

**Supplementary Tables:**

**Supplementary Table 1:** List of the 242 hypoxia/reoxygenation marker genes collected from literature and databases

**Supplementary Table 2:** Contingency tables used in the fisher exact test to test the association between cancer progression stages and identified subpopulations.

**Supplementary Table 3:** List of the 62 hypoxia/reoxygenation marker (HRM) genes.

**Supplementary Table 4:** List of the gene markers of the hypoxia and reoxygenation populations.

**Supplementary Table 5:** Numbers of genes that are significantly up-/down- regulated in the hypoxia and reoxygenation populations in each cancer types and the number of pathways enriched by these genes.

**Supplementary Table 6:** List of the pathways enriched by up regulated genes in hypoxia and reoxygenation population.

**Supplementary Table 7:** Detailed parameters of the regression analysis that correlate log mutation rate to the population proportions. The significance of each linear regression is examined by F test.

ACAT1	COL6A1	FGF21	IL18	PDGFB	TBK1
ACAT2	CP	FGF22	IL4	PDGFC	TEF
ACTA2	CSPG4	FGF23	IL6	PDGFD	TEK
ADAMTS1	CXCL10	FGF3	IL8	PDGFRB	TF
ADAMTS2	CXCR4	FGF4	IRF1	PDK3	TFF3
ADM	DDIT3	FGF5	ITGA5	PECAM1	TFR2
ADRA1A	DDIT4	FGF6	ITGAV	PF4	TFRC
ADRA1B	DEC1	FGF7	ITGB1	PFKFB3	TGFA
AHNAK	DES	FGF8	ITGB3	PFKP	TGFB1
AK3	DLL4	FGF9	ITGB5	PGAM1	TGFB2
ALDOA	DUSP1	FIGF	JAG1	PGF	TGFB3
ANGPT1	E2F1	FLT1	JAG2	PGK1	TGFBR1
ANGPT2	E2F3	FLT4	JMY	PIM1	TGFBR2
ANXA1	EDN1	FOS	JUN	PKM2	TGFBR3
ANXA5	EDN2	FOXO3	JUNB	PLAUR	TGM2
ATF4	EFNB2	FTL	KDR	PLG	TH
BBC3	EGF	GAPDH	L1CAM	PLOD1	THBS1
BCAR1	EGFR	GBE1	LDHA	PLOD2	THBS2
BIK	EGLN1	HERPUD1	LECT1	POLR1A	TIE1
BIRC5	EGLN3	HERPUD2	LOX	POLR2A	TIMP1
BMP2	ENG	HGF	LRPAP1	PRL	TIMP2
BNIP3	ENO1	HIF1A	MAFF	PROM1	TIMP3
BNIP3L	ENPEP	HK1	MDM2	PRPS1	TIMP4
BTG1	EPAS1	HK2	MIF	PRPS2	TMEM45A
CA12	EPO	HMOX1	MMP13	PTGS2	TNFAIP3
CA9	ERO1L	HSF1	MXI1	RORA	TNFSF15
CALR	EZH2	HSP90B1	NFKB1	SAT1	TNNI1
CCL2	F2	HSPA5	NOS1	SERPINB5	TNNI2
CCNA1	F3	HYOU1	NOS2	SERPINC1	TNNI3
CCNA2	FGF1	ID1	NOS3	SERPINE1	TRPC1
CCNB1	FGF10	ID2	NOTCH1	SLC16A1	TXN
CCNE1	FGF11	ID3	NOTCH2	SLC16A3	VASH1
CCNG2	FGF12	IFNA1	NOTCH3	SLC2A1	VASH2
CD99	FGF13	IFNB1	NOTCH4	SLC2A3	VEGFA
CDH1	FGF14	IGF1R	NRN1	SLC2A4	VEGFB
CDH2	FGF16	IGF2	NRP1	SPARC	VEGFC
CDH5	FGF17	IGFBP1	P4HA1	SPP1	VHL
CDKN1B	FGF18	IGFBP2	P4HA2	STC1	VIM
CHGA	FGF19	IGFBP3	P4HA3	STC2	XRCC5
COL18A1	FGF2	IGFBP5	PDGFA	TAGLN	XRCC6
COL5A1	FGF20				

