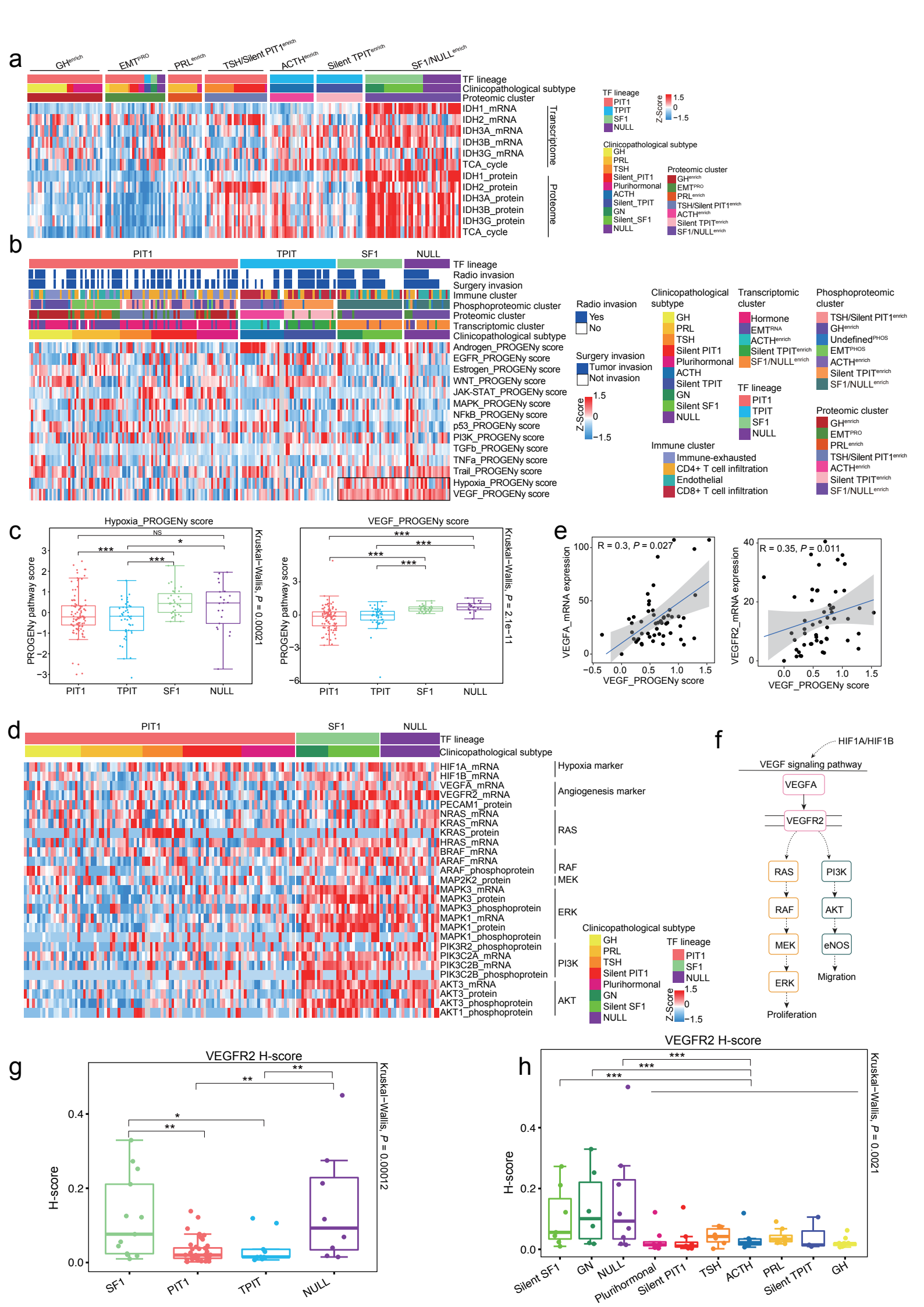
a
GH enrich
EMT PRO
PRL enrich
TSH/Silent PIT1 enrich
ACTH enrich
Silent TPIT enrich
SF1/NULL enrich
TF lineage
Clinicopathological subtype
Proteomic cluster
IDH1_mRNA
IDH2_mRNA
IDH3A_mRNA
IDH3B_mRNA
IDH3G_mRNA
TCA_cycle
IDH1_protein
IDH2_protein
IDH3A_protein
IDH3B_protein
IDH3G_protein
TCA_cycle
Transcriptome
Proteome
TF lineage
PIT1
TPIT
SF1
NULL
Z-Score
1.5
0
−1.5
Clinicopathological subtype
GH
PRL
TSH
Silent_PIT1
Plurihormonal
ACTH
Silent_TPIT
GN
Silent_SF1
NULL
Proteomic cluster
GH enrich
EMT PRO
PRL enrich
TSH/Silent PIT1 enrich
ACTH enrich
Silent TPIT enrich
SF1/NULL enrich
b
PIT1
TPIT
SF1
NULL
TF lineage
Radio invasion
Surgery invasion
Immune cluster
Phosphoproteomic cluster
Proteomic cluster
Transcriptomic cluster
Clinicopathological subtype
Androgen_PROGENy score
EGFR_PROGENy score
Estrogen_PROGENy score
WNT_PROGENy score
JAK-STAT_PROGENy score
MAPK_PROGENy score
NFkB_PROGENy score
p53_PROGENy score
PI3K_PROGENy score
TGFb_PROGENy score
TNFa_PROGENy score
Trail_PROGENy score
Hypoxia_PROGENy score
VEGF_PROGENy score
Radio invasion
Yes
No
Surgery invasion
Tumor invasion
Not invasion
Z-Score
1.5
0
−1.5
Clinicopathological subtype
GH
PRL
TSH
Silent PIT1
Plurihormonal
ACTH
Silent TPIT
GN
Silent SF1
NULL
Transcriptomic cluster
Hormone
EMT RNA
ACTH enrich
Silent TPIT enrich
SF1/NULL enrich
TF lineage
PIT1
TPIT
SF1
NULL
Phosphoproteomic cluster
TSH/Silent PIT1 enrich
GH enrich
Undefined PHOS
EMT PHOS
ACTH enrich
Silent TPIT enrich
SF1/NULL enrich
Proteomic cluster
GH enrich
EMT PRO
PRL enrich
TSH/Silent PIT1 enrich
ACTH enrich
Silent TPIT enrich
SF1/NULL enrich
Immune cluster
Immune-exhausted
CD4+ T cell infiltration
Endothelial
CD8+ T cell infiltration
c
Hypoxia_PROGENy score
PROGENy pathway score
Kruskal–Wallis, P = 0.00021
NS
*
***
***
PIT1
TPIT
SF1
NULL
VEGF_PROGENy score
PROGENy pathway score
Kruskal–Wallis, P = 2.1e−11
***
***
***
***
PIT1
TPIT
SF1
NULL
e
R = 0.3, P = 0.027
VEGFA_mRNA expression
VEGF_PROGENy score
R = 0.35, P = 0.011
VEGFR2_mRNA expression
VEGF_PROGENy score
d
PIT1
SF1
NULL
TF lineage
Clinicopathological subtype
HIF1A_mRNA
HIF1B_mRNA
VEGFA_mRNA
VEGFR2_mRNA
PECAM1_protein
NRAS_mRNA
KRAS_mRNA
KRAS_protein
HRAS_mRNA
BRAF_mRNA
ARAF_mRNA
ARAF_phosphoprotein
MAP2K2_protein
MAPK3_mRNA
MAPK3_protein
MAPK3_phosphoprotein
MAPK1_mRNA
MAPK1_protein
MAPK1_phosphoprotein
PIK3R2_phosphoprotein
PIK3C2A_mRNA
PIK3C2B_mRNA
PIK3C2B_phosphoprotein
AKT3_mRNA
AKT3_protein
AKT3_phosphoprotein
AKT1_phosphoprotein
Hypoxia marker
Angiogenesis marker
RAS
RAF
MEK
ERK
PI3K
AKT
Clinicopathological subtype
GH
PRL
TSH
Silent PIT1
Plurihormonal
GN
Silent SF1
NULL
TF lineage
PIT1
SF1
NULL
Z-Score
1.5
0
−1.5
f
HIF1A/HIF1B
VEGF signaling pathway
VEGFA
VEGFR2
RAS
PI3K
RAF
AKT
MEK
eNOS
ERK
Migration
Proliferation
g
VEGFR2 H-score
H-score
Kruskal–Wallis, P = 0.00012
*
**
**
**
SF1
PIT1
TPIT
NULL
h
VEGFR2 H-score
H-score
Kruskal–Wallis, P = 0.0021
***
***
***
Silent SF1
GN
NULL
Plurihormonal
Silent PIT1
TSH
ACTH
PRL
Silent TPIT
GH

