SUPPORTING INFORMATION

Physicochemical Stability and Protein Corona Profiling on the Interaction of Iron Oxide Nanoparticles with Human Tear

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Figure S1

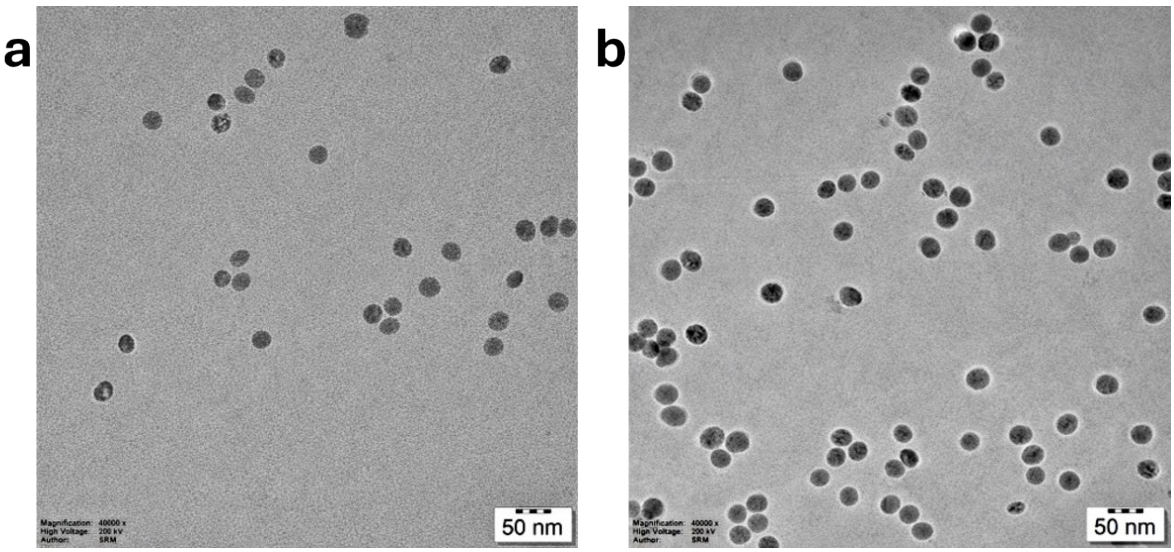

Fig. S1. Transmission electron microscopy (TEM) images of pristine IONP and protein corona adsorbed iron oxide nanoparticles (IONP@TPC). (a) Pristine IONPs showing well-dispersed, spherical morphology. (b) IONPs after incubation with tear extract (IONP@TPC), demonstrating the formation of a protein corona, visible as a surrounding lighter halo layer due to negative staining. Scale bar: 50 nm.

Table S1. Proteins detected in LC–MS/MS workflow-matched blanks (IONPs without tear extract) processed under identical conditions.

Uniprot ID	Protein	Normalised Abundance
P00761	Trypsin precursor	29241.59
Q15646	2'-5'-oligoadenylate synthetase like protein	15373.93
P26189	ADA regulatory protein	12727.3
P04264	Keratin_ type II cytoskeletal 1	12670.57
P13645	Keratin_ type I cytoskeletal 10	11809.91
P35527	Keratin_ type I cytoskeletal 9	10239.7
P35908	Keratin_ type II cytoskeletal 2 epidermal	8889.117
P05782	Keratin_ type I cytoskeletal 47 kDa	3935.511
P31025	Von Ebner's gland protein precursor (VEG protein)	2866.323
P00695	Lysozyme C precursor	2183.692
P13647	Keratin_ type II cytoskeletal 5	1688.301
P81605	Dermcidin precursor (Preproteolysin)	884.0416
P02533	Keratin_ type I cytoskeletal 14	495.3467
P48669	Keratin_ type II cytoskeletal 6F	447.8473
P02538	Keratin_ type II cytoskeletal 6A	352.8479
P05069	Type-1Aa cytolytic delta-endotoxin	348.306

