Table S1. Amino acid concentrations in pancreatic tumor and benign adjacent tissues. Concentrations in nmol/mg (wet weight) and µM (assuming 1g = 1ml). Quantitation was performed by using ^{13}C-labeled standards for each amino acid, which were added before extraction. Values are means of 8 tissue pairs ± SD.

AA	nmol/mg		µM	
	Benign adjacent	Tumor	Benign adjacent	Tumor
Alanine	3.17 ± 2.38	0.96 ± 0.46	3168.3 ± 2379.0	960.8 ± 464.8
Arginine	0.12 ± 0.09	0.14 ± 0.07	118.5 ± 92.4	136.9 ± 70.0
Asparagine	0.28 ± 0.05	0.18 ± 0.05	277.9 ± 52.8	182.4 ± 48.4
Aspartate	0.82 ± 0.47	0.36 ± 0.20	821.1 ± 471.9	362.9 ± 200.9
Glutamate	3.75 ± 2.48	2.35 ± 1.39	3746.2 ± 2479.5	2345.6 ± 1386.2
Glutamine	1.71 ± 0.64	0.69 ± 0.34	1705.2 ± 644.6	692.2 ± 337.5
Glycine	2.53 ± 2.03	0.99 ± 0.49	2529.6 ± 2027.0	988.7 ± 491.0
Histidine	0.27 ± 0.23	0.13 ± 0.07	268.9 ± 234.6	129.2 ± 65.9
(iso)Leucine	0.25 ± 0.08	0.34 ± 0.05	245.7 ± 76.0	337.1 ± 51.0
Lysine	0.45 ± 0.32	0.27 ± 0.13	453.3 ± 321.1	267.6 ± 130.5
Methionine	0.04 ± 0.02	0.06 ± 0.02	35.6 ± 17.4	59.4 ± 16.5
Phenylalanine	0.07 ± 0.06	0.07 ± 0.06	75.0 ± 57.8	74.7 ± 55.4
Proline	0.62 ± 0.49	0.33 ± 0.16	621.6 ± 485.4	329.5 ± 162.2
Serine	0.49 ± 0.34	0.19 ± 0.08	485.4 ± 340.5	187.9 ± 82.0
Threonine	0.44 ± 0.34	0.18 ± 0.07	436.5 ± 344.3	183.3 ± 71.3
Tryptophan	0.04 ± 0.01	0.05 ± 0.01	42.1 ± 10.0	51.5 ± 9.7
Tyrosine	0.09 ± 0.05	0.15 ± 0.05	94.2 ± 54.0	154.0 ± 53.5
Valine	0.36 ± 0.20	0.35 ± 0.14	358.3 ± 201.0	355.0 ± 138.0

