Methods

TiO_2 nanotube fabrication. TiO_2 nanotube arrays were formed via anodic oxidation in an electrolytic solution containing 0.2M Sodium Citrate Tribasic, 1M Sodium Hydrogen Sulfate, and 0.1M Potassium Fluoride, with Sodium Hydroxide added to adjust the pH of the solution. Titanium foil (0.25mm thick, 99.7% purity, Alfa Aesar) were anodized at a constant DC potential for 17 hours in a two-electrode electrochemical cell with a platinum foil as the counter electrode. The average length and pore diameter of the nanotubes were scaled by varying the pH of the electrolyte and the DC potential during anodization. Nanotubes 1 μm in length with an average pore diameter of 30 nm were prepared by anodization using 10 V bias in the 4 pH electrolyte. Nanotubes 1 μm in length with an average pore diameter of 100 nm were prepared by anodization using 20 V bias in a 2 pH electrolyte. All samples were subsequently rinsed in DI water and annealed at a temperature of 500 °C in oxygen ambient to crystallize the nanotubes. Heating and cooling rates of 1 °C/min were used with a dwell time of 6 hours. Surfaces were sterilized with 70% ethanol and UV prior to use in tissue culture.

HAEC and HAoSMC culture. Primary human aortic endothelial cells (HAECs) and primary human vascular smooth muscle cells (HAoSMCs) (Lonza, Walkersville, MD) were cultured according to manufacturer's instructions using Lonza's HAEC and HAoSMC complete media. The cells were cultured in a humidified 95% air/5% CO_2 incubator at 37°C. Cells used in this experiment were passaged less than 15 times.

RNA isolation for microarray. HAECs and HAoSMCs were seeded at 5×10^4 cells/cm^2 on flat and nanotube substrates. Cells were harvested after 24 hours using Qiagen's RNeasy kit (Valencia, CA) according to manufacturer's instructions. Concentration and purity of isolated RNA was measured using a NanoDrop spectrophotometer (Thermo Fisher Scientific, Wilmington, DE)

Microarray. Sample preparation, labeling, and array hybridizations were performed according to standard protocols from the UCSF Shared Microarray Core Facilities and Agilent Technologies (http://www.arrays.ucsf.edu and http://www.agilent.com). Total RNA quality was assessed using a Pico Chip on an Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, CA). RNA was amplified and labeled with Cy3-CTP using the Agilent low RNA input fluorescent linear amplification kits following the manufacturers protocol. Labeled cRNA was assessed using the Nanodrop ND-100 (Thermo Fisher Scientific), and equal amounts of Cy3 labeled target were hybridized to Agilent whole human genome 4x44K Ink-jet arrays. Hybridizations were performed for 14 hrs, according to the manufacturer's protocol. Arrays were scanned using the Agilent microarray scanner and raw signal intensities were extracted with Feature Extraction v10.1 software. A total of 19 arrays were hybridized and represent 4 biological replicates for each group (with the exception of group VSMC-NT30, which has 3 biological replicates).

Differential expression analysis. The following terminology is used to discuss the results of our analysis:

M – $\log_2$ (S2/S1). Log 2 based fold change of entity of interest. M=1 means two-fold increase in S2 compared to S1. M=0 means equal expression. M=-1 means 2 fold down-regulation.

aveA–average $\log_2$ based intensity of the same probe across all arrays, a proxy for gene expression level

B - log posterior odds ratios, ratio between the probability that a given gene is **differentially expressed (DE)** over the probability that a given gene is not differentially expressed; B≥0 means equal or more probability that a gene is DE than non-DE.[1]

FDR – False Discovery Rate, which is the percentage of falsely declared DE genes among the set of declared DE genes. A FDR cutoff of 0.01 indicates that 1% of the declared DE genes are expected to false positives.[2]

AdjP – Adjusted p-value, which controls for family-wise error rates, the probability of having more than one false discovery. An adjusted p-value cutoff of 0.01 indicates that the declared DE set has 1% chance to have more than one false positive.