Table S2. Complete list of all Proteins Identified in human tear extract

Uniprot ID	Protein	Normalised Abundance	GRAVY Score	Molecular Weight (kDa)	Isoelectric Point
P31025	Lipocalin-1	480030.9	-0.2409	19249.79	5.3926
P61626	Lysozyme C	247753.6	-0.1946	16536.85	9.3804
P02788	Lactotransferrin	230697.4	-0.337	78181.11	8.5036
Q16378	Proline-rich protein 4	183385.8	-1.1157	15096.55	6.4998
O75556	Mammaglobin-B	156136	0.0705	10883.73	5.4756
P01876	Immunoglobulin heavy constant alpha 1	141768.7	-0.2103	42848.01	5.4267
P25311	Zinc-alpha-2-glycoprotein	131960.1	-0.5758	34258.29	5.7082
P12273	Prolactin-inducible protein	130552.4	0.1753	16572.28	8.2586
P01834	Immunoglobulin kappa constant	130353.5	-0.5374	11764.9	6.1116
P01036	Cystatin-S	128826.9	-0.3993	16214.18	4.9506
P0DOY2	Immunoglobulin lambda constant 2	82134.59	-0.4443	11293.43	6.9092
P06703	Protein S100-A6	81632.88	-0.2889	10179.62	5.3234
O95968	Secretoglobin family 1D member 1	63599.47	0.5044	9898.02	9.4121
P01833	Polymeric immunoglobulin receptor	60920.91	-0.3407	83282.6	5.5852
Q9GZZ8	Extracellular glycoprotein lacritin	54922.14	-0.2464	14245.9	5.4378
P02538	Keratin_ type II cytoskeletal 6A	48441.63	-0.4385	60044.23	8.0906
Q99935	Opiorphin prepropeptide	39760.39	-0.0435	27216.13	10.4215
P13645	Keratin_ type I cytoskeletal 10	31470.93	-0.6236	58826.39	5.1343
P04264	Keratin_ type II cytoskeletal 1	31027.22	-0.6258	66037.94	8.1506
P01591	Immunoglobulin J chain	30328.29	-0.3377	18098.4	5.1155
P13647	Keratin_ type II cytoskeletal 5	30017.76	-0.428	62377.61	7.5835
P02768	Albumin	25553.74	-0.3539	69365.96	5.917
P35527	Keratin_ type I cytoskeletal 9	19223.68	-0.7006	62063.61	5.1362
P0DOX2	Immunoglobulin alpha-2 heavy chain	18243.75	-0.2352	48933.62	6.2346
P0DOX8	Immunoglobulin lambda-1 light chain	17865.81	-0.4477	22829.89	6.3438
Q96DA0	Pancreatic adenocarcinoma up-regulated factor	15090.55	-0.0244	18878.39	5.3814
P35908	Keratin_ type II cytoskeletal 2 epidermal	14734.17	-0.4709	65432.1	8.0735
P61769	Beta-2-microglobulin	14376.39	-0.3765	13714.4	6.0587
P01037	Cystatin-SN	13796.99	-0.4404	16387.46	6.7273
P06702	Protein S100-A9	12773.08	-0.8702	13241.85	5.7131
A0M8Q6	Immunoglobulin lambda	11831.43	-0.4575	11253.46	8.5037

