Supplementary Information

Supplementary Figure 1. CD31^{low} cells in human angiosarcomas and in angiosarcoma-derived cell lines. **(A)** Representative CD31 immunohistochemical stainings in four human angiosarcomas cases demonstrating variable numbers of scattered cells with low CD31 expression (dotted lines). **(B)** Representative CD31 FACS analysis of the newly established HAMON angiosarcoma cell line showing a significant population of CD31^{low} cells (highlighted in blue). (C) Quantification of the CD31-gated fraction of all indicated cell lines. (HUVEC, HDMEC, HAMON n=2; EA.hy926 n=3; ISO-HASc.1 n=6; ASM n=7).

Supplementary Figure 2. CD31^{low} angiosarcoma cells are more resistant against doxorubicin-induced cell death. (A) Quantitative densitometric analysis of the apoptosis markers presented in **Figure 4B**. Values are presented as ratio of representative cleaved form versus unprocessed full-length protein from PARP, caspase-3 and caspase-7 (n=3). **(B)** Corresponding isotype-PE controls from FACS analysis presented in **Figure 4C**. **(C)** Representative microscopic bright field images demonstrating morphologic differences between parental and doxo-surviving ASM cells. Doxo-surviving cells had a more elongated, spidle-like morphology and **(D)** lost their capacity to form vascular-like tubes even after 18 hours incubation.

Supplementary Figure 3. Pharmacological screen in CD31^{high} angiosarcoma cells identified ROS scavengers retrieving colony formation capacity. (A) Western blot analysis of cell death markers showed no difference in spontaneous apoptosis (Caspase-3) and autophagy (Beclin-1 and LC3) between the two CD31 sublines. However, CD31^{low} cells presented marked differences in basal DNA damage level (indicated by γ-H2AX) compared to CD31^{high} cells **(B)** CD31^{high} cells were treated for 24 hours with indicated compounds and 1x10^3/well were seeded in methylcellulose and incubated for 10 days and assayed for formed colonies (Ctrl: n=22, NAC: n=3, Fer-1: n=6, Trolox: n=5, MG: n=2, all others: n=3). **(C)** Representative picture of CD31^{high} cells/colonies formed after 10 days in methylcellulose prior treated with or without 1 mM NAC treatment for 24 hours. **(D)** CD31^{low} cell were treated for 24 hours with indicated oxidative oxidative stressors sodium arsenit (AsN). 1x10^3/well were seeded in methylcellulose and incubated for 10 days and assayed for formed colonies (n=6). All data are mean ± SEM and were analyzed using unpaired t-test (D) (*$p < 0.05$; ***$p < 0.001$).

Supplementary Figure 4. Validation of the CD31-YAP-redox-axis in normal and malignant endothelial cells. (A) Quantification of flow cytometric determined cytoplamic ROS levels via DCF

fluorescence in parental and doxo-suriving ASM cells. (See also **Figure 4C** and *experimental procedures* for further details). **(B)** Immunoblot analysis revealed increased YAP levels and decreased levels of the DNA damage marker γ-H2AX in doxo-surviving cells compared to parental ASM cells. **(C)** Gating strategy after ISO-HASc.1 AS cells were sorted according their CD31 levels. **(D)** Immunoblot analysis demonstrated marked differences in CD31 expression. **(E)** Freshly sorted $CD31^{low}$ ISO-HASc.1 presented significantly enhanced cell growth and **(F)** colony formation capacity in methylcellulose (n=3) compared to respective $CD31^{high}$ counterparts (magnification 100x). **(G)** $CD31^{low}$ cells contain significantly lower levels of cytoplamic ROS as determined by flow cytometric DCF fluorescence (n=3). **(H)** Immunoblot analysis confirmed higher amounts of YAP and suppressed p-AKT (Ser473) and γ-H2AX levels in $CD31^{low}$cells compared to $CD31^{high}$ cells. **(I)** Murine endothelial cells isolated from CD31-knockout mice ($CD31^{-/-}$) present a more spindle-form fibroblastic morphology compared to the cobblestone morphology of $CD31^{+/+}$ endothelial cells. **(J)** Immunoblot analysis demonstrated an enrichment of YAP in $CD31^{-/-}$ cells and a suppression of p-Akt (Ser473) and γ-H2AX compared to $CD31^{+/+}$ endothelial cells. **(K)** Representative FACS analysis demonstrates lower basal level of cytoplasmic ROS (determined by FACS-based DCF fluorescence) in $CD31^{-/-}$ cells compared to wild-type $CD31^{+/+}$ cells. All data are mean ± SEM and were analyzed using unpaired t-test (*$p < 0.05$).

Supplementary Figure 5. EndoMT transcription factor Slug is enriched in $CD31^{low}$ cells. Western blot analysis demonstrates increased level of Slug in conjunction with suppressed VE-Cadherin levels in $CD31^{low}$ cells compared to $CD31^{high}$ cells.