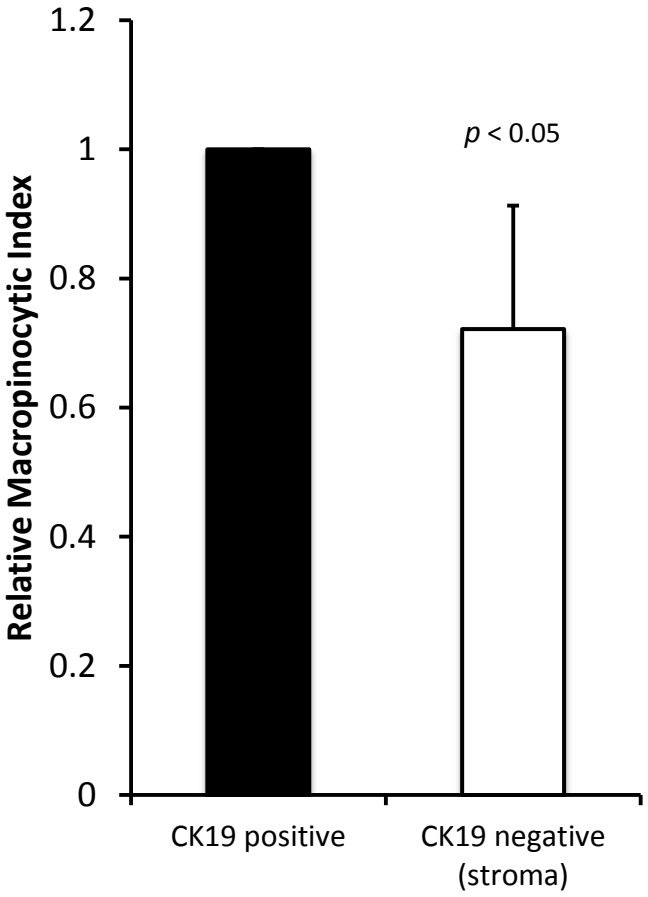

Figure S1. Quantification of macropinocytosis in human pancreatic tumors. Macropinocytic index of CK19-positive cells versus the stroma was computed as previously described (ref 21 of main text) and data are presented relative to the values obtained for the CK19-positive cells from the same sections. Error bar indicates mean values ± s.d, from 3 different patients, *p*-value is by paired t-test.

