Molecular Mechanisms of Squamous Cell Carcinoma Tumor Stem Cell Creation via High Nitric Oxide (HNO) Adaptation

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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 hypermalignant 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 (NCCs) to high amounts of the free radical nitric oxide (HNO). In the present study, we looked at the mechanisms by which normal squamous cell carcinomas become cancer stem cells via HNO adaptation. Squamous cells are thin, flat cells which line the surface of the skin, hollow organs of the body, and respiratory and digestive tracts. This study analyzed the genetic differences between cancer stem cells and their predecessors.

HYPOTHESIS/OBJECTIVE

Adaptation to HNO in five human head and neck cell lines will result in the specific dysregulation of certain genes. Such a study will elucidate the mechanisms by which cancer cells become cancer stem cells.

METHODS

1) Gene chip analysis was performed pre- and post- HNO adaptation.
2) The gene chip analysis data showed the changes in the regulation of genes for each cell line overall during the adaptation.
3) A computer program in the Java was created to determine which genes were up- or down-regulated across cell lines to understand the mechanisms behind the transformation
4) Biological pathways which were up- or down-regulated during the adaptation were looked at using the gene data

RESULTS

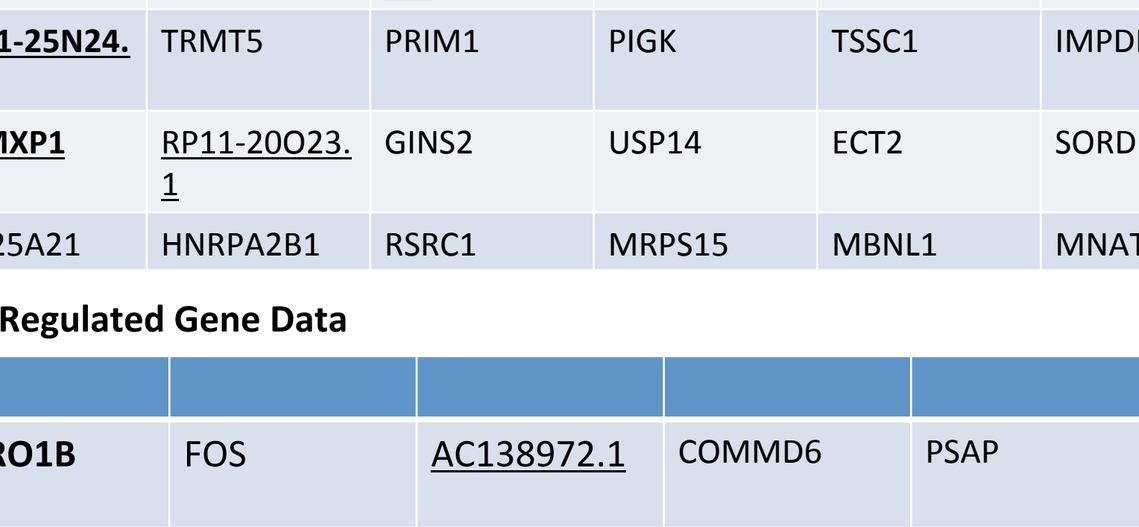
Down-Regulated Gene Data

PDHA1	AC093509.1	FAM129A	GLO1	R3HDM1	SHCBP1	DHX9	CENPN	SSRP1	KIAA0907	SKP2
RBMX	AC109456.3-1	C19orf48	IMPAD1	CD2AP	TK1	MOSC1	KIAA1984	NDUFS2	STAMBP	MFSD2
RP6-159A1.2	AC100793.8	RP11-551G24.2	ANLN	TPX2	SMC2	NCAPD2	GLUD1	WARS2	AIFM1	NRG1
RP11-25N24.3	TRMT5	PRIM1	PIGK	TSSC1	IMPDH2	CDK7	GLUD2	GOSR1	ATF1	MTHFS
RBMXP1	RP11-20O23.1	GINS2	USP14	ECT2	SORD	MRPS36	CDK2	SNTB1	CLPB	LAMA3
SLC25A21	HNRPA2B1	RSRC1	MRPS15	MBNL1	MNAT1	PCCB	PRKAR1B	SNRPA	KIAA0101	RFC4

