

Supplemental Table S1. The number of identified proteins in the proteome analysis of the tissue interstitial fluids

Patient ID	Type	Replicate	No. of protein identified	FDR (%) ^a	No. of protein	Overlap (%) ^b
P01	TIF	Exp. 1	1649	0.06	1815	1511 (83.3)
		Exp. 2	1677	0.02		
	NIF	Exp. 1	1229	0.04	1416	1118 (79.0)
		Exp. 2	1305	<0.01		
P02	TIF	Exp. 1	1952	0.03	2118	1786 (84.3)
		Exp. 2	1952	0.06		
	NIF	Exp. 1	1083	0.04	1226	980 (79.9)
		Exp. 2	1123	<0.01		
P04	TIF	Exp. 1	1813	0.02	1952	1660 (85.0)
		Exp. 2	1799	0.04		
	NIF	Exp. 1	1120	0.02	1228	996 (81.1)
		Exp. 2	1104	0.03		
P05	TIF	Exp. 1	1634	0.07	1740	1401 (80.5)
		Exp. 2	1507	0.03		
	NIF	Exp. 1	1163	<0.01	1270	947 (74.6)
		Exp. 2	1054	0.02		
P10	TIF	Exp. 1	1553	0.07	1719	1390 (80.9)
		Exp. 2	1556	0.04		
	NIF	Exp. 1	1109	<0.01	1239	961 (77.6)
		Exp. 2	1091	0.08		
P12	TIF	Exp. 1	1524	0.11	1685	1279 (75.9)
		Exp. 2	1440	0.03		
	NIF	Exp. 1	1104	0.04	1322	1015 (76.8)
		Exp. 2	1233	0.05		
P13	TIF	Exp. 1	1969	0.03	2150	1837 (85.4)
		Exp. 2	2018	0.01		
	NIF	Exp. 1	1065	<0.01	1182	966 (81.7)
		Exp. 2	1083	0.06		
P14	TIF	Exp. 1	1275	0.06	1787	1219 (68.2)
		Exp. 2	1731	0.03		
	NIF	Exp. 1	881	0.03	936	755 (80.7)
		Exp. 2	810	0.09		
P15	TIF	Exp. 1	1889	0.01	2132	1772 (83.1)
		Exp. 2	2015	0.05		
	NIF	Exp. 1	1685	0.04	1890	1509 (79.8)
		Exp. 2	1714	0.04		
P17	TIF	Exp. 1	1803	0.04	1937	1625 (83.9)
		Exp. 2	1759	<0.01		
	NIF	Exp. 1	988	<0.01	1048	840 (80.2)
		Exp. 2	900	<0.01		
Average	TIF		1726	0.035	1904	- (81.1)
			1142			
	NIF				1276	-(79.1)

^a The false-discovery rate (FDR) was determined as the peptides assigned to random database over target database.

^b The number of overlapping member between duplicate experiments. The percentage was determined from the number of overlaps over the number of total proteins in duplicates.

Supplemental Table S4. The possible secretion routes of proteins identified in TIFs and NIFs