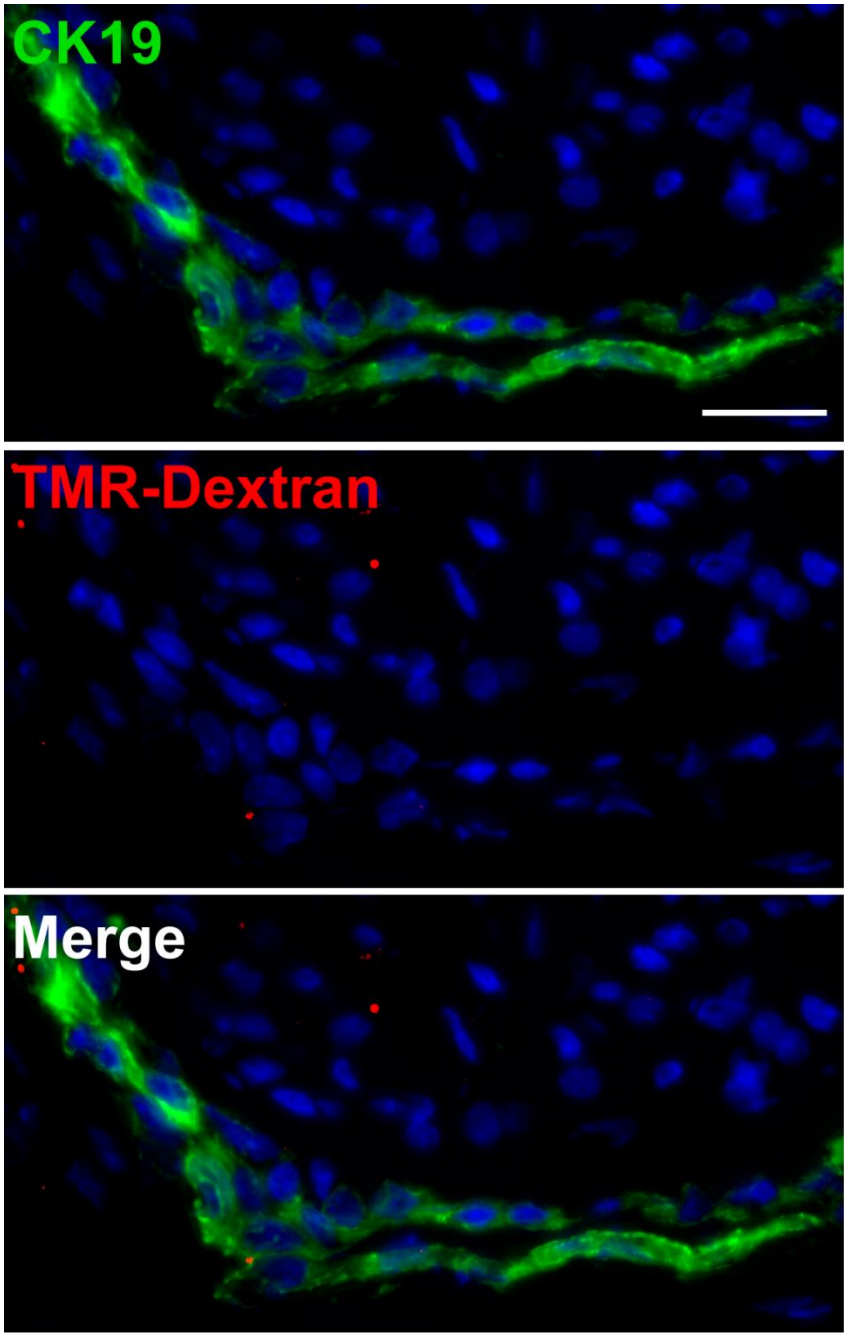

Figure S2. Few macropinosomes are present in the normal pancreatic tissue adjacent to PDAC tumors. An *ex vivo* macropinocytosis uptake assay using TMR-dextran as a marker of macropinosomes (red) indicates that CK19-positive ductal cells (green) display low levels of macropinocytosis. DAPI staining (blue) identifies nuclei. Images shown are Z-stack projections and are representative of five independent samples. Scale bar is 20 μm.

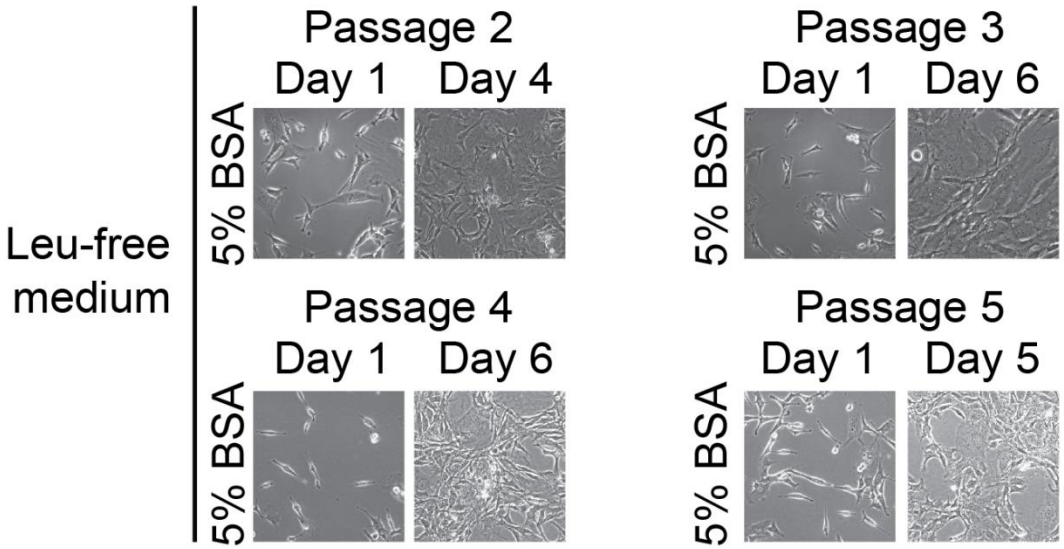

Figure S3. Ras-mutant pancreatic cells are capable of indefinite growth in medium lacking leucine supplemented with physiological levels of serum protein. KRPC cells which had grown to confluence in leucine-free medium supplemented with 50 g/L BSA were continually passaged in this medium without exposure to leucine-containing medium.