**Supplementary Table 1.** List of the 242 hypoxia/reoxygenation marker genes collected from literature and databases

**BRCA:**

	<b>Stage I</b>	<b>Stage II</b>	<b>Stage III</b>	<b>Stage IV</b>
<b>Angiogenesis</b>	3	10	3	0
<b>Hypoxia</b>	8	69	9	1
<b>Reoxygenation</b>	9	35	13	1

**COAD:**

	<b>Stage I</b>	<b>Stage II</b>	<b>Stage III</b>	<b>Stage IV</b>
<b>Angiogenesis</b>	4	10	8	3
<b>Hypoxia</b>	3	17	20	10
<b>Reoxygenation</b>	4	7	23	10

**LUAD:**

	<b>Stage I</b>	<b>Stage II</b>	<b>Stage III</b>	<b>Stage IV</b>
<b>Angiogenesis</b>	28	20	17	1
<b>Hypoxia</b>	31	19	12	7
<b>Reoxygenation</b>	20	8	6	1

**Supplementary Table 2:** Contingency tables to test the association between cancer progression stages and identified subpopulations.

ACTA2	FLT1	SERPINE1
ADM	FLT4	SLC16A1
ANGPT1	HGF	SLC16A3
ANGPT2	HIF1A	SLC2A1
CCL2	ID3	SLC2A4
CCNA1	ITGA5	SPP1
CCNA2	ITGAV	TEK
CCNB1	ITGB1	TGFA
CCNE1	ITGB3	TGFB1
CDH1	ITGB5	TGFB3
CDH2	KDR	TGFBR1
CDH5	LDHA	TGFBR2
COL6A1	MDM2	TGFBR3
CSPG4	NOS2	THBS1
DES	PDGFRB	TIE1
E2F1	PECAM1	VASH1
E2F3	PGF	VEGFA
EFNB2	POLR1A	VEGFB
ENG	POLR2A	VEGFC
EPAS1	PROM1	VHL
EZH2	PTGS2	

**Supplementary Table 3.** List of the 62 hypoxia/reoxygenation marker (HRM) genes

Hypoxia population markers	Reoxygenation population markers
LDHA	SLC2A4
HIF1A	DES
SLC16A1	TIE1
SLC16A3	TEK
SLC2A1	SERPINE1
VHL	HGF
VEGFA	FLT4
CCNE1	ITGB3
CCNA2	ITGA5
CCNB1	PECAM1
E2F1	THBS1
POLR1A	CDH5
CDH1	KDR
E2F3	FLT1
EZH2	CSPG4
ADM	VASH1
TGFA	CCL2
	TGFBR3
	ENG
	TGFBR2
	PDGFRB
	EPAS1
	VEGFB
	VEGFC
	PGF
	ANGPT2

**Supplementary Table 4.** Gene markers of the hypoxia and reoxygenation populations.

<b>BRCA</b>		
	<b>Hypoxia population</b>	<b>Reoxygenation population</b>
<b>Up regulated genes</b>	6617	6106
<b>Down regulated genes</b>	6296	6489
<b>Pathways enriched by up regulated genes</b>	175	65
<b>Pathways enriched by down regulated genes</b>	21	193

  

<b>COAD</b>		
	<b>Hypoxia population</b>	<b>Reoxygenation population</b>
<b>Up regulated genes</b>	3867	6231
<b>Down regulated genes</b>	6204	4094
<b>Pathways enriched by up regulated genes</b>	235	345
<b>Pathways enriched by down regulated genes</b>	156	225

  

<b>LUAD</b>		
	<b>Hypoxia population</b>	<b>Reoxygenation population</b>
<b>Up regulated genes</b>	5091	5045
<b>Down regulated genes</b>	5149	5088
<b>Pathways enriched by up regulated genes</b>	252	134
<b>Pathways enriched by down regulated genes</b>	42	275

**Supplementary Table 5.** Numbers of genes that are significantly up-/down- regulated in the hypoxia and reoxygenation populations in each cancer types and the number of pathways enriched by these genes.

