Identifying potential new drug targets in hypermutated colorectal cancer consensus subtype I

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INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent carcinoma in the world[1]. Development of colorectal tumors is related mainly to dietary and sedentarism, and recent lifestyle changes in many populations contribute to the rise in CRC cases. Recently, the Colorectal Cancer Subtyping Consortium (CRCSC), a joint effort involving multiple research groups, has identified and characterized four consensus molecular subtypes (CMS)[2]. This new classification allows us to better understand CRC and develop new therapy strategies based on each subtype features. Our aim was to investigate the Microsatellite Instability Immune (CMS 1) subtype, in order to identify new potential druggable targets. This subtype is characterized by hypermutation, CpG island methylator phenotype, immune infiltration, BRAF mutations, and worse survival after relapse.

CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

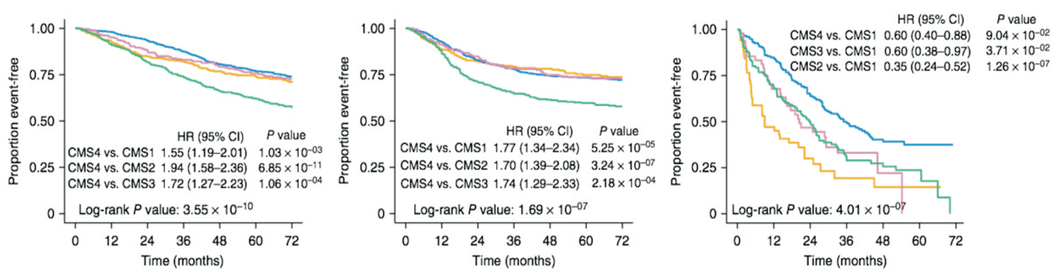
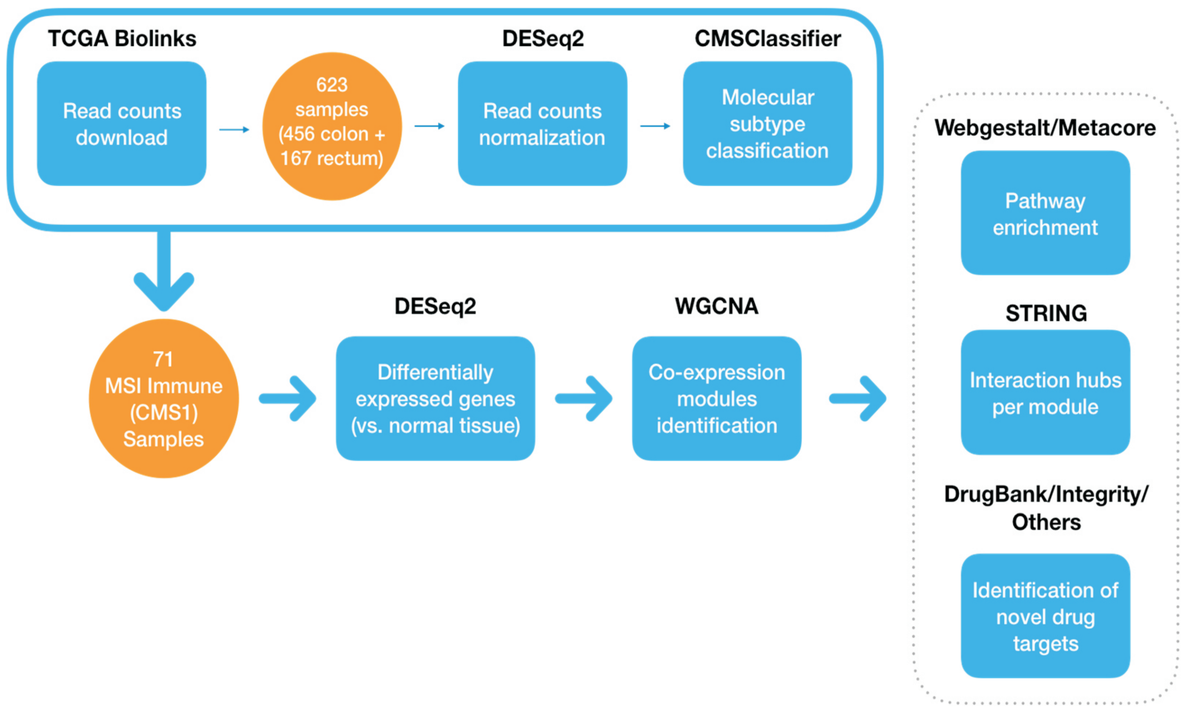


Figure 1 – Consensus molecular subtypes (CMS) characteristics and survival rates for each of them. Adapted from Guinney et al. (2015)[2].

METHODS



RESULTS

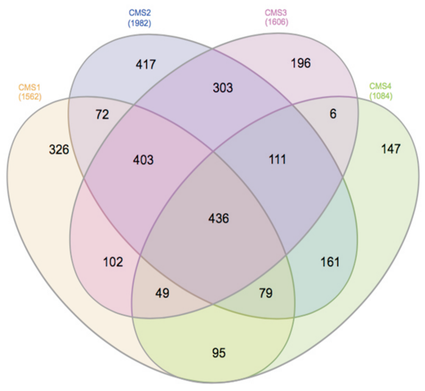


Figure 2 – Differentially expressed genes for each subtype vs. normal tissue.