Patient ID	Type	No. of identified proteins (percentage)						Percentage of predicted proteins
		Total	Classical secretion ^a	Nonclassical secretion ^b	Exosome ^c	Membrane protein ^d	Other ^e	
P01	TIF	1815	280 (15.4)	635 (35.0)	785 (43.3)	3 (0.2)	112 (6.2)	93.8
	NIF	1416	273 (19.3)	468 (33.1)	599 (42.3)	4 (0.3)	72 (5.1)	94.9
P02	TIF	2118	276 (13.0)	697 (32.9)	952 (44.9)	5 (0.2)	188 (8.9)	91.1
	NIF	1226	244 (19.9)	402 (32.8)	524 (42.7)	5 (0.4)	51 (4.2)	95.8
P04	TIF	1952	297 (15.2)	671 (34.4)	819 (42.0)	7 (0.4)	158 (8.1)	91.9
	NIF	1228	222 (18.1)	410 (33.4)	523 (42.6)	3 (0.2)	70 (5.7)	94.3
P05	TIF	1740	246 (14.1)	592 (34.0)	786 (45.2)	4 (0.2)	112 (6.4)	93.6
	NIF	1270	246 (19.4)	395 (31.1)	562 (44.3)	4 (0.3)	63 (5.0)	95.0
P10	TIF	1719	240 (14.0)	601 (35.0)	755 (43.9)	3 (0.2)	120 (7.0)	93.0
	NIF	1239	274 (22.1)	402 (32.4)	502 (40.5)	4 (0.3)	57 (4.6)	95.4
P12	TIF	1685	232 (13.8)	568 (33.7)	764 (45.3)	4 (0.2)	117 (6.9)	93.1
	NIF	1322	244 (18.5)	442 (33.4)	562 (42.5)	4 (0.3)	70 (5.3)	94.7
P13	TIF	2150	297 (13.8)	746 (34.7)	922 (42.9)	6 (0.3)	179 (8.3)	91.7
	NIF	1182	259 (21.9)	396 (33.5)	475 (40.2)	2 (0.2)	50 (4.2)	95.8
P14	TIF	1787	211 (11.8)	587 (32.8)	822 (46.0)	5 (0.3)	162 (9.1)	90.9
	NIF	936	184 (19.7)	307 (32.8)	419 (44.8)	2 (0.2)	24 (2.6)	97.4
P15	TIF	2132	250 (11.7)	708 (33.2)	949 (44.5)	6 (0.3)	219 (10.3)	89.7
	NIF	1890	277 (14.7)	677 (35.8)	796 (42.1)	7 (0.4)	133 (7.0)	93.0
P17	TIF	1937	249 (12.9)	641 (33.1)	892 (46.1)	2 (0.1)	153 (7.9)	92.1
	NIF	1048	197 (18.8)	344 (32.8)	456 (43.5)	2 (0.2)	49 (4.7)	95.3
All	TIF	3068	436 (14.2)	1019 (33.2)	1218 (39.7)	11 (0.4)	384 (12.5)	87.5
	NIF	2240	381 (17.0)	793 (35.4)	881 (39.3)	13 (0.6)	172 (7.7)	92.3
	Total	3313	516 (15.6)	1094 (33.0)	1262 (38.1)	18 (0.5)	423 (12.8)	87.2

^a Proteins predicted by the SignalP program to be secreted via the classical secretion pathway (SignalP probability > 0.90).

^b Proteins predicted to be secreted by the nonclassical secretion pathway using SignalP and SecretomeP (SignalP probability < 0.90 and SecretomeP score > 0.50).

^c Proteins with SignalP probability < 0.90 and SecretomeP score < 0.50 are present in ExoCarta database.

^d Proteins predicted by the TMHMM to form integral membrane proteins that were not predicted to be secreted via the classical, nonclassical secretion and exosome.

^e Proteins that could not be classified as classical, nonclassical, exosome, or membrane proteins.

Supplemental Table S6. Number of proteins differentially expressed in each TIF sample

Characteristics	OSCC patients										Average
	P01	P02	P04	P05	P10	P12	P13	P14	P15	P17	
No. of proteins	2029	2306	2093	1943	1969	1912	2278	1953	2477	2080	2057
SD ^a	2.13	2.20	2.17	2.17	2.32	2.10	2.14	2.30	2.11	2.21	2.19
Over-expression ^b	196	312	254	207	234	205	325	260	232	279	250
Under-expression ^c	146	81	107	105	162	124	97	106	159	96	118

^a Standard deviation (SD) for all the TIF/NIF ratios of proteins in each sample.

^b Number of proteins with ratios above mean plus one SD and FDR < 0.1.

^c Number of proteins with ratios less mean minus one SD and FDR < 0.1.