Raw log-intensities are normalized using *quantile* normalization method that is proposed by Bolstad *et al*.[3] No background subtraction was performed, and the median feature pixel intensity was used as the raw signal before normalization.

A one-way ANOVA model is formulated and specific contrasts are formulated to examine the two pairwise comparisons of interest. Moderated t-statistic, B statistic, false discovery rate and p-value for each gene were obtained. Adjusted p-values were produced by the method proposed by Holm.[4] All procedures were carried out using functions in the R package *limma in Bioconductor*.[5, 6] Shortlists for HAECs were generated using the criteria of $B \geq 0$ and Nominal $P \leq 0.001$. Shortlists for HAoSMCs were generated using the criteria of $B > 0$, Nominal $P \leq 0.001$, and fold-change > 2 (i.e. absolute value of $\log_2$ fold-change > 1).

Quantitative Polymerase Chain Reaction. For confirmation of microarray data, cells were seeded at 5×10^4 cells/cm^2 on flat and nanotube surfaces. In addition, ECs were also seeded at 5×10^3 cells/cm^2 for low density experiments. After 24 hours, samples were harvested using Ambion/Applied Biosystems's Cell to C_T kit (Foster City, CA). Lysis, RT-PCR, and qPCR were performed according to manufacturer's instructions using a StepOne Plus instrument (Applied Biosystems). Primers for each target were designed by Primer Express 3.0 software (Applied Biosystems) or obtained from the National Cancer Institute's Quantitative PCR Primer Database (http://web.ncifcrf.gov/rtp/gel/primerdb/) for the following genes: FST (forward primer – 5'-CAGTAAGTCGGATGAGCCTGTCT, reverse primer – 5'-CAGCTTCCTTCATGGCACACT), ATF3 (forward – 5'-CTGCCCGCCTTTCATCTG,

reverse – 5’-CAGACACTGCTGCCTGAATCC), EGR1 (forward – 5’-TTTGCCAGGAGCGATGAAC, reverse – 5’-CCGAAGAGGCCACAACACTT), YAP1 (forward – 5’-CGTCCAGCAAGATACTTTAATCCTCTAT, reverse – 5’-CTGTGAAAGAGGTCAGCAATACATT), and GAPDH (forward – 5’-TGCACCACCAACTGCTTAGC, reverse – 5’-GGCATGGACTGTGGTCATGAG). Each experimental condition was performed three times (n=3). Expression levels of the genes were measured in technical triplicates.

Supplemental Information

Microarray data has been submitted to the GEO (accession number: GSE17676) and can be found at the following address:

http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?token=zhinfukqcyiqebk&acc=GSE17676