	constant 7				
P05783	Keratin_ type I cytoskeletal 18	10453.31	-0.5556	48057.24	5.3369
P01877	Immunoglobulin heavy constant alpha 2	9879.015	-0.2317	42333.45	5.4173
P01871	Immunoglobulin heavy constant mu	9835.262	-0.2646	51922.94	5.7954
P05109	Protein S100-A8	8928.45	-0.3968	10834.38	6.5107
P0DOX7	Immunoglobulin kappa light chain	8244.98	-0.4542	23378.81	6.905
P63104	14-3-3 protein zeta/delta	8119.121	-0.6208	27744.79	4.7262
B9A064	Immunoglobulin lambda-like polypeptide 5	7636.522	-0.4037	23062.98	9.0807
P00738	Haptoglobin	7260.739	-0.4212	45204.78	6.1264
P20061	Transcobalamin-1	6766.981	-0.1263	48206.15	4.9637
P10909	Clusterin	6532.979	-0.6646	52494.01	5.8904
A5A3E0	POTE ankyrin domain family member F	5734.672	-0.6794	121443.3	5.8249
P60709	Actin_ cytoplasmic 1	5575.683	-0.1997	41736.29	5.2905
Q15782	Chitinase-3-like protein 2	5486.236	-0.1915	43500.2	7.1112
P04792	Heat shock protein beta-1	5027.81	-0.5668	22782.23	5.9776
P22079	Lactoperoxidase	5005.09	-0.3812	80286.95	8.8881
P06312	Immunoglobulin kappa variable 4-1	4970.707	-0.143	13379.89	5.0863
A0A0B4J1V0	Immunoglobulin heavy variable 3-15	4946.613	-0.0958	12925.64	8.8423
P80303	Nucleobindin-2	4860.156	-1.0364	50222.13	5.0257
P01619	Immunoglobulin kappa variable 3-20	4632.657	-0.1302	12556.96	4.8532
Q08380	Galectin-3-binding protein	4586.502	-0.1345	65330.24	5.1283
P80188	Neutrophil gelatinase-associated lipocalin	4563.024	-0.2677	22587.79	9.0209
P09211	Glutathione S-transferase P	4307.996	-0.1214	23355.55	5.4334
Q13421	Mesothelin	4263.175	-0.1057	68984.84	6.0289
P0DMV8	Heat shock 70 kDa protein 1A	3778.859	-0.3835	70051.37	5.4809
O95678	Keratin_ type II cytoskeletal 75	3551.294	-0.4517	59559.68	7.6046
P01034	Cystatin-C	3465.064	-0.1116	15799.05	9.0009
P09228	Cystatin-SA	3358.834	-0.3248	16444.51	4.8482
P30838	Aldehyde dehydrogenase_ dimeric NADP-preferring	3116.277	-0.2011	50394.37	6.1129
A0A0C4DH41	Immunoglobulin heavy variable 4-61	3103.914	-0.0297	13065.75	9.359
P55058	Phospholipid transfer protein	2973.702	0.0892	54738.79	6.5325
P01768	Immunoglobulin heavy variable 3-30	2880.293	-0.0479	12946.62	9.097
O76013	Keratin_ type I cuticular Ha6	2807.574	-0.3722	52246.52	4.899
P06396	Gelsolin	2756.513	-0.4146	85696.46	5.8964
P26447	Protein S100-A4	2744.597	-0.5644	11728.4	5.8507

