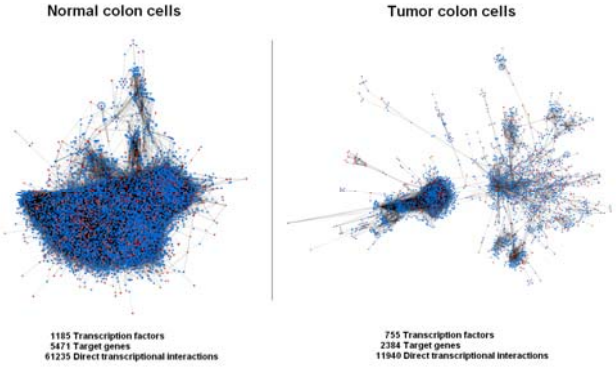


Figure 1. Gene regulatory networks of normal and tumor colon cells.

• Functional analysis of tumor regulatory network displayed classical cancer-related biological processes significantly enriched, (Table 1) among others.

GO ID	Description	Adjusted pvalue (FDR)
5576	Extracellular region	3.00E-09
2376	Immune system process	1.13E-05
7165	Signal transduction	2.32E-05
32502	Developmental process	0.0002

Table 1. GO categories overrepresented in tumor regulatory network.

• Regarding the behavior of network nodes, transcription factors(TF) and its targets, these can be classified into the following four lists (only show the top 15):

TF that increase their activity in Tumors

Gene	Out-degree in Normal	Out-degree in Tumor
SNAI2	1	119
MMP14	10	121
AEBP1	103	186
BASP1	43	123
HCLS1	91	170
TFEC	6	84
DKK3	41	112
COL1A1	62	131
CD86	74	141
MAFB	125	189
NOTCH3	18	82
GLI2	37	100
TGFB1	1	61
GREM1	14	70
HOPX	46	102

TF that decrease their activity in Tumors

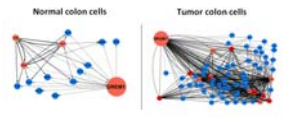
Gene	Out-degree in Normal	Out degree in Tumor
NPM1	581	11
PRNP	404	0
YAP1	375	0
DNM2	353	0
RBPMS	353	0
MLX	348	0
RHOQ	347	1
CAV1	402	82
PRR13	304	0
MORF4L1	302	3
SMAD5	281	0
CEBPG	273	0
PHB	281	9
SIRT7	269	0
NFIA	264	0

Over-regulated targets in Tumors

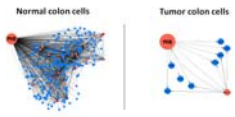
Gene	Type	In-degree in Normal	In-degree in Tumor
BGN	Target	0	29
NNMT	Target	3	32
CDH11	Target	1	24
RAB31	Target	20	42
MXRA8	Target	3	23
RFTN1	Target	8	28
CFH	Target	3	20
COL3A1	Target	14	31
CTHRC1	Target	0	17
EMILIN1	Target	12	28
ENTPD1	Target	12	28
MRC2	Target	7	23
STAU1	Target	1	17
AXL	Target	9	24
OLFML2B	Target	10	25

Under-regulated targets in Tumors

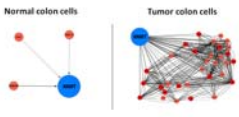
Gene	Type	In-degree in Normal	In-degree in Tumor
C11orf58	Target	72	0
NAP1L1	Target	72	0
NPM1	TF	71	2
YAP1	TF	63	0
ATRX	TF	63	1
PRNP	TF	58	0
BBX	TF	55	0
ZBTB4	TF	57	2
CCDC50	Target	56	2
NFIA	TF	54	0
ANXA5	Target	53	0
PRKD3	Target	53	0
SMAD5	TF	52	0
SORBS2	Target	52	0
DIP2C	Target	51	0



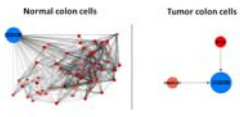
GREM1 neighborhood.



PHB neighborhood.



NNMT neighborhood.



CCDC50 neighborhood.

Conclusions

• Inference of gene regulatory networks at the whole-genome level has allowed us to detect a generalized loss of transcriptional activity in colon tumors, which had not been described before.

• This finding will allow a better comprehension of the transcriptional regulatory programs altered in colon cancer.

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