Supplementary Figure 1. VEGF stimulation leads to significantly increased expression of EZH2 and increased methylation of H3K27 in lung adenocarcinoma cell lines overexpressing VEGFR-2. A, Western blot of EZH2 and VEGFR-2 expression in lung adenocarcinoma cell lines. B, Western blot and mRNA expression of EZH2 in lung adenocarcinoma cell lines stimulated with VEGF. C, *miR-101* expression in lung adenocarcinoma cell lines stimulated with VEGF. EZH2 mRNA and miR-101 expression in lung adenocarcinoma cell lines as determined using qRT-PCR. $*P < 0.05$, $**P < 0.03$.

Supplementary Figure 2. Effect of VEGF stimulation in the expression of EZH2, E2F3 HIF-1α and miR-101. A, We analyzed the *E2F1* and *E2F3* mRNA expression in lung adenocarcinoma cell lines stimulated with VEGF. VEGF stimulation induced *E2F3* expression ($*P < 0.05$) but not *E2F1* expression, in cell lines expressing VEGFR-2 (HCC515, HCC193, HCC4006, HCC461, and HCC1171) and not in a cell line lacking expression of VEGFR-2 (A549). B, Western blot of EZH2, E2F3 and HIF-1α expression in lung adenocarcinoma cell lines stimulated with VEGF. VEGF stimulation leads to significantly co-expression of EZH2, E2F3 and HIF-1α in lung adenocarcinoma cell lines overexpressing VEGFR-2. C and D, Knockdown of *VEGFR-2* expression by treatment with siRNA decreased the expression of EZH2, E2F3 and HIF-1α and increase miR-101 expression. Western blots of VEGFR-2 (*siKDR*), EZH2, E2F3 and HIF-1α expression in the lung adenocarcinoma cell lines HCC461 and HCC4006 upon knockdown of VEGFR-2 expression by treatment with siRNA-3 following VEGF stimulation. E, Overexpression of VEGFR-2 (pKDR) increased the expression of EZH2, E2F3 and HIF-1α and decrease miR-101 expression following VEGF stimulation in A549 cells. MiR-

101 expression in lung adenocarcinoma cell as determined using qRT-PCR. *$P < 0.05$, **$P < 0.03$.

Supplementary Figure 3. Hypoxia increase in co-expression of *EZH2* and *HIF-1α,* and decrease *miR-101* in lung adenocarcinoma cell lines. A, EZH2 expression. B, *HIF-1α* expression and C, *miR-101* expression in lung adenocarcinoma cell lines HCC4006 and HCC461 in hypoxia condition. *$P < 0.05$, **$P < 0.03$

Supplementary Figure 4. *miR-101* overexpression decrease EZH2 expression. A, EZH2 protein, B, *EZH2* mRNA expression and C, *miR-101* expression in HCC461 cell line transfected with *miR-101-3p* mimic and stimulated in the presence or absence of VEGF. Transfection of *miR-101* inhibits the expression of EZH2 mRNA and protein and remained unchanged in response to exposure to VEGF in HCC461 cells. *$P < 0.05$, **$P < 0.03$, ***$P < 0.001$.

Supplementary Figure 5. Effect of treatment with DZNep on lung adenocarcinoma cell viability. To determine the effect of DZNep on cell viability, we treated lung adenocarcinoma cell lines with increasing doses of DZNep (range, 0-10 μM) and observed that DZNep decreased the cell viability from 15% in H2073 and A549 cells with high and intermediate EZH2 expression, respectively, and 30% in HCC4006 cells with low EZH2 expression.

Supplementary Figure 6. Overexpression of VEGFR-2 induces EZH2 expression and decrease the sensitivity to cisplatin. Overexpression of VEGFR-2 (pKDR) in A549 cell line which lacks expression of VEGFR-2 increased the expression of EZH2 and decrease the sensitivity to cisplatin. The decrease in sensitivities to cisplatin produced by the overexpression of VEGFR-2, was reversed by EZH2 knockdown and more strongly by inhibition with treatment with DZNep.