Exploring mitochondrial gene expression in progression to colorectal cancer

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BACKGROUND

Colorectal cancer (CRC) is the third most diagnosed cancer and has the second highest rate of cancer-related death in the United States.[1]

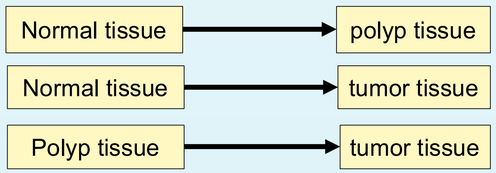
Despite advances in cancer research, uncertainty remains about the origin and progression of normal tissue to cancerous tissue, especially with regards to the role that mitochondrial metabolic pathways play. Numerous factors, such as excess ROS production and alternative mitochondrial resource allocation may influence tumorigenesis.

Identifying mitochondrial genes that are dysregulated across different stages of colorectal tissue provides insight into the progression of metabolic dysfunction and development of disease.

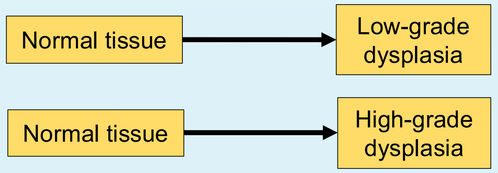
METHODS

This analysis was conducted using publicly available data from NIH's Gene Expression Omnibus database. Gene expression was compared across normal, polyp, and cancerous CRC tissue samples. The MitoCarta list was then used to find significantly dysregulated mitochondrial genes.

Datasets 1 and 3 compared the gene expressions of:



Dataset 3 also compared the gene expression of:



FINDINGS

1) MitoCarta genes with significant up- or downregulation compared to normal tissue.

Dataset 1

Polyp vs. Normal	log FC	Tumor vs. Normal	log FC
ARMCX1	-2.32	ACADS	-2.23
BCL2A1	-2.32	ACSL6	3.02
BNIP3	-2.63	ADHFE1	-2.50
CPS1	4.97	AKR1B10	-3.74
EFHD1	-2.19	FABP1	-3.07
GLDC	-2.62	HIGD1A	-2.26
HIGD1A	-2.03	HMGCS2	-3.66
HPDL	2.00	LDHD	-3.01
MAOB	-2.86	MTHFD1L	2.24
MOCS1	-2.25	NEU4	-2.38
MSRB3	-2.60	PDK4	-2.62
PDE2A	-2.34	PYCR1	2.12
PYCR1	2.26	RECQL4	2.25
SLC25A34	-2.55	SLC25A34	-3.15

Dataset 2

Polyp vs. Normal	log FC	Tumor vs. Normal	log FC
ACAA1	-2.35	ACACA	-2.63
ACACA	-2.21	ACAD10	2.10
ADCY10	-2.12	ACOT11	2.22
AKR1B10	-3.77	AKR1B10	-3.28
BID	2.93	ARG2	2.05
COX5A	2.03	BID	2.14
CPT2	-4.62	CA5B	-3.20
DUS2	-2.41	CPT2	-4.58
FDXR	2.02	FKBP8	-3.31
FKBP8	-2.81	FOXRED1	-2.55
GTPBP3	-2.43	GTPBP3	-2.04
MRPL24	-2.31	IFI27	-2.24
MRPL54	2.10	MRPL23	2.03
MRPS35	-2.39	MRPS35	-2.63
MTERF4	-2.04	MSRA	-2.48
MYO19	-2.06	MYO19	-2.33
NDUFB5	-2.94	NDUFB6	-2.08
NDUFB6	-2.06	PIF1	-2.38
NDUFS5	2.02	PNPO	-3.41
NDUFV1	-2.07	SLC25A20	2.16
NIT1	-3.09	SOD2	-2.41
NLN	2.09	THEM4	-3.52
PDE2A	-2.23	TIMM13	2.00
PHB	-2.19		
PIF1	-2.80		
PNPO	-3.67		
SHMT2	-2.32		
SLC25A20	2.11		
SLC25A27	2.70		
SOD2	-2.57		
SPG7	-2.27		
SYNJ2BP	-2.31		
THEM4	-3.58		
TIMM21	-2.23		
TTC19	-3.12		

Dataset 3

Low Grade vs. Normal	log FC	High Grade vs. Normal	log FC	Adenocarcinoma vs. Normal	log FC
ACAT1	-2.55	ACAT1	-2.35	ACADS	-2.10
AGXT	-2.45	ACSL6	2.46	ACAT1	-2.19
BCL2A1	-2.24	AGXT	-2.52	ACSL6	2.93
BCL2L11	-2.07	AKR1B10	-2.46	AGXT	-2.21
BID	2.36	BCL2A1	-2.57	AKR1B10	-3.52
COX7A1	-3.77	BCL2L11	-2.09	ARG2	2.16
ECHDC3	-2.10	COQ10B	-2.18	BCL2	-2.51
HIGD1A	-2.25	COX7A1	-3.32	C15orf48	-2.54
MICU3	-2.92	CPS1	2.56	CKMT2	-4.10
MOCS1	-2.14	ECHDC3	-2.49	FKBP10	2.15
MSRB3	-2.16	HIGD1A	-2.77	GPT2	2.44
NEU4	-2.04	LDHD	-2.48	HIGD1A	-2.57
SLC25A21	2.14	MAOA	-2.34	HMGCS2	-2.52
		MICU3	-2.64	LDHD	-3.72
		MSRB3	-2.27	MAOA	-2.46
		MTHFD1L	2.00	MTHFD1L	2.36
		NEU4	-2.48	NEU4	-2.41
		PXMP2	-2.12	PINK1	-2.13
		SLC25A20	-2.15	PXMP2	-2.10
				RECQL4	2.23
				SCP2	-2.02

Figure 1. Green indicates upregulated genes in both polyp and adenocarcinoma (tumor) stages. Red represents downregulated genes in both polyp and adenocarcinoma stages. Purple depicts genes that were dysregulated in both low- and high-grade dysplasia stages, but not significantly in the tumor stage.

DISCUSSION

- *AKR1B10* helps regulate metabolism and break down toxic compounds[2]
- Downregulated in all 3 datasets at tumor stage
- Downregulated in datasets 2 and 3 at polyp stage
- Early-stage downregulation of *AKR1B10* may indicate intestinal cells are incurring increased damage prior tumorigenesis

- *SLC25* family member genes are key in the transportation of substrate across the mitochondrial inner membrane[3]
- Dysregulated across all 3 datasets in polyp stage
- Dysregulated at tumor stage in datasets 1 and 2
- Early dysregulation of *SLC25* genes may imply that altered substrate traffic through the mitochondria proceeds tumorigenesis

- *HIGD1A* encodes for a mitochondrial inner membrane protein that helps maintain metabolic homeostasis and cell survival[4]
- Downregulated in all 3 datasets at polyp stage
- Downregulated in datasets 1 and 2 at tumor stage
- Polyp stage downregulation of *HIGD1A* indicates early changes to mitochondrial respiration

- Datasets 1 and 3, with data from Japan and China respectively, had more overlapping dysregulated gene expression
- Epidemiological research shows that dietary factors such as red meat, whole grain, calcium, and fiber intake can influence CRC risk[5]
- Similarities between Datasets 1 and 3 may indicate that diet influences which genes become dysregulated

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