Supplementary Figure legends

Supplementary Figure 1. Endothelial cell-secreted EGF induces phenotypic changes consistent with EMT in head and neck squamous cell carcinoma cells. (**A-C**) UM-SCC-1 cells were starved overnight and treated with 50 ng/ml EGF (**A**) or endothelial cell conditioned medium (**B**) for indicated time points. (**C**) UM-SCC-1 cells were starved overnight and then treated with endothelial cell conditioned medium with or without 10 μg/ml EGF neutralizing antibody for 24 hours. Western blots were performed for EGFR N-cadherin (**A**,**C**), Vimentin, Snail (**A**-**C**) and Twist (**C**).

Supplementary Figure 2. Endothelial cell-secreted factors enhance the motility of HNSCC. (**A,B**) UM-SCC-1 cells were cultured in 6-well plates, starved overnight and scratched with a 1,000-μl loading tip, then incubated with endothelial cell conditioned medium (**A**) for 24 hours. (**B**) Graph depicting “scratch” width over time in response to endothelial cell conditioned medium. Asterisk depict $p<0.05$ within time point.

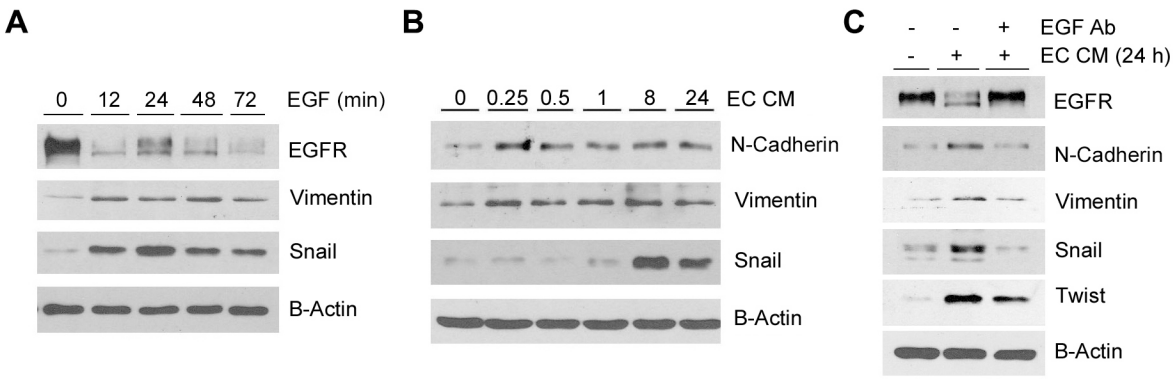
Supplementary Figure 3. Endothelial cell-secreted factors activate STAT3, Akt and ERK signaling. (**A**,**B**) UM-SCC-1 cells were starved overnight and treated with endothelial cell conditioned medium (**A**) or 50 ng/ml EGF (**B**) for indicated time points. Western blots were performed for P-EGFR, EGFR, P-Stat3, Stat3, P-Akt, Akt, P-ERK and ERK.

Supplementary Figure 4. Endothelial cell-secreted EGF induces Snail expression via PI3K/Akt signaling. (**A-D**) UM-SCC-1 cells were starved overnight, pre-incubated with 20 μM Stat3 inhibitor (Stattic V), 20 μM PI3K/Akt inhibitor (Ly294002), 20 μM MEK1/2 inhibitor (UO126) for 1 hour, and then exposed to 50 ng/ml EGF (**A,B,D**) or endothelial cell conditioned medium (**C**) for

indicated time points. Western blots were performed for P-EGFR, EGFR, P-Stat3, Stat3 (**A**), P-Akt, Akt, P-ERK, ERK (**A**,**D**) and Snail (**B-D**).

Supplementary Figure 5. EGF enhances the fraction of cancer stem-like cells. HNSCC cells (UM-SCC-1, UM-SCC-22A and UM-SCC-22B) were starved overnight and incubated with 50 ng/ml EGF for 24 hours, ALDH activity and CD44 expression were determined with the Aldefluor kit and immunoreactivity, and cells were analyzed by flow cytometry. Graphs depicting representative flow cytometry plots for cells analyzed in Figure 6A.