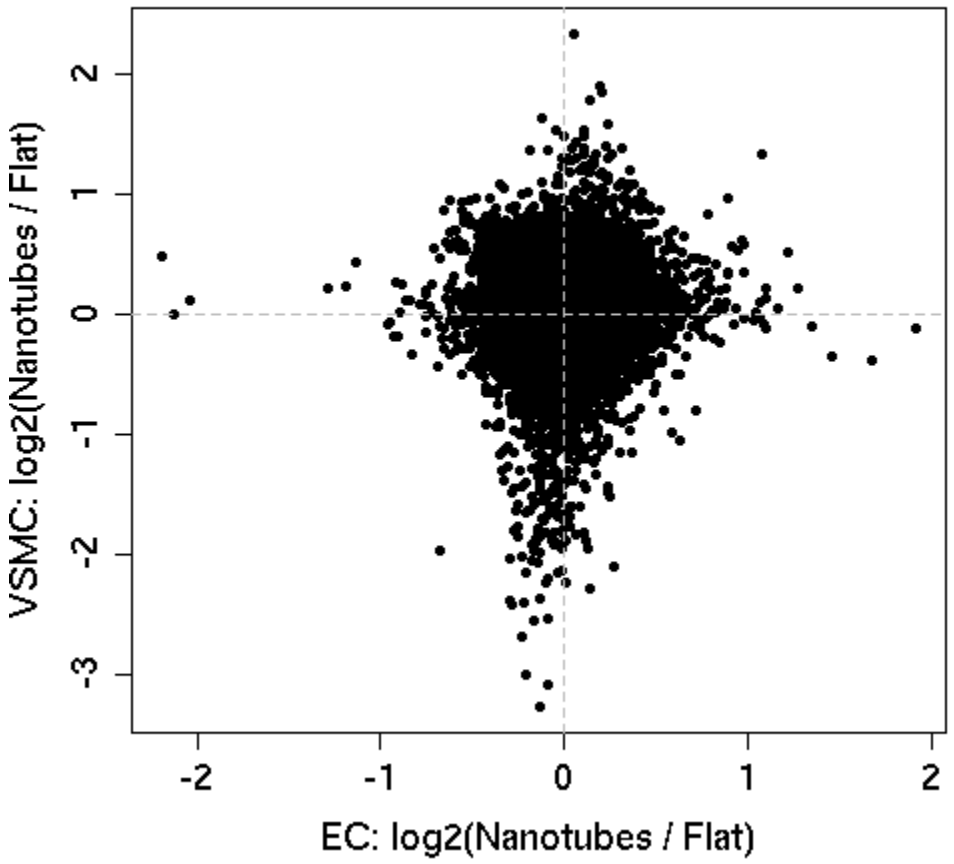

Figure S1: MM plot of gene expression for VSMCs vs. ECs.