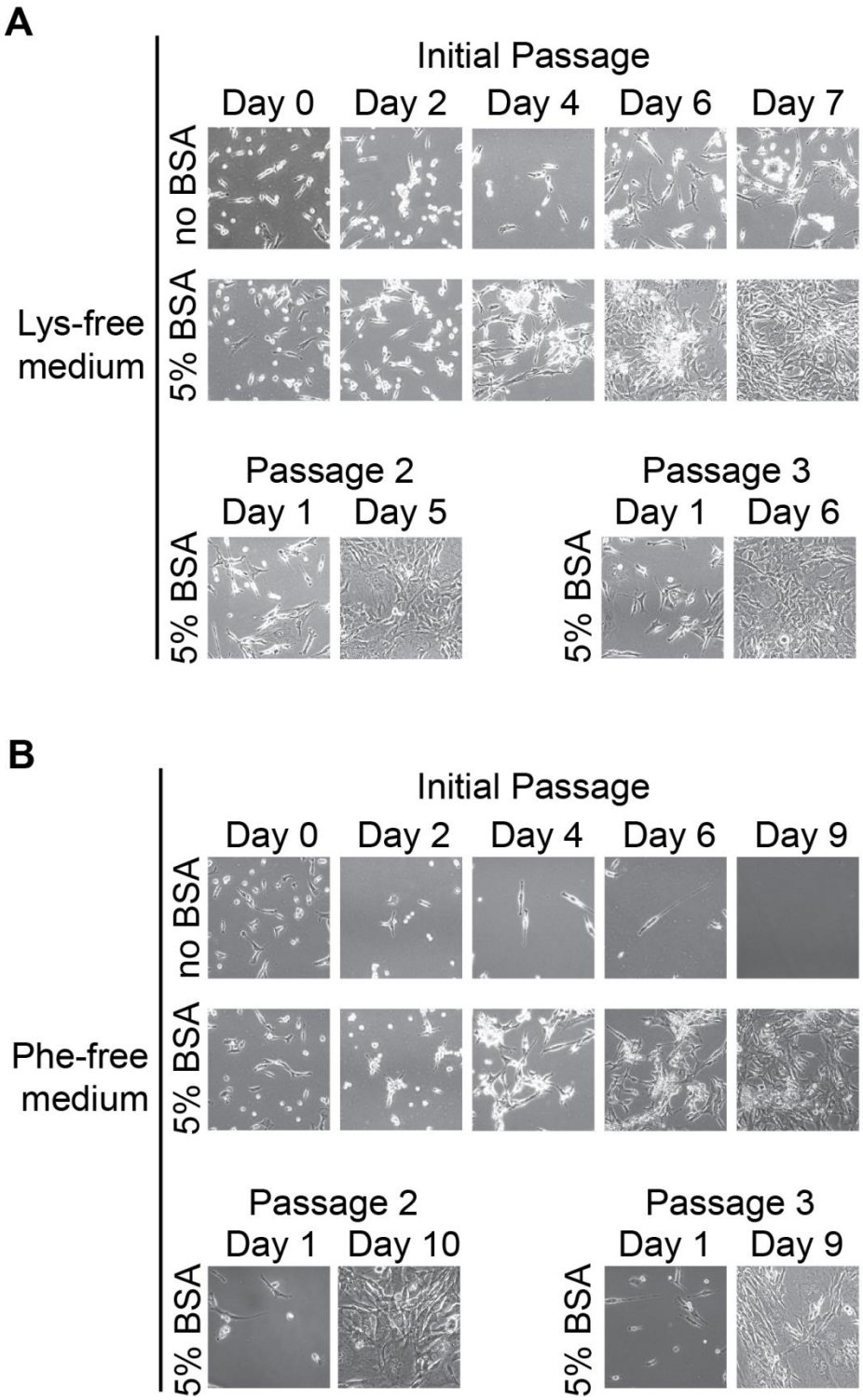

Figure S4. Ras-mutant pancreatic cells are capable of indefinite growth in medium lacking lysine or phenylalanine supplemented with physiological levels of serum protein. Images of KRPC cells cultured in lysine- (A) or phenylalanine-free (B) medium in the presence or absence of supplemented (50 g/L) BSA.

