Tumor Stem Cell (TSC) Creation via High Nitric Oxide (HNO) Adaptation in Adenocarcinomas (ACs

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INTRODUCTION

Cancer relapse or recurrence is defined as the return of cancer or its signs/symptoms after a period of improvement. Surgery may not remove all cancer cells and leave behind a few which cannot be detected by scans or other tests. It is also possible that some tumor cells are resistant to chemotherapy or radiation. Although many cancer cells are killed by these treatments, there may exist a few which contain a different genetic makeup which allows them to survive. These hyper malignant cancer cells, or cancer stem cells (CSCs), have been associated with causing cancer relapse. It has also been predicted that these CSCs are created through the adaptation of normal cancer cells to high amounts of the free radical nitric oxide (HNO). In the present study, we looked at the mechanisms by which normal adenocarcinomas, or cancerous glandular epithelial tissues, become cancer stem cells via HNO adaptation.

HYPOTHESIS/OBJECTIVE

Adaptation to high concentrations of nitric oxide (HNO) causes adenocarcinomas to exhibit an aggressive phenotype, similar to that of cancer stem cells. This occurs because the epigenetics of certain pathways, including cellular respiration, is changed.

METHODS

Cell lines: Five human squamous carcinoma cell lines, SCC016 (tongue), SCC040 (tongue), SCC056 (tongue), SCC114 (FOM (floor of mouth)), and SCC116 (alveolar ridge), were studied. Treated cell lines were slowly exposed to increasing concentrations of the nitric oxide donor DETA NONOate, reaching a maximum of 600 mM. The HNO and Parental cell lines were exposed to increasing concentrations of $FeCl_{2..}$ A computer program in Java was created to determine which genes were up or down regulated across the cell lines to understand the mechanisms behind the transformation. This gene data was documented to delineate which were up down regulated specifically in the adenocarcinoma cell lines.

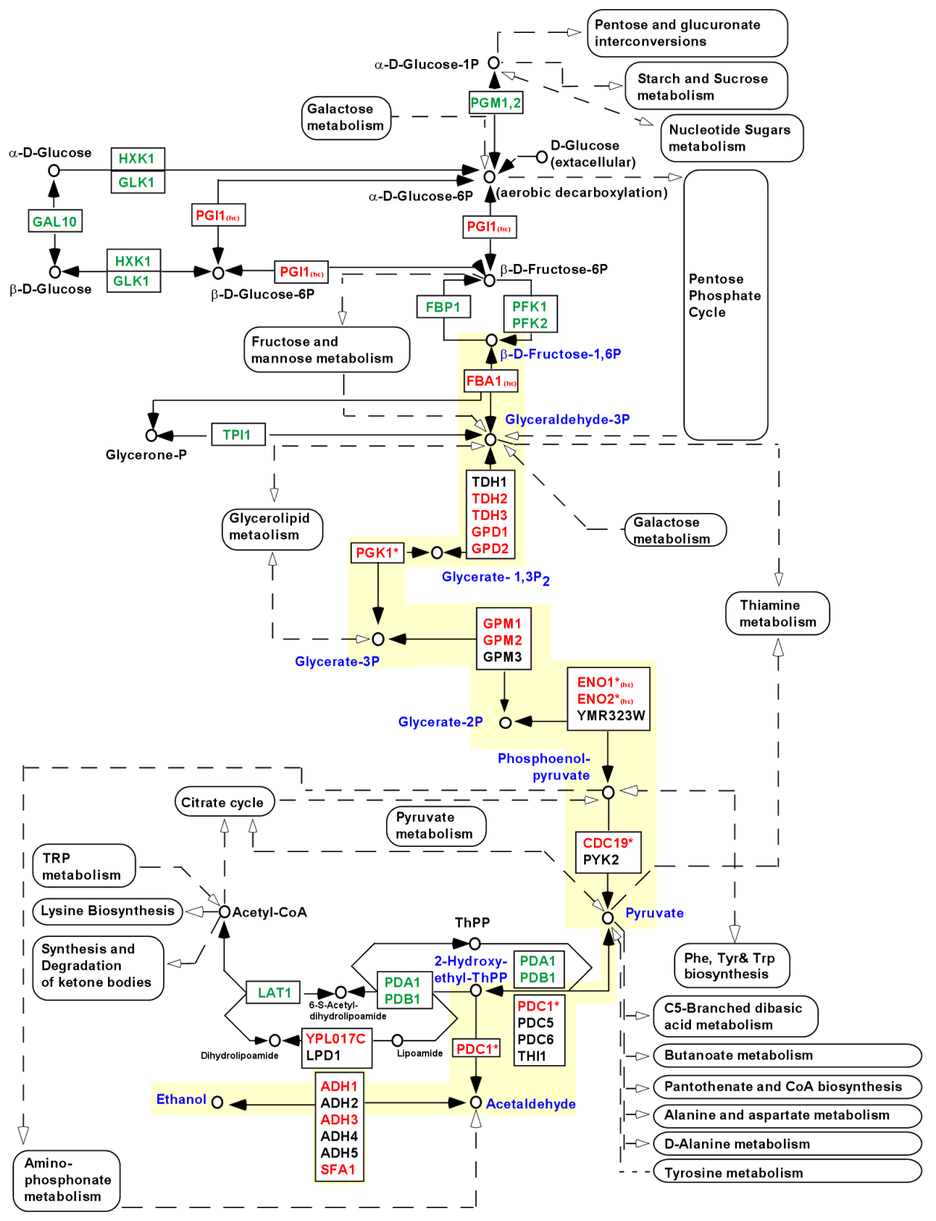
RESULTS

Down-Regulated Genes

PDHA1	APOA1BP	DNTTIP1	MPV17	AC004490.1	LSM7
TRAPPC2L	MYL6	ATP6V0D1	LDHB	LDHBP	ISOC2
SLC35B1	PLP2	STC2	SRF	RP6-159A1.2	RBMX
RP11-255N24.3	RBMXP1	POLR1C	NOP16	MAT2A	RP11-572H4.2

Up-Regulated Genes

PTBP2	S100A6	CORO1B	RAB5B	MALAT1
HK1	NCKAP1	COX7	SLC38A2	TBC1D9B
SAT1	PSMA7	FAM96B		



Oncogenic glycolysis pathway in a human cell.

CONCLUSION

•Noting a common gene function overlap occurring between PDHA-1 and LDHB, it is possible that because of the downregulation of these cellular respiration related genes and the decreased amount of associated compounds e.g. pyruvate, the method through which the cancerous cell acquires energy may not be through aerobic cellular respiration. COX7C, a part of the cytochrome c oxidase, which serves as the final enzyme in the electron transfer chain, is significantly up-regulated. These epigenetic changes suggest that HNO-adapted cancer cells follow another pathway to obtain energy. As pyruvate is prevalent in the TCA cycle which is aerobic, perhaps cancerous cells manage undergoing only glycolysis to obtain their necessary amounts of energy. Furthermore, the decrease in mRNA processing suggests that cancer impedes at least on a superficial level the processes of transcription and/or translation and ultimately protein synthesis.

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