<b>Pathways enriched by up regulated genes in hypoxia population</b>
ACTIN_CYTOSKELETON_ORGANIZATION_AND_BIOGENESIS
ACTIN_FILAMENT_BASED_PROCESS
ANATOMICAL_STRUCTURE_MORPHOGENESIS
AXONOGENESIS
BASEMENT_MEMBRANE
BASOLATERAL_PLASMA_MEMBRANE
BLOOD_COAGULATION
CAMP_MEDIATED_SIGNALING
CELL_MATRIX_ADHESION
CELL_PROJECTION
CELL_SUBSTRATE_ADHESION
CELL_SURFACE_RECEPTOR_LINKED_SIGNAL_TRANSDUCTION_GO_0007166
COAGULATION
COLLAGEN
CYCLIC_NUCLEOTIDE_MEDIATED_SIGNALING
ENZYME_ACTIVATOR_ACTIVITY
ENZYME_LINKED_RECEPTOR_PROTEIN_SIGNALING_PATHWAY
EXTRACELLULAR_MATRIX
EXTRACELLULAR_MATRIX_PART
EXTRACELLULAR_REGION
EXTRACELLULAR_REGION_PART
FOCAL_ADHESION_FORMATION
G_PROTEIN_SIGNALING_COUPLED_TO_CAMP_NUCLEOTIDE_SECOND_MESSENGER
GLYCOSAMINOGLYCAN_BINDING
GROWTH_FACTOR_BINDING
GTPASE_ACTIVATOR_ACTIVITY
GTPASE_REGULATOR_ACTIVITY
GUANYL_NUCLEOTIDE_EXCHANGE_FACTOR_ACTIVITY
HEMOSTASIS
INTEGRAL_TO_MEMBRANE
INTEGRAL_TO_PLASMA_MEMBRANE
INTERCELLULAR_JUNCTION_ASSEMBLY
INTRINSIC_TO_MEMBRANE
INTRINSIC_TO_PLASMA_MEMBRANE
KEGG_COMPLEMENT_AND_COAGULATION_CASCADES
KEGG_DILATED_CARDIOMYOPATHY
KEGG_ECM_RECEPTOR_INTERACTION
KEGG_FOCAL_ADHESION
KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM
KEGG_MAPK_SIGNALING_PATHWAY
KEGG_NEUROACTIVE_LIGAND_RECEPTOR_INTERACTION
KEGG_PATHWAYS_IN_CANCER
KEGG_TGF_BETA_SIGNALING_PATHWAY

KEGG_VASCULAR_SMOOTH_MUSCLE_CONTRACTION
MEMBRANE
MEMBRANE_ORGANIZATION_AND_BIOGENESIS
MEMBRANE_PART
NEGATIVE_REGULATION_OF_RNA_METABOLIC_PROCESS
NEGATIVE_REGULATION_OF_TRANSCRIPTION_DNA_DEPENDENT
NEGATIVE_REGULATION_OF_TRANSCRIPTION_FROM_RNA_POLYMERASE_II_PROMOTER
PID_ANGIOPHOTINRECEPTOR_PATHWAY
PID_AP1_PATHWAY
PID_AVB3_INTEGRIN_PATHWAY
PID_EPOPATHWAY
PID_FAK_PATHWAY
PID_IL6_7PATHWAY
PID_INTEGRIN1_PATHWAY
PID_INTEGRIN3_PATHWAY
PID_LPA4_PATHWAY
PID_LYMPHANGIOGENESIS_PATHWAY
PID_LYSOPHOSPHOLIPID_PATHWAY
PID_SYNDECAN_1_PATHWAY
PID_THROMBIN_PAR1_PATHWAY
PID_VEGF_VEGFR_PATHWAY
PLASMA_MEMBRANE
PLASMA_MEMBRANE_PART
PROTEIN_AMINO_ACID_PHOSPHORYLATION
PROTEINACEOUS_EXTRACELLULAR_MATRIX
RAS_GUANYL_NUCLEOTIDE_EXCHANGE_FACTOR_ACTIVITY
REACTOME_AXON_GUIDANCE
REACTOME_COLLAGEN_FORMATION
REACTOME_EXTRACELLULAR_MATRIX_ORGANIZATION
REACTOME_G_ALPHA_S_SIGNALLING_EVENTS
REACTOME_INTEGRIN_CELL_SURFACE_INTERACTIONS
REACTOME_PLATELET_ACTIVATION_SIGNALING_AND_AGGREGATION
REACTOME_SIGNALING_BY_PDGF
REACTOME_SIGNALING_BY_RHO_GTPASES
REACTOME_SMOOTH_MUSCLE_CONTRACTION
REACTOME_SYNTHESIS_OF_PIP2_AT_THE_PLASMA_MEMBRANE
REACTOME_VEGF_LIGAND_RECEPTOR_INTERACTIONS
RECEPTOR_ACTIVITY
RECEPTOR_MEDIATED_ENDOCYTOSIS
REGULATION_OF_ANATOMICAL_STRUCTURE_MORPHOGENESIS
REGULATION_OF_BIOLOGICAL_QUALITY
REGULATION_OF_BODY_FLUID_LEVELS
REGULATION_OF_G_PROTEIN_COUPLED_RECEPTOR_PROTEIN_SIGNALING_PATHWAY
REGULATION_OF_NEUROGENESIS