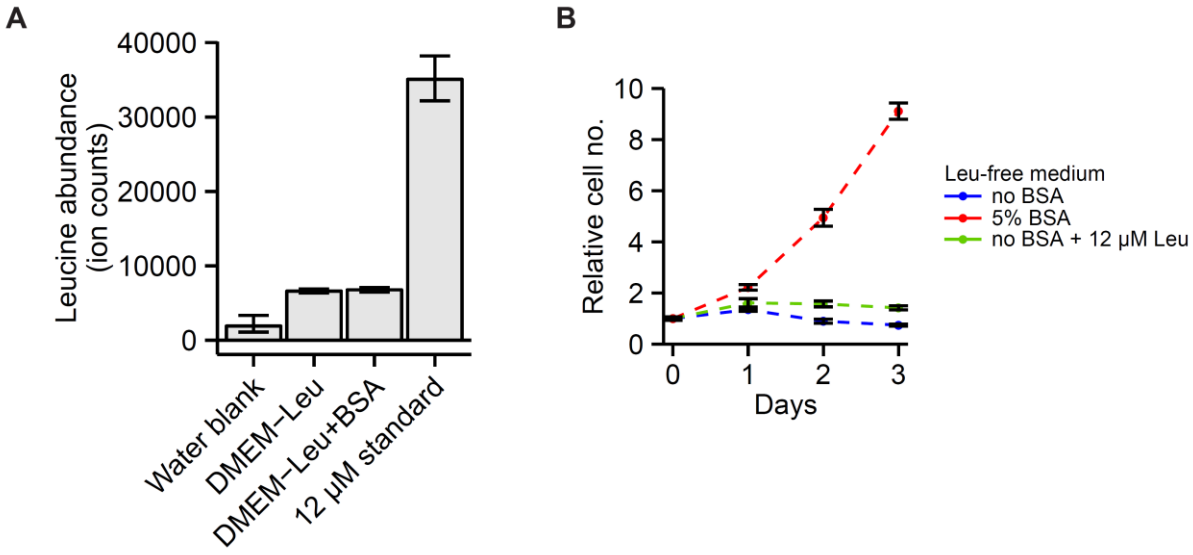

Figure S5. Growth of KRPC cells in leucine-free medium with 50 g/L serum protein cannot be explained by the presence of contaminating leucine. (A) Leucine-free medium with or without 50 g/L BSA as well as a water blank and a 12 µM leucine standard solution were extracted and analyzed by LC-MS (methods). (B) KRPC cells were grown in leucine-free medium supplemented with 50 g/L BSA , 12 µM leucine, or with no supplement, and cell number was measured every 24 h.