Supplementary Figure 6. Endothelial cell-secreted EGF dose not increase blood vessel density in tumors *in vivo*. Xenografts tumors were generated by the co-transplantation of UM-SCC-22B and control primary human endothelial cells (HDMEC). (**A**) Immunohistochemistry for showing P-EGFR-positive tumor cells (brown) surrounding blood vessels. Black arrows point to P-EGFR-positive tumor cells, and red arrows point to blood vessels. (**B** and **C**) Blood vessels were immunostained for Factor VIII in tissues from xenograft tumors generated by the co-transplantation of UM-SCC-22B/HDMEC-shRNA-C or UM-SCC-22B/HDMEC-shRNA-EGF into immunodeficient mice. (**C**) Graph depicting microvessel density. Blood vessels were counted at 200x magnification (10 fields from each tumor, 10 tumors per experimental condition).



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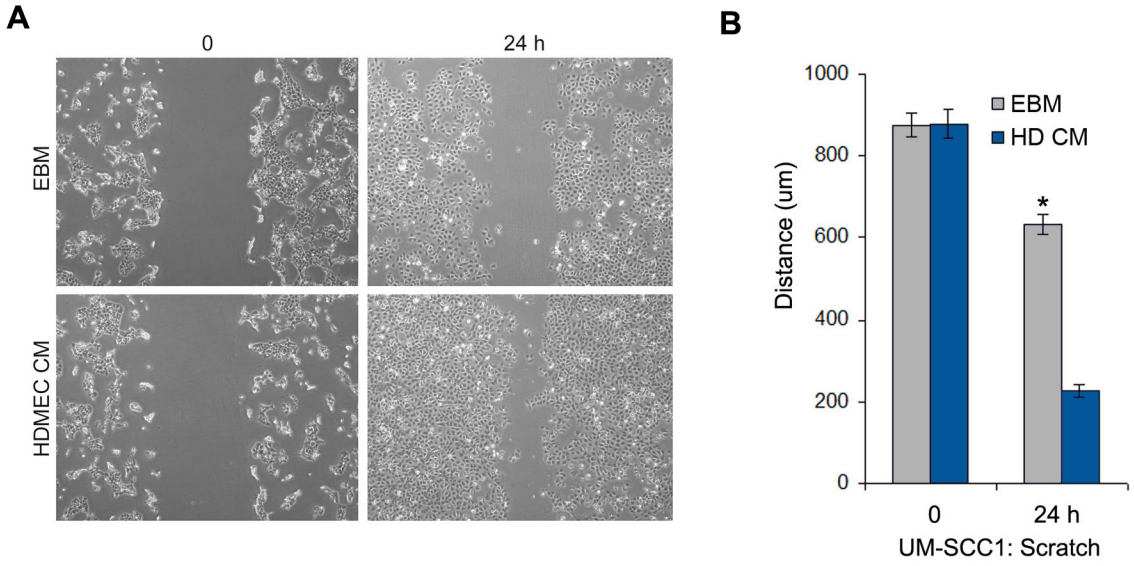

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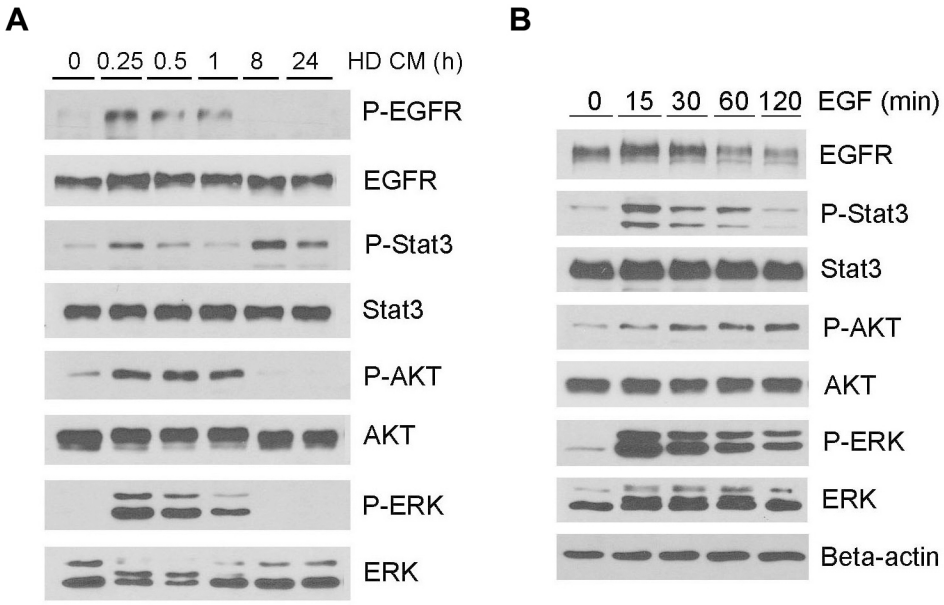