P81605	Dermcidin	2735.68	-0.2245	11283.73	6.0861
P01701	Immunoglobulin lambda variable 1-51	2721.161	-0.1735	12248.55	6.5042
P02533	Keratin_ type I cytoskeletal 14	2468.642	-0.5371	51560.91	5.0877
P06733	Alpha-enolase	2320.416	-0.2214	47168.4	7.0118
P01857	Immunoglobulin heavy constant gamma 1	2285.508	-0.2699	43911.38	6.5496
P14618	Pyruvate kinase PKM	2267.849	-0.1281	57936.24	7.955
P30041	Peroxiredoxin-6	2133.604	-0.2098	25034.67	5.997
P01624	Immunoglobulin kappa variable 3-15	1981.495	-0.0809	12495.95	5.1446
P12035	Keratin_ type II cytoskeletal 3	1924.802	-0.3889	64416.23	6.1169
P27348	14-3-3 protein theta	1919.922	-0.5118	27763.94	4.6834
P07339	Cathepsin D	1729.75	0.0231	44551.71	6.1041
P31941	DNA dC->dU-editing enzyme AP	1622.496	-0.4256	23011.75	6.3446
P30740	Leukocyte elastase inhibitor	1420.22	-0.2488	42741.29	5.9037
P21980	Protein-glutamine gamma-glutamyltransferase 2	1370.92	-0.2827	77327.94	5.1073
P01780	Immunoglobulin heavy variable 3-7	1340.955	-0.0513	12942.58	6.2148
P01011	Alpha-1-antichymotrypsin	1234.322	-0.0652	47650.3	5.3278
P17931	Galectin-3	1206.368	-0.3952	26152	8.5759
P01593	Immunoglobulin kappa variable 1D-33	959.3381	-0.206	12848.33	4.5278
P01700	Immunoglobulin lambda variable 1-47	954.6687	-0.2128	12283.45	5.5532
P07737	Profilin-1	925.1827	-0.1164	15054.07	8.436
P30044	Peroxiredoxin-5_ mitochondrial	907.6692	0.1523	22086.17	8.9278
Q06830	Peroxiredoxin-1	822.9324	-0.2648	22110.09	8.2724
A0A0B4J1X5	Immunoglobulin heavy variable 3-74	810.0765	0.0128	12839.47	8.9057
P00352	Aldehyde dehydrogenase 1A1	758.339	-0.1627	54861.2	6.2972
P05787	Keratin_ type II cytoskeletal 8	670.3539	-0.5973	53703.63	5.5194
A0A0A0MS15	Immunoglobulin heavy variable 3-49	535.0162	-0.0101	13055.78	8.8419

Table S3. Biological Functions of Proteins identified in IONP@TPC.

Protein	Function
P61626 Lysozyme C	Lysozyme C is a major antimicrobial protein in tears that primarily protects the ocular surface by breaking down bacterial cell walls. In addition to its antibacterial activity, it also contributes to immune regulation and mucosal defense, helping maintain ocular surface health and protection against infections.[1]
P02788 Lactotransferrin	Lactoferrin is an abundant iron-binding antimicrobial glycoprotein in tears that protects the eye through multiple mechanisms, including inhibition of bacterial and viral pathogens, sequestration of iron to prevent microbial growth, and modulation of inflammatory and immune responses at the ocular surface.[1]

O95968 Secretoglobin family 1D member 1	Lipophilin A shows homology to the C1 and C2 components of prostatein (also known as estramustine-binding protein), a major secretory protein of the rat prostate.[2] Lipophilins are present in tears as two isoforms (A and B) and belong to the uteroglobin superfamily, a group of small secreted proteins known for their anti-inflammatory properties, steroid-binding ability, and regulation by steroid hormones.[3]
O75556 Mammaglobin-B	Although Mammaglobin, a uteroglobin protein, is a promising diagnostic marker for breast cancer,[4] function of this in tears is still not known. However, it has been reported that mammaglobin-B was also found to be decreased in evaporative dry eye disease and increased in contact lens users.[5]
Q9GZZ8 Extracellular glycoprotein lacritin	Lacritin is an endogenous tear glycoprotein secreted by lacrimal acinar cells that enhances basal tear secretion and exhibits mitogenic activity in lacrimal and corneal epithelial cells. Its restricted glandular expression and prosecretory signaling functions highlight its potential autocrine/paracrine role in ocular surface maintenance and therapeutic applications.[6,7]
Q16378 Proline-rich protein 4	PRR4 has been implicated in the regulation of the tear proteome during reflex tearing and is considered a potential contributor to ocular surface protection and maintenance of tear film homeostasis. Transcriptomic studies have shown that PRR4 is specifically synthesized by acinar cells of the human lacrimal gland, supporting its potential as a biomarker of lacrimal gland functional efficiency. Increased abundance of PRR4 has also been reported in reflex tears, suggesting its involvement in the clearance of ocular irritants and maintenance of ocular surface stability.[8]
P31025 Lipocalin-1	Lipocalin-1 (LCN-1), a member of the lipocalin superfamily, is known for its ability to bind a broad range of lipophilic ligands and is suggested to primarily function in lipid scavenging.[9] In tear fluid, LCN-1 has been reported to scavenge lipids from hydrophobic surfaces and transfer them into the aqueous tear phase, thereby contributing to the maintenance of tear film integrity and ocular surface stability.[10]
P12273 Prolactin-inducible protein	Prolactin-inducible protein (PIP), also known as gross cystic disease fluid protein-15 (GCDFP-15), is expressed in several exocrine tissues including the lacrimal, salivary, and sweat glands. PIP expression is regulated by hormones such as androgens, estrogens, and prolactin, which are important for ocular surface homeostasis and maintenance of corneal structural integrity. Although the precise biological function of PIP remains unclear, emerging evidence suggests its involvement in host defense and immune modulation, and it has also been proposed as a potential predictive biomarker for keratoconus.[11,12]