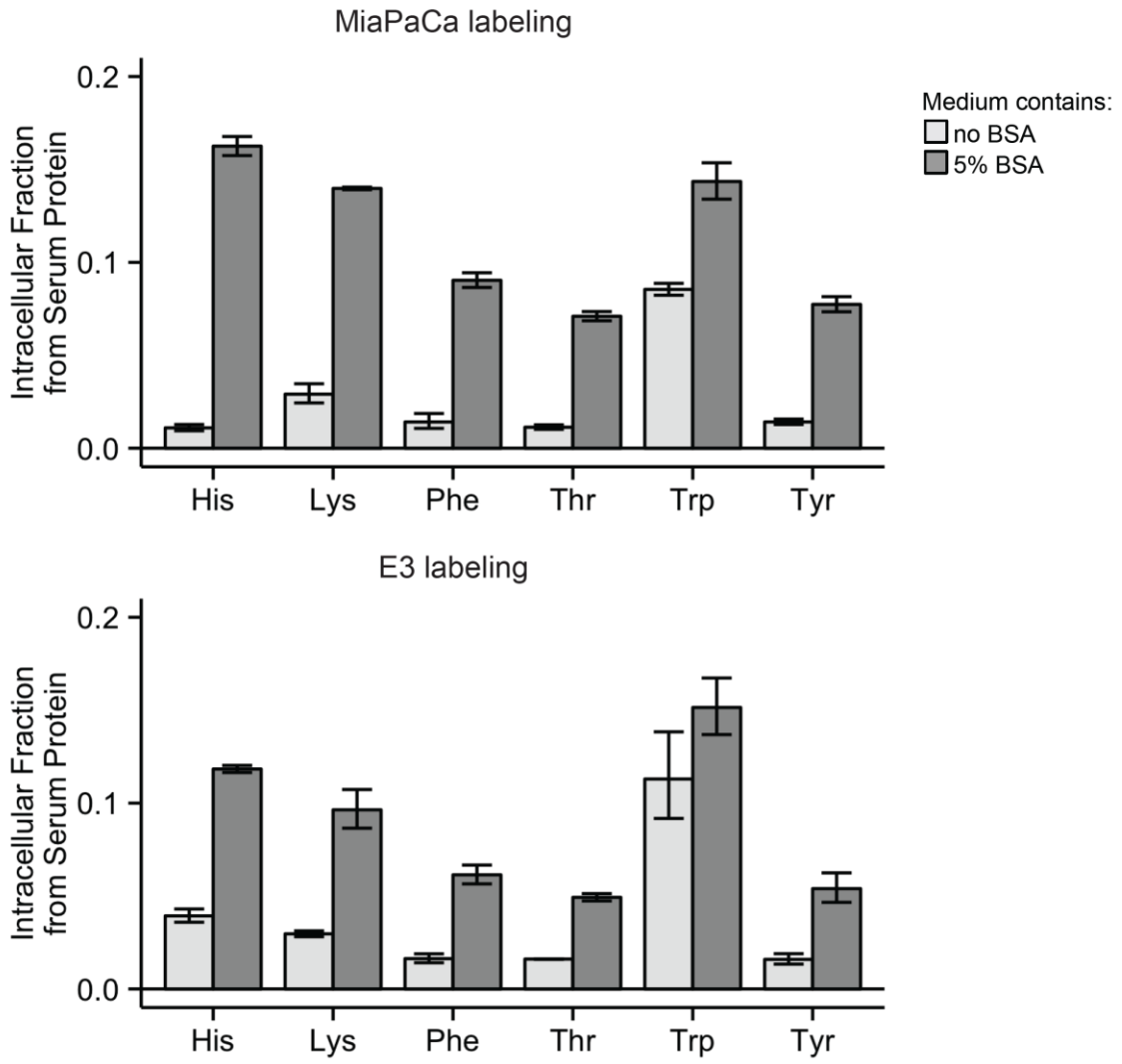

Figure S6. Stable isotope tracing reveals significant contribution of serum protein to amino acid pools in human PDAC cells. MiaPaCa2 (A) and E3 (B) cells were grown in ^{13}C, ^{15}N-DMEM for five generations, after which they were transferred to ^{13}C, ^{15}N-DMEM with amino acids present at 10% DMEM concentrations in the presence or absence of supplemented (50 g/L) BSA. After 24 h, metabolites were extracted, and the fractional contribution of serum protein to intracellular amino acid pools is shown.