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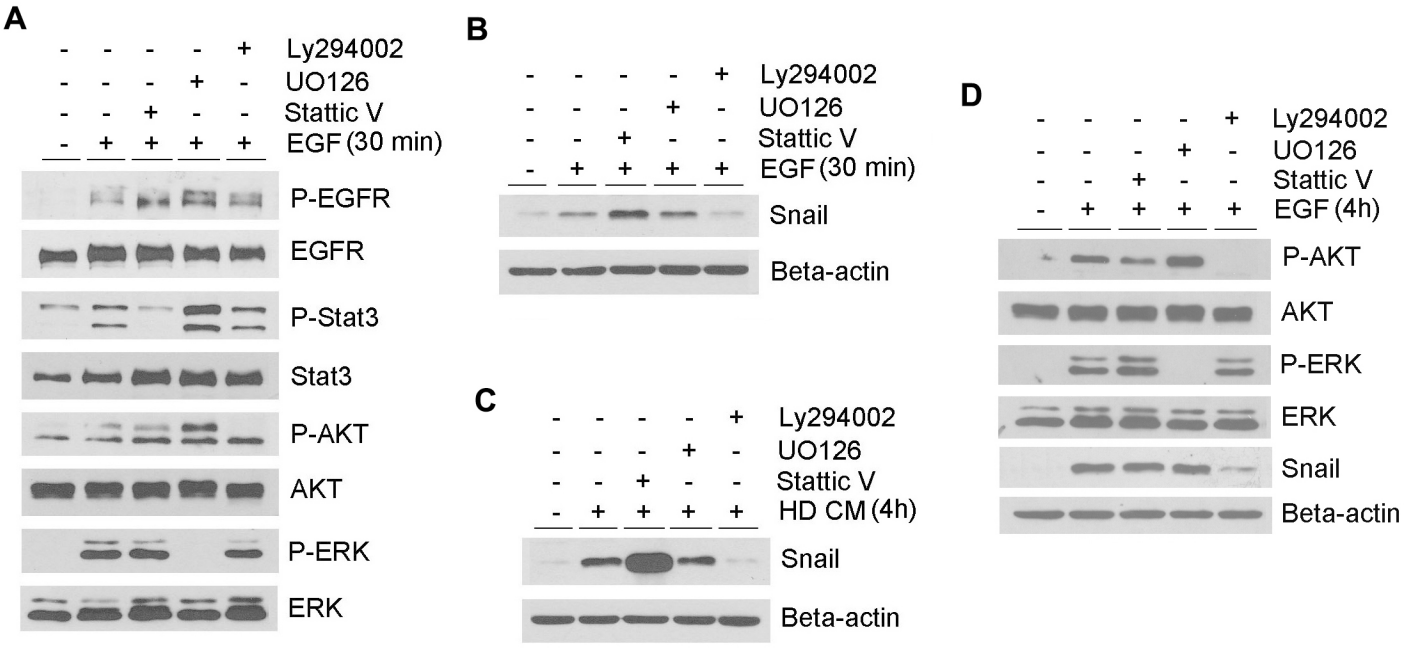