REGULATION_OF_SIGNAL_TRANSDUCTION
RESPONSE_TO_EXTERNAL_STIMULUS
SMALL_GTPASE_REGULATOR_ACTIVITY
TRANSMEMBRANE_RECEPTOR_ACTIVITY
TRANSMEMBRANE_RECEPTOR_PROTEIN_KINASE_ACTIVITY
TRANSMEMBRANE_RECEPTOR_PROTEIN_SERINE_THREONINE_KINASE_SIGNALING_PATHWAY
TRANSMEMBRANE_RECEPTOR_PROTEIN_TYROSINE_KINASE_ACTIVITY
VOLTAGE_GATED_SODIUM_CHANNEL_ACTIVITY
WOUND_HEALING

<b>Pathways enriched by up regulated genes in reoxygenation population</b>
ACTIN_CYTOSKELETON_ORGANIZATION_AND_BIOGENESIS
ACTIN_FILAMENT_BASED_PROCESS
ANATOMICAL_STRUCTURE_MORPHOGENESIS
AXONOGENESIS
BASEMENT_MEMBRANE
BASOLATERAL_PLASMA_MEMBRANE
BLOOD_COAGULATION
CAMP_MEDIATED_SIGNALING
CELL_MATRIX_ADHESION
CELL_PROJECTION
CELL_SUBSTRATE_ADHESION
CELL_SURFACE_RECEPTOR_LINKED_SIGNAL_TRANSDUCTION_GO_0007166
COAGULATION
COLLAGEN
CYCLIC_NUCLEOTIDE_MEDIATED_SIGNALING
ENZYME_ACTIVATOR_ACTIVITY
ENZYME_LINKED_RECEPTOR_PROTEIN_SIGNALING_PATHWAY
EXTRACELLULAR_MATRIX
EXTRACELLULAR_MATRIX_PART
EXTRACELLULAR_REGION
EXTRACELLULAR_REGION_PART
FOCAL_ADHESION_FORMATION
G_PROTEIN_SIGNALING_COUPLED_TO_CAMP_NUCLEOTIDE_SECOND_MESSENGER
GLYCOSAMINOGLYCAN_BINDING
GROWTH_FACTOR_BINDING
GTPASE_ACTIVATOR_ACTIVITY
GTPASE_REGULATOR_ACTIVITY
GUANYL_NUCLEOTIDE_EXCHANGE_FACTOR_ACTIVITY
HEMOSTASIS
INTEGRAL_TO_MEMBRANE
INTEGRAL_TO_PLASMA_MEMBRANE

INTERCELLULAR_JUNCTION_ASSEMBLY
INTRINSIC_TO_MEMBRANE
INTRINSIC_TO_PLASMA_MEMBRANE
KEGG_COMPLEMENT_AND_COAGULATION_CASCADES
KEGG_DILATED_CARDIOMYOPATHY
KEGG_ECM_RECEPTOR_INTERACTION
KEGG_FOCAL_ADHESION
KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM
KEGG_MAPK_SIGNALING_PATHWAY
KEGG_NEUROACTIVE_LIGAND_RECEPTOR_INTERACTION
KEGG_PATHWAYS_IN_CANCER
KEGG_TGF_BETA_SIGNALING_PATHWAY
KEGG_VASCULAR_SMOOTH_MUSCLE_CONTRACTION
MEMBRANE
MEMBRANE_ORGANIZATION_AND_BIOGENESIS
MEMBRANE_PART
NEGATIVE_REGULATION_OF_RNA_METABOLIC_PROCESS
NEGATIVE_REGULATION_OF_TRANSCRIPTION_DNA_DEPENDENT
NEGATIVE_REGULATION_OF_TRANSCRIPTION_FROM_RNA_POLYMERASE_II_PROMOTER
PID_ANGIOPOIETINRECEPTOR_PATHWAY
PID_AP1_PATHWAY
PID_AVB3_INTEGRIN_PATHWAY
PID_EPOPATHWAY
PID_FAK_PATHWAY
PID_IL6_7PATHWAY
PID_INTEGRIN1_PATHWAY
PID_INTEGRIN3_PATHWAY
PID_LPA4_PATHWAY
PID_LYMPHANGIOGENESIS_PATHWAY
PID_LYSOPHOSPHOLIPID_PATHWAY
PID_SYNDECAN_1_PATHWAY
PID_THROMBIN_PAR1_PATHWAY
PID_VEGF_VEGFR_PATHWAY
PLASMA_MEMBRANE
PLASMA_MEMBRANE_PART
PROTEIN_AMINO_ACID_PHOSPHORYLATION
PROTEINACEOUS_EXTRACELLULAR_MATRIX
RAS_GUANYL_NUCLEOTIDE_EXCHANGE_FACTOR_ACTIVITY
REACTOME_AXON_GUIDANCE
REACTOME_COLLAGEN_FORMATION
REACTOME_EXTRACELLULAR_MATRIX_ORGANIZATION
REACTOME_G_ALPHA_S_SIGNALLING_EVENTS
REACTOME_INTEGRIN_CELL_SURFACE_INTERACTIONS
REACTOME_PLATELET_ACTIVATION_SIGNALING_AND_AGGREGATION