Q96DA0 Pancreatic adenocarcinoma up-regulated factor	Pancreatic adenocarcinoma up-regulated factor (PAUF/ZG16B) is a secreted glycoprotein reported to exhibit pro-metastatic, pro-angiogenic, and immunomodulatory functions in several cancers; however, its specific physiological role in the eye or ocular diseases remains unclear. PAUF has been shown to enhance β-catenin expression and transcriptional activity, while PAUF knockdown reduces β-catenin signaling. Since Wnt/β-catenin signaling is critical for retinal vascular development and blood–retinal barrier integrity, PAUF may potentially influence these ocular processes, although this has not yet been experimentally validated.[13]
P04264 Keratin, type II cytoskeletal 1	Keratin 1 (KRT1) is a type II intermediate filament protein involved in structural support and stress protection in stratified epithelia, including the ocular surface. Although not a cornea-specific keratin like KRT3 and KRT12, it is associated with the keratin cytoskeletal network that maintains corneal epithelial cell shape, mechanical resilience, transparency, and barrier function. During epithelial injury, stress-associated keratins such as KRT14 and KRT17 contribute to limbal stem cell proliferation, migration, and corneal wound healing.[14,15]
P01876 Immunoglobulin heavy constant alpha 1	Immunoglobulin A1 (IgA1) is a major mucosal immunoglobulin that mediates immune exclusion by binding pathogens and toxins at mucosal surfaces, including the ocular surface, thereby preventing microbial adhesion and invasion with minimal inflammation. Through interaction with the polymeric immunoglobulin receptor (pIgR), IgA1 undergoes epithelial transcytosis to form secretory IgA, the predominant immunoglobulin in tears and conjunctival secretions. At the ocular surface, secretory IgA contributes to first-line defense, immune homeostasis, and protection against microbial colonization and conjunctival infections, while IgA dysregulation or deficiency may impair mucosal immunity and increase susceptibility to recurrent ocular infections.[16,17]
P01834 Immunoglobulin kappa constant	Immunoglobulin kappa constant (IGKC) encodes the constant region of κ light chains that are essential for antibody assembly, antigen recognition, and B-cell receptor formation. At the ocular surface, κ-containing IgG and IgA antibodies in tears and conjunctival secretions contribute to humoral immunity by neutralizing pathogens, supporting immune exclusion, and maintaining adaptive immune responses in the conjunctiva and lacrimal gland. Although IGKC has no known eye-specific effector function, it is important for the formation of functional antibodies that protect the cornea and conjunctiva from microbial invasion.[18,19]