Supplementary information, Fig. S7 Proteomic and transcriptomic alternations associated with tumorigenesis in SF1 lineage and NULL tumors.

a Heatmap analysis of mitochondrial citrate cycle enzymes and TCA cycle pathway in 200 PitNET cohort based on transcriptome and proteome data.

b Heatmap showing the PROGENy scores of 14 cancer-relevant pathways among PIT1, TPIT, SF1 lineages and NULL tumors.

c Boxplots showing the PROGENy scores of Hypoxia and VEGF signaling pathways. Kruskal-Wallis test was used to test if any of the differences among the subgroups were statistically significant. Wilcoxon rank-sum test was used to estimate the significance of two subgroups, $*P < 0.05$, $***P < 0.001$, NS (not significant).

d Heatmap showing the expression of hypoxia markers, angiogenesis markers, and other cancer-related genes at the mRNA, protein and phosphoprotein levels.

e Scatterplots describing Spearman's correlation of VEGF PROGENy score with the mRNA levels of VEGFA (left) and VEGFR2 (right).

f Summary model with activation of VEGF downstream pathways including RAS/RAF/MEK/ERK and PI3K-AKT which may lead to proliferation and migration in SF1 lineage and NULL tumors.

g Boxplot showing H-score of VEGFR2 among PIT1, TPIT, SF1 lineages and NULL tumors. Kruskal-Wallis test was used to test if any of the differences among the subgroups were statistically significant. Wilcoxon rank-sum test was used to estimate the significance of two subgroups, $*P < 0.05$, $**P < 0.01$.

h Boxplot showing H-score of VEGFR2 among silent SF1, GN, and NULL as compared with other clinicopathological subtypes (Wilcoxon rank-sum test, $***P < 0.001$). Kruskal-Wallis test was used to test if any of the differences among the subgroups were statistically significant.