**Supplementary Methods and Results.**

*Microarray Analysis*

To analyze basal levels of gene expression, HN4 cells stably transfected with an EPS8 expression plasmid, or empty vector as control, were cultured to 70% confluence, washed three times in serum-free medium, and maintained in the absence of serum for 24h. Total RNA was prepared as previously described [29], and 5μg aliquots reverse-transcribed using Superscript II (Invitrogen Life Technologies, Carlsbad, CA). The resultant cDNAs were purified (Quickclean, BD Clontech), ethanol precipitated, dried, resuspended in 0.1M $NaHCO_3$, and directly labeled with Cy3 or Cy5 dyes (Amersham Biosciences, Piscataway, NJ) for 1h at ambient temperature. Probes were purified using Nucleospin columns (BD Clontech, Palo Alto, CA), and concentrated in TE buffer pH7.4 to a final volume of 11μl. Glass slide arrays (HsOperon vB2.2 p11-3 ) containing 21406 features were obtained from the National Cancer Institute microarray core, prehybridized in 5xSSC/0.1% SDS/1% BSA for 1h at 42°C, then hybridized with the probe cocktail containing Cy3/5 labeled cDNAs together with 10μg COT-1 DNA, 4μg yeast tRNA, and 10μg polyA, in 50% formamide/10xSSC/5% SDS, for 16h at 42°C. Arrays were washed to 0.05xSSC at ambient temperature, dried, and scanned on an Axon array reader using GenePix v4.0 software. Data were analyzed using the mAdb analysis tools (http://nciarray.nci.nih.gov/). Experiments were carried out on two biological replicates. Genes showing greater than 1.8-fold increase in expression relative to the reference sample were scored as being overexpressed. Table S1 shows a list of EPS8-upregulated genes, with fold increase in expression compared to vector-transfected controls.

*Function-Based Analysis of Array Data*

To provide further characterization of data from microarray experiments, a list of overexpressed genes was imported and analyzed using the **D**atabase for **A**nnotation, **V**isualization and **I**ntegrated **D**iscovery software (DAVID; http://david.abcc.ncifcrf.gov/), using the gene functional classification tool with medium stringency. Nine clusters of functionally-related genes were identified, the highest two of which had enrichment scores of 15.12 and 5.85. These are shown in Fig. S1. Heatmaps were generated from these data and are shown in Fig. S2 (A&B). Data were also analyzed using Ingenuity Pathway Analysis software to generate networks of associated molecules. Using this software, seven networks were identified, including those enriched for molecules associated with cell cycle (Fig. S3), as well as DNA replication/ recombination/repair, cancer/dermatological diseases/conditions, and cellular compromise/drug metabolism (not shown).

Figure S1. *Functional annotation of upregulated genes*. The list of EPS8-upregulated genes, obtained from microarray analysis, was analyzed using the functional annotation clustering tool in DAVID. The enrichment score is based on the EASE scores (modified Fisher Exact p-value) of each term member, with a higher score indicating greater enrichment.

Figure S2. *Heatmap of cell cycle-related genes in EPS8-overexpressing cells*. Heatmaps obtained from functionally annotated gene clusters, obtained as described in

Fig. S1. Green color indicates the relationship of a gene with a particular Gene Ontology (GO) term.

Figure S3. *Cell cycle-related protein network in EPS8-expressing cells*. A list of gene products (Table S1), obtained from microarray experiments, showing 1.8 fold or greater overexpression in HN4/EPS8 cells, was analyzed using Ingenuity Pathway Analysis software. Enrichment for cell cycle gene products is shown. Solid lines denote direct interactions; broken lines denote indirect interactions.

Figure S4. *EGF and EPS8 can induce similar and contrasting gene expression profiles*. Cells were serum-starved for 24h, then left untreated or stimulated with EGF, as indicated. 24h later, RNA was prepared and expression of the indicated genes determined by qRT-PCR following reverse transcription.

Figure S5. *FOXM1 knockdown reduces expression of cell cycle regulators in HN4/EPS8 cells*. HN4/EPS8 cells were stably transfected with non-targeting control (NTC) or FOXM1-shRNA plasmids. Expression of the indicated cell cycle regulators was determined by qRT-PCR, as described in Methods.

Figure S6. *FOXM1 knockdown reduces CXCL8 expression*. HN12 (upper panel) or HN4/EPS8 (lower panel) were stably transfected with non-targeting control (NTC) or FOXM1-shRNA plasmids. Expression of CXCL8 was determined by qRT-PCR, as described in Methods.

Figure S7. *Nicotine induces expression of EPS8 and FOXM1*. HN4 cells were treated with the indicated concentrations of nicotine or with solvent alone. 24h later, cell lysates were prepared and western blotted with the indicated antibodies.

Figure S8. *The human CXCL5 promoter contains a consensus FOXM1 binding motif.* DNA sequence upstream of the CXCL5 proximal promoter, as identified by Chang and coworkers [65], was searched for the presence of a FOXM1 binding motif [66] using the Clustal W2 sequence alignment tool [67]. Sites identified by Chang *et al*. [65] are underlined and the TATA box is boxed.

Figure S9. *AKT inhibition reduces cell motility*. HN4/EPS8 cells with CXCL5 knockdown were subjected to wound-healing assays in the presence of AKT inhibitor or solvent alone, as described in Methods.

Table S1. *Expression profiling of EPS8-overexpressing cells*. HN4/V and HN4/EPS8 cells were cultured in the absence of serum, RNA prepared, labeled and hybridized to a 21K cDNA microarray, as described in Supplementary Methods. Genes showing EPS8-dependent upregulation are listed, together with fold increase compared to controls.