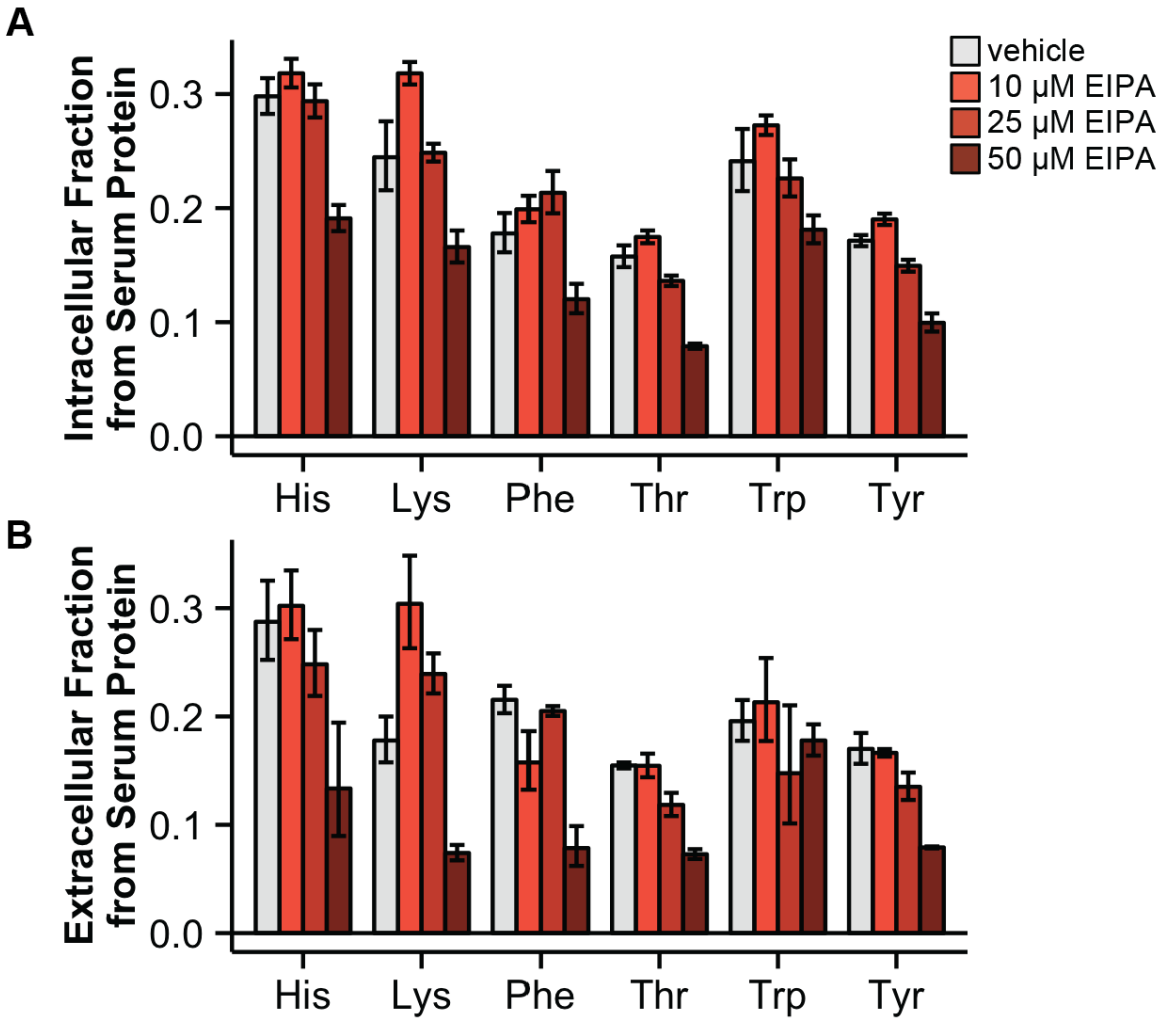

Figure S7. EIPA, an inhibitor of macropinocytosis, reduces intracellular (A) and extracellular (B) serum protein-derived amino acid pools in a dose-dependent fashion. Note that inhibition of macropinocytosis by EIPA may be incomplete, even at the highest tested dose of 50 µM (further dose escalation resulted in general cellular toxicity and was thus not feasible). Data are means ± SE of $n \geq 3$. The effect of EIPA on unlabeled fraction was significant for all intracellular amino acids (panel A) and for all media amino acids except histidine and tryptophan (panel B) (ANOVA, $p < 0.05$).

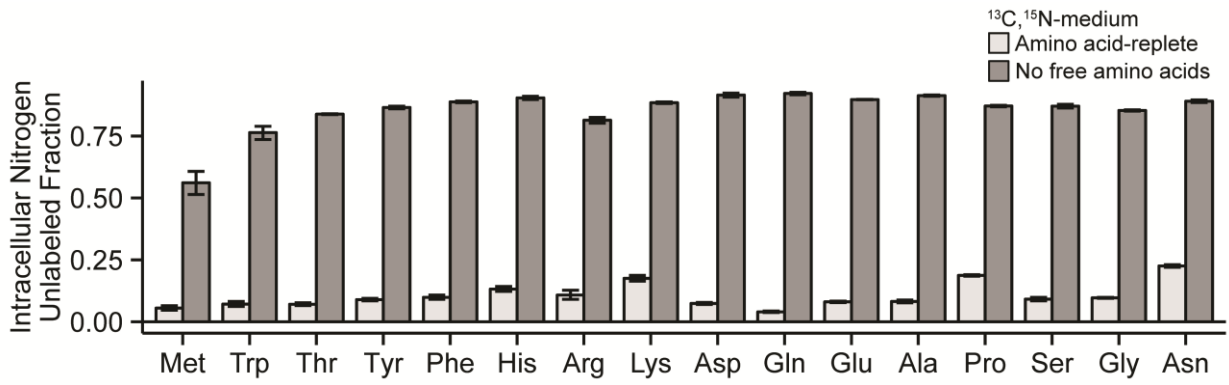

Figure S8. Fractional contribution of serum protein-derived nitrogen to intracellular amino acid pools. KRPC cells were grown in amino acid-free medium and supplemented with physiological levels of albumin (5%). Data are means ± SE of $n \geq 3$.