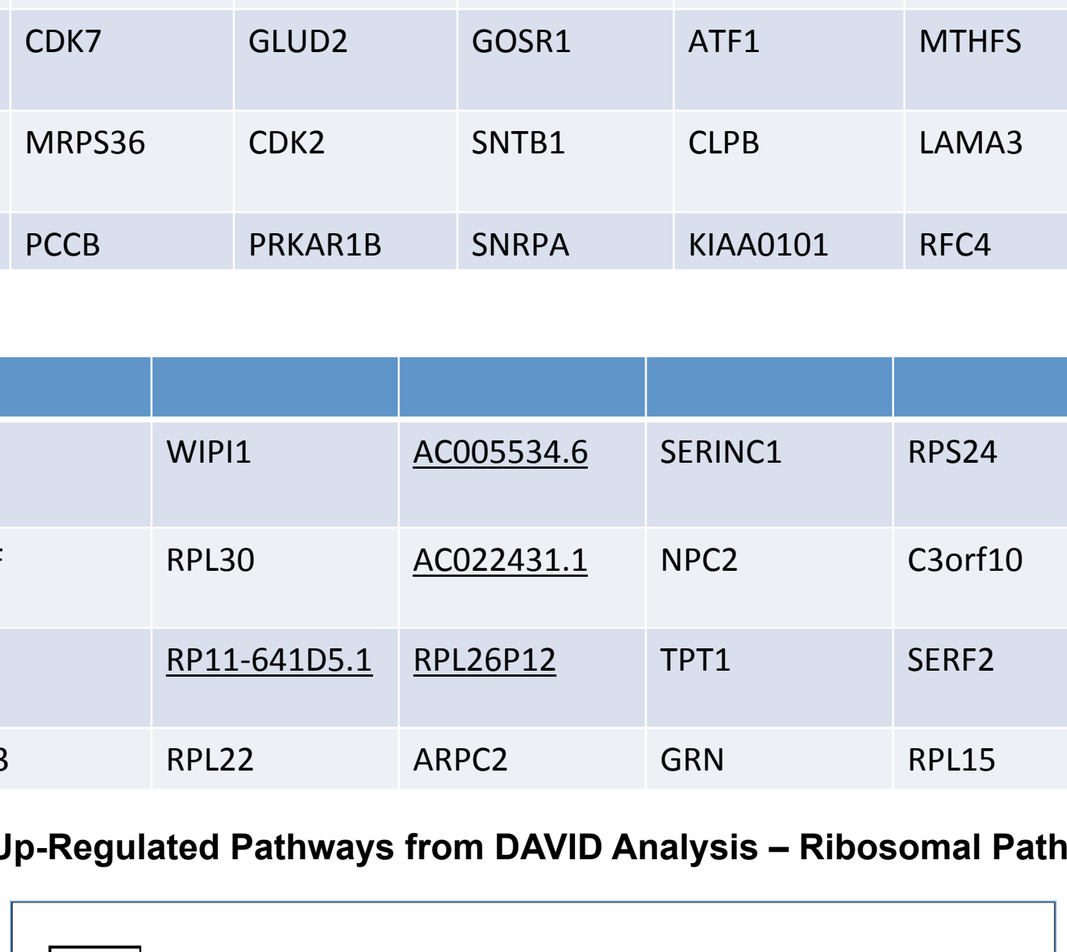
Up-Regulated Gene Data

CORO1B	FOS	AC138972.1	COMMD6	PSAP	CD63	WIPI1	AC005534.6	SERINC1	RPS24
COX7C	LCN2	KYNU	NRBF2	MVD	HLA-F	RPL30	AC022431.1	NPC2	C3orf10
PSMA7	CYP1A1	CTSC	RPL37AP1	STARD10	OPTN	RP11-641D5.1	RPL26P12	TPT1	SERF2
GPNMB	S100P	RPL37	RPL37A	CBR1	EX0C3	RPL22	ARPC2	GRN	RPL15

Down-Regulated Pathways from DAVID Analysis – Cell Cycle Pathways



Up-Regulated Pathways from DAVID Analysis – Ribosomal Pathway



CONCLUSION

Adaptation to HNO results in the up-regulation of ribosomal proteins in human H&N cell lines (SCC-016, SCC-040, SCC-056, SCC-114, SCC-116). This up-regulation is understandable, as HNO-adapted / CSCs are very aggressive and thus, produce more proteins in a given amount of time, compared to normal cells. HNO-adaptation also causes the down-regulation of critical genes involved in the cell cycle and DNA replication. This down-regulation perhaps causes genomic instability, which in turn drives the creation of CSCs and thus recurrence of the disease in patients. The pathways can potentially be targeted (inhibited or augmented) to inhibit the conversion of cancer cells to CSCs.

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