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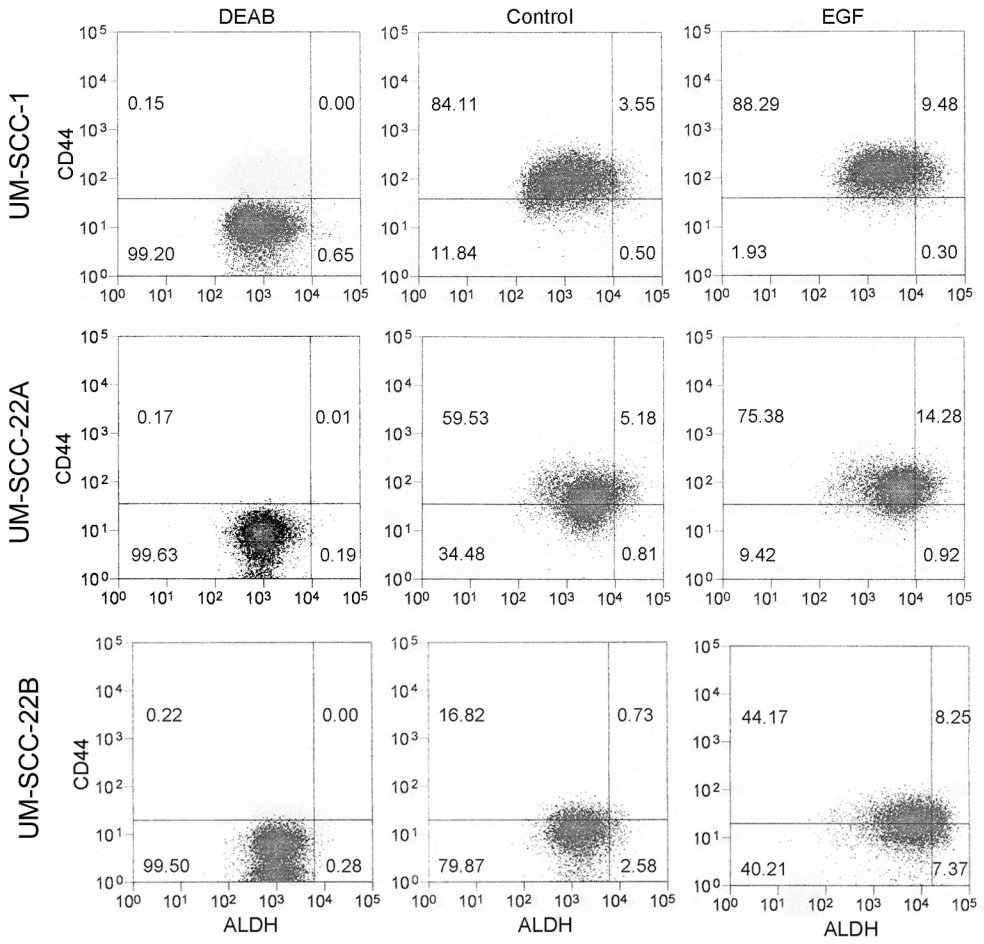

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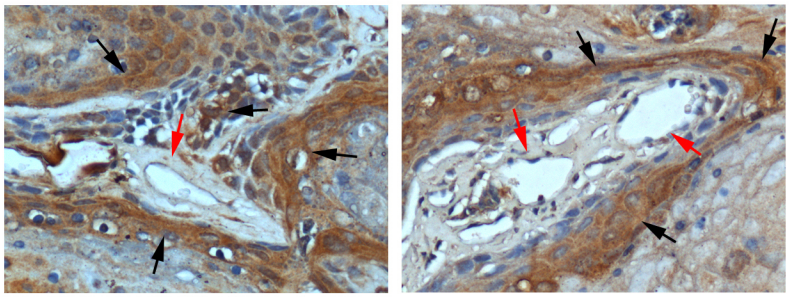
A



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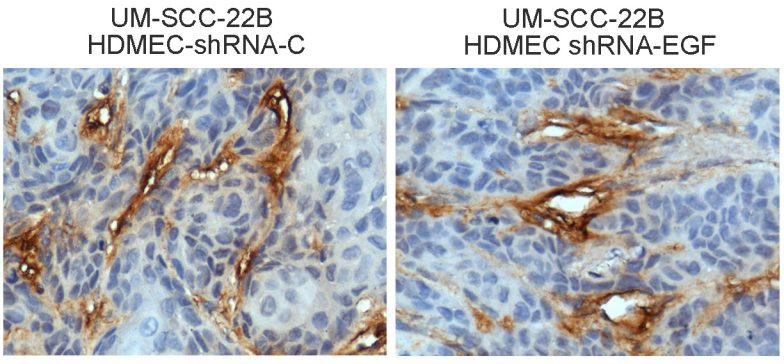

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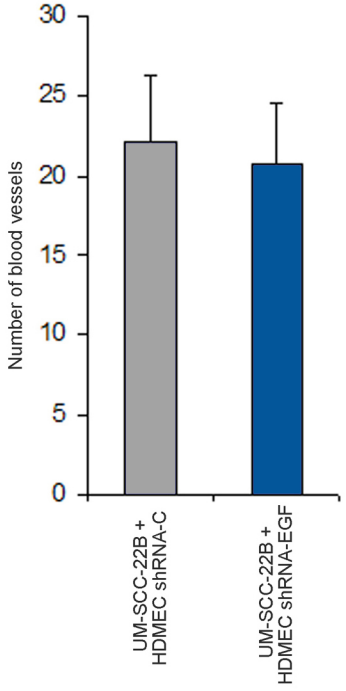

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