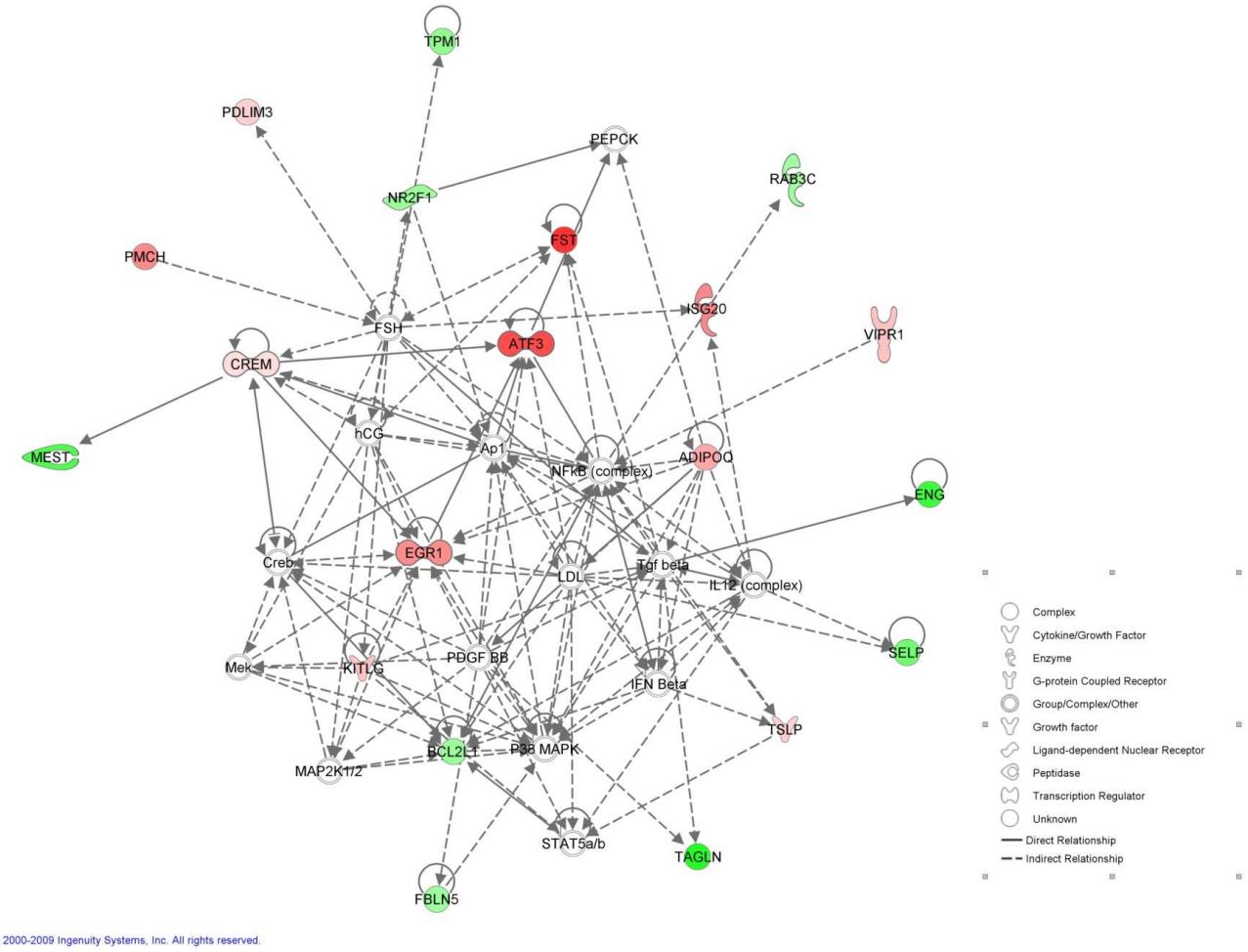

Figure S2. Original top network plot for ECs generated by Ingenuity Pathway Analysis. Red indicates upregulation, green down regulation. Intensity of color is proportional to magnitude of change.