REACTOME_SIGNALING_BY_PDGF
REACTOME_SIGNALING_BY_RHO_GTPASES
REACTOME_SMOOTH_MUSCLE_CONTRACTION
REACTOME_SYNTHESIS_OF_PIP3_AT_THE_PLASMA_MEMBRANE
REACTOME_VEGF_LIGAND_RECEPTOR_INTERACTIONS
RECEPTOR_ACTIVITY
RECEPTOR_MEDIATED_ENDOCYTOSIS
REGULATION_OF_ANATOMICAL_STRUCTURE_MORPHOGENESIS
REGULATION_OF_BIOLOGICAL_QUALITY
REGULATION_OF_BODY_FLUID_LEVELS
REGULATION_OF_G_PROTEIN_COUPLED_RECEPTOR_PROTEIN_SIGNALING_PATHWAY
REGULATION_OF_NEUROGENESIS
REGULATION_OF_SIGNAL_TRANSDUCTION
RESPONSE_TO_EXTERNAL_STIMULUS
SMALL_GTPASE_REGULATOR_ACTIVITY
TRANSMEMBRANE_RECEPTOR_ACTIVITY
TRANSMEMBRANE_RECEPTOR_PROTEIN_KINASE_ACTIVITY
TRANSMEMBRANE_RECEPTOR_PROTEIN_SERINE_THREONINE_KINASE_SIGNALING_PATHWAY
TRANSMEMBRANE_RECEPTOR_PROTEIN_TYROSINE_KINASE_ACTIVITY
VOLTAGE_GATED_SODIUM_CHANNEL_ACTIVITY
WOUND_HEALING

**Supplementary Table 6.** List of the pathways enriched by up regulated genes in hypoxia and reoxygenation population

y: log mutation rate of the samples of	x: proportion of	a	p.value	b	p.value
breast cancer early stage	reoxygenation population	0.6909	4.43E-02	3.5522	<2e-16
breast cancer early stage	hypoxia population	-1.0348	2.00E-04	4.2601	<2e-16
breast cancer advanced stage	reoxygenation population	1.2305	0.11	3.2861	3.92E-16
breast cancer advanced stage	hypoxia population	-1.609	0.00182	4.4795	< 2e-16
colon cancer early stage	reoxygenation population	1.2857	0.324	4.8172	6.24E-09
colon cancer early stage	hypoxia population	-0.4926	0.5	5.757	<2e-16
colon cancer advanced stage	reoxygenation population	0.441	0.643	4.7863	7.11E-12
colon cancer advanced stage	hypoxia population	-0.1209	0.823	5.076	<2e-16
lung cancer early stage	reoxygenation population	4.301	4.97E-05	2.587	< 2e-16
lung cancer early stage	hypoxia population	-2.5184	2.92E-06	6.247	< 2e-16
lung cancer advanced stage	reoxygenation population	4.218	0.00028	6.431	1.10E-10
lung cancer advanced stage	hypoxia population	-3.107	0.00096	3.616	< 2e-16

**Supplementary Table 7.** Detailed parameters of the regression analysis that correlate log mutation rate to the population proportions. The significance of each linear regression is examined by F test.