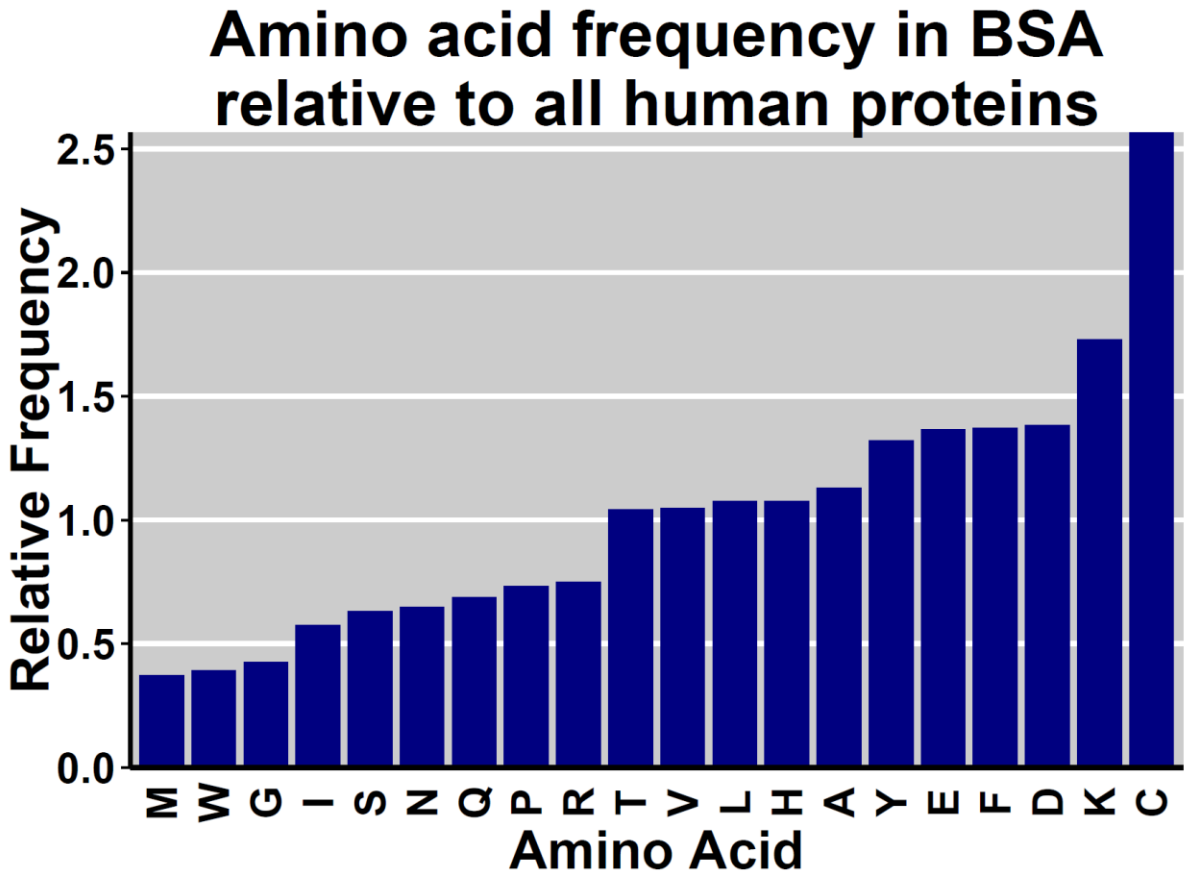

Figure S9. Amino acid frequency in bovine serum albumin relative to human proteome.