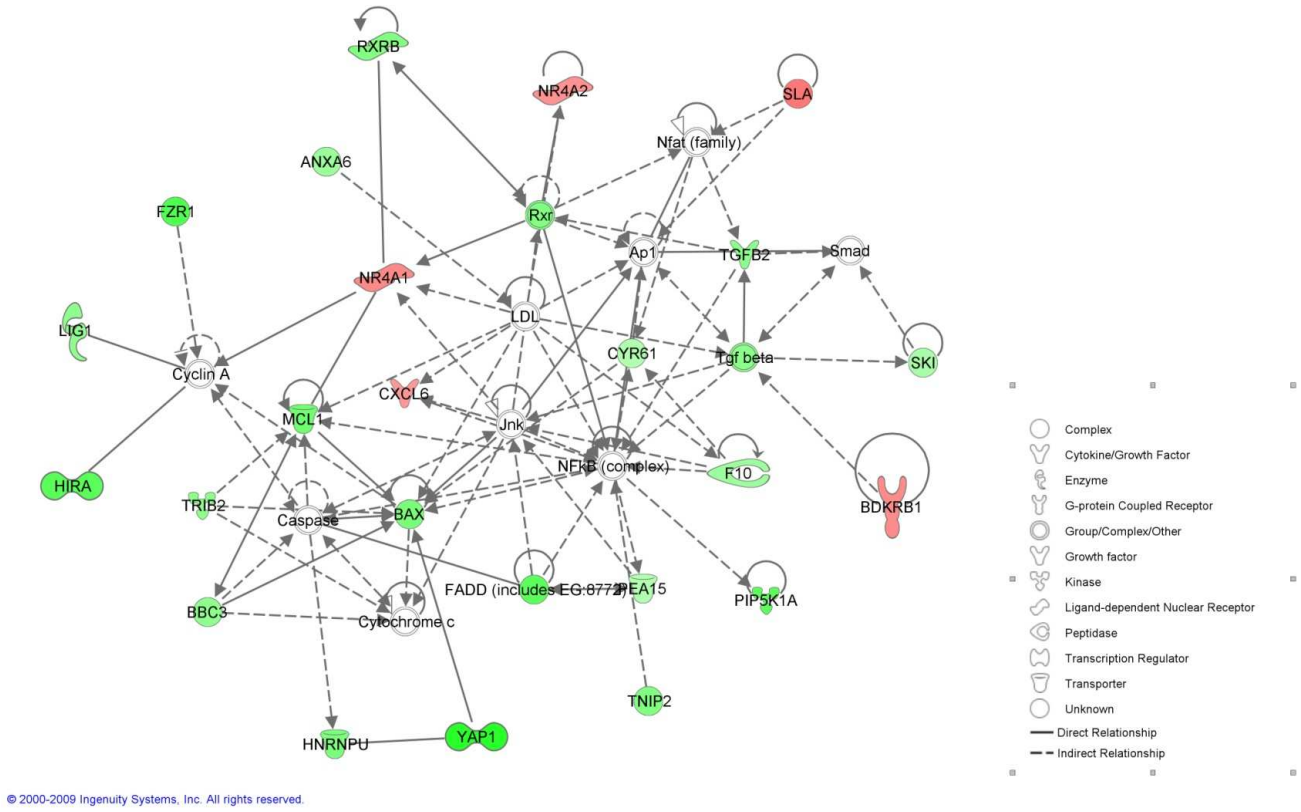

Figure S3. Original top network plot for VSMCs generated by Ingenuity Pathway Analysis. Red indicates upregulation, green down regulation. Intensity of color is proportional to magnitude of change.

Table S1: Genes significantly affected by exposure to nanotubes are listed according to their affect on a specific process. Those that have been shown in literature to inhibit a process are listed on the left two columns, and those that promote the process are listed on the right columns. Superscript refers to literature identified through IPA's curated findings that support all of the gene's classification(s). Data from these tables were used to plot Figures 1B and 4B.

A. Human Aortic Endothelial Cells

Proliferation/Cell Cycle Progression

Inhibit	log2FC.NTvsTi	Promote	log2FC.NTvsTi
CCL23[7, 8]	-0.84	ENG[9, 10]	-0.83
TPM1[11, 12]	-0.47	RPS15A[13]	-0.33
FBLN5[14]	-0.41	TNS3[15]	0.34
CAPRIN2[16]	-0.19	CREM[17]	0.3
PFDN5[18]	-0.32	TSLP[19-21]	0.43
NOV[22]	0.6	KITLG[23-25]	0.54
GPR68[26]	0.63	VIPR1[27]	0.56
ADIPOQ[28-30]	0.8	TNXB[31, 32]	0.55
		ISG20[33]	1.1
		EGR1[34, 35]	1.04
		ATF3[36, 37]	1.67
		FST[38]	1.91

Migration

Inhibit	log2FC.NTvsTi	Promote	log2FC.NTvsTi
ENG[9, 10]	-0.83	TPM1[11, 12]	-0.47
		FBLN5[14]	-0.41
		KITLG[23-25]	0.54

		MFI2[39]	0.6
		NOV[22]	0.6
		ADIPOQ[28-30]	0.8
		CCR3[40]	1.03
		FST[38]	1.91

Inflammation/Coagulation

Inhibit	log2FC.NTvsTi	Promote	log2FC.NTvsTi
KITLG[23-25]	0.54	CCL23[7, 8]	-0.84
TNXB[31, 32]	0.55	SELP[41]	-0.61
		GPR4[42, 43]	-0.49
		IL13RA1[44]	-0.34
		TSLP[19-21]	0.43

Apoptosis/Cell Death

Inhibit	log2FC.NTvsTi	Promote	log2FC.NTvsTi
NR2F1[45]	-0.42	CAPRIN2[16]	-0.19
GPX3[46]	0.34	ITPR3[47]	0.44
TSLP[19-21]	0.43	CREM[17]	0.3
NEK8[48]	0.67		
ADIPOQ[28-30]	0.8		
SLC12A2[49]	0.72		
PPID[40, 50]	0.84		
EGR1[34, 35]	1.04		
ATF3[36, 37]	1.67		