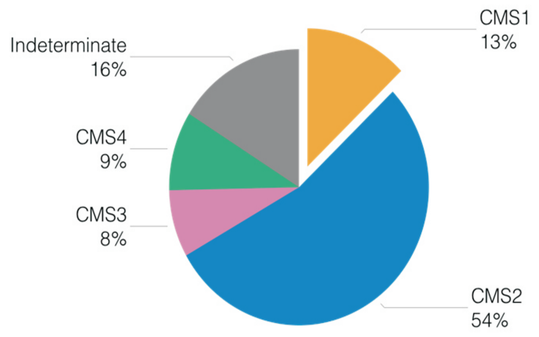
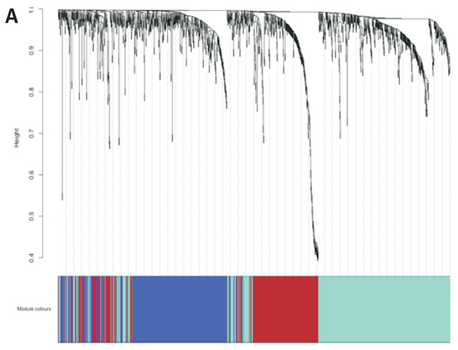


Figure 3 – CMS classification for TCGA primary tumor samples.

A



B

ID	Name	#Gene	FDR
hsa04976	Bile secretion - Homo sapiens (human)	11	1.63e-05
hsa00040	Pentose and glucuronate interconversions - Homo sapiens (human)	8	1.95e-05
hsa05204	Chemical carcinogenesis - Homo sapiens (human)	11	2.51e-05
hsa00982	Drug metabolism - cytochrome P450 - Homo sapiens (human)	10	3.72e-05
hsa00830	Retinol metabolism - Homo sapiens (human)	9	1.49e-04
hsa00980	Metabolism of xenobiotics by cytochrome P450 - Homo sapiens (human)	9	3.07e-04
hsa00053	Ascorbate and aldarate metabolism - Homo sapiens (human)	6	3.07e-04
hsa04975	Fat digestion and absorption - Homo sapiens (human)	7	3.07e-04
hsa00140	Steroid hormone biosynthesis - Homo sapiens (human)	8	3.07e-04
hsa00910	Nitrogen metabolism - Homo sapiens (human)	5	3.07e-04
hsa00983	Drug metabolism - other enzymes - Homo sapiens (human)	7	4.93e-04
hsa00860	Porphyrin and chlorophyll metabolism - Homo sapiens (human)	6	2.66e-03
hsa04964	Proximal tubule bicarbonate reclamation - Homo sapiens (human)	4	1.72e-02
hsa04972	Pancreatic secretion - Homo sapiens (human)	7	4.03e-02

C

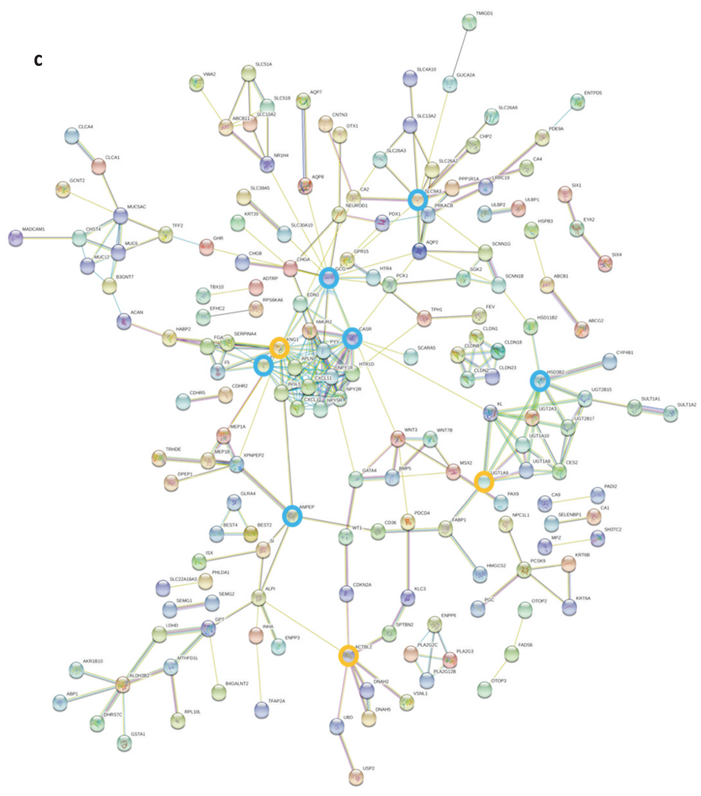


Figure 4 – (A) Gene clustering based on expression. Color labels represent co-expression modules generated by WGCNA. (B) KEGG pathways enriched using Webgestalt's Overrepresentation Enrichment Analysis (ORA) for genes in the blue WGCNA module. (C) Protein-protein interaction network using proteins encoded by the genes included in the blue WGCNA module. Some of the potential hub genes are circled in blue. Potential hub genes differentially expressed exclusively by CMS1 are circled in yellow.

NEXT STEPS

Genes that interact with a higher number of genes in different pathways are more likely to disrupt said pathways when targeted by therapy. Genes in other modules and pathways more likely to result in better prognosis when targeted by drugs will be evaluated. This analysis will be made on the other subtypes as well. Drugs selected by these analyses will be validated in CRC-derived cell lines.

REFERENCES

1 – BRENNER, H. et al.Colorectal cancer. The Lancet , v. 383 , n.9927 , p. 1490 – 1502, 2014.

2 – GUINNEY, J. et al. The consensus molecular subtypes of colorectal cancer. Nature Medicine, v. 21, n. 11, p.

Projeto Gráfico: Área de Edição e Produção de Materiais Técnico-Científicos /INCA

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