B. Human Aortic Vascular Smooth Muscle Cells

Proliferation/Cell Cycle Progression

Inhibit	log2FC.NTvsTi	Promote	log2FC.NTvsTi
HIRA[51]	-2.4	YAP1[52, 53]	-3.09
IGF2R[54, 55]	-1.83	FADD[56, 57]	-2.38
VPS18[58]	-1.6	PRPF19[59]	-2.15
KCTD11[60]	-1.43	GBF1[61]	-2.13
ATF5[62, 63]	-1.36	MCL1[64, 65]	-2.07
HMOX1[66, 67]	-1.06	FUS[68, 69]	-2.04
EREG[70, 71]	1.02	RALGDS[72, 73]	-2.02
BDKRB2[74, 75]	1.17	H19[76]	-1.92
NR4A2[77, 78]	1.22	IGF2R[54, 55]	-1.83
BDKRB1[75, 79, 80]	1.3	SFRS5[81,82]	-1.82
NR4A1[83, 84]	1.33	RXRB[85-87]	-1.81
SLA[88, 89]	1.53	TGFB2[90, 91]	-1.67
		LIG1[92]	-1.61
		SEMA4C[93]	-1.56
		F10[94, 95]	-1.42
		NCL[96]	-1.42
		ARRB1[97, 98]	-1.32
		PPP1R8[99]	-1.26
		THG1L[100]	-1.26
		RCC1[101]	-1.25
		SKI[102, 103]	-1.25
		ITGA2[104]	-1.2
		PEA15[105, 106]	-1.12
		CYR61[107]	-1.12
		EWSR1[108]	-1.1

		RBBP6[109]	-1.08
		WASF2[110]	-1.02
		EREG[70, 71]	1.02

Migration

Inhibit	log2FC.NTvsTi	Promote	log2FC.NTvsTi
ABHD2[111]	-1.95	PRKAG1[29]	-2.69
TMBIM1[112]	-1.21	HNRPAB[113]	-2.15
SOCS3[114, 115]	-1.01	SEMA4C[93]	-1.56
		ARRB1[97, 98]	-1.32
		PDLIM2[116]	-1.23
		ITGA2[104]	-1.2
		WASF2[110]	-1.02
		MYO10[117]	-1.01
		CD151[118]	-1
		BDKRB1[75, 79, 80]	1.29
		HAS1[119]	1.36
		IRS2[120]	2.32

Inflammation/Coagulation

Inhibit	log2FC.NTvsTi	Promote	log2FC.NTvsTi
EXT1[121]	-1.16	LAMP1[122, 123]	-2.23
ADAMTS13[124]	1.2	RALGDS[72, 73]	-2.02
GLIS2[125]	1.52	PEAR1[126]	-1.8
SLA[88, 89]	1.53	ATRN[127]	-1.63
		CHST2[128]	-1.58
		F10[94, 95]	-1.42
		CXCL6[129]	1.16
		BDKRB1[75, 79, 80]	1.3

Apoptosis/Cell Death

Inhibit	log2FC.NTvsTi	Promote	log2FC.NTvsTi
YAP1[52, 53]	-3.09	FADD[56, 57]	-2.38
PRPF19[59]	-2.15	LAMP1[122, 123]	-2.23
MCL1[64, 65]	-2.07	AQP3[130]	-2.1
SFRS5[81, 82]	-1.82	FUS[68, 69]	-2.04
RXRB[85-87]	-1.81	BAX[131]	-1.92
TNIP2[132]	-1.81	IGF2R[54, 55]	-1.83

DNAJB2[133]	-1.72	TRIB2[134]	-1.67
ATF5[62, 63]	-1.36	BBC3[135]	-1.61
THG1L[100]	-1.26	UACA[136]	-1.49
SKI[102, 103]	-1.25	NCL[96]	-1.42
PEA15[105, 106]	-1.12	TNKS2[137]	-1.31
RBBP6[109]	-1.08	SDHC[138]	-1.17
HMOX1	-1.06	SOCS3[114, 115]	-1.01
BDKRB2[74, 75]	1.17	NR4A1[83, 84]	1.33
NR4A2[77, 78]	1.22		
BDKRB1[75, 79, 80]	1.29		
IRS2[120]	2.32		

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