P06702 Protein S100-A9	Protein S100-A9 (S100A9/calprotectin) is a damage-associated molecular pattern (DAMP) protein implicated in ocular surface inflammation and innate immune activation. Together with S100A8, it regulates neutrophil chemotaxis and inflammatory responses in ocular disorders such as dry eye disease, meibomian gland dysfunction, pterygium, corneal neovascularization, keratitis, uveitis, retinal neuroinflammation, and glaucoma, with elevated expression consistently reported in inflammatory ocular conditions.[20,21]
Q99935 Opiorphin prepropeptide	Involved in the protection of the ocular surface, maintenance of ocular surface homeostasis, and modulation of pain signaling/pain relief mechanisms.[22]
P35527 Keratin, type I cytoskeletal 9	Keratin 9 (P35527, KRT9) is a palmoplantar-specific type I intermediate filament; there is currently no evidence that it has a specific physiological ocular function, and it is not part of the normal corneal/ocular surface keratin repertoire that maintains eye structure or transparency.[23]
P12035 Keratin, type II cytoskeletal 3	Keratin 3 (P12035, KRT3; keratin, type II cytoskeletal 3) is a cornea-specific intermediate filament protein that, together with keratin 12 (KRT12), is essential for the structural integrity, transparency, and barrier function of the corneal epithelium; mutations cause Meesmann corneal dystrophy and epithelial fragility.[24–26]
P01877 Immunoglobulin heavy constant alpha 2	Immunoglobulin heavy constant alpha 2 (IGHA2) encodes the constant region of the IgA2 heavy chain and contributes to ocular mucosal immunity as a component of secretory IgA in tears. Along with IgA1, IgA2 participates in first-line ocular surface defense by neutralizing pathogens and toxins, agglutinating microbes, and preventing their adhesion to the corneal and conjunctival epithelium. As part of the tear secretory IgA pool, IGHA2 plays an important role in maintaining ocular surface sterility and immune homeostasis, although no distinct ocular-specific function separate from IgA1 has been established.[27,28]
P01591 Immunoglobulin J chain	Immunoglobulin J chain has a crucial but indirect ocular function. It is involved in the formation and epithelial transport of polymeric IgA and IgM, thereby enabling secretory IgA mediated immune protection on the ocular surface.[29]
P01833 Polymeric	Polymeric immunoglobulin receptor (pIgR) is a key component of ocular mucosal immunity, functioning as the epithelial receptor responsible for transporting locally produced dimeric IgA and pentameric IgM across lacrimal and conjunctival epithelia into the tear film. This process generates secretory IgA (SIgA) and secretory IgM

immunoglobulin receptor	(SIgM), with SIgA representing the predominant immunoglobulin in tears. By enabling the secretion of SIgA/SIgM, pIgR supports non-inflammatory immune exclusion at the ocular surface through agglutination and neutralization of pathogens without excessive complement activation, thereby contributing to ocular surface protection and immune homeostasis.[30,31]
P25311 Zinc-alpha-2-glycoprotein	Zinc-alpha-2-glycoprotein (ZAG, P25311/AZGP1) is a secreted lipid-mobilizing glycoprotein that is consistently detected in tear film and intraocular fluids; in ophthalmology, it appears to support tear film stability and ocular surface defense and is emerging as a biomarker and potential modulator in fungal keratitis and proliferative diabetic retinopathy. supporting movement of small molecules and contributing to tear film stability, likely via lipid binding and transport.[32,33]
P04792 Heat shock protein beta-1	Heat shock protein beta-1 (P04792; HSPB1/HSP27) is a small heat-shock chaperone widely expressed in ocular tissues where it protects cells, especially retinal ganglion cells and corneal epithelium from stress-induced damage, but in some contexts, it may also contribute to retinal degeneration. HSPB1 exerts powerful neuroprotective effects in retinal ganglion cells (RGCs) via several mechanisms: molecular chaperone activity, stabilization of cytoskeletal elements (e.g., actin), and regulation of apoptosis by interacting with key apoptotic proteins. It can inhibit apoptosis by sequestering cytochrome c, modulating caspase activation, and interacting with components of the apoptotic machinery, thereby increasing survival of stressed RGCs in retinal disease models.[34,35]
P05109 Protein S100-A8	In ophthalmology, protein S100-A8 is a key pro-inflammatory mediator in ocular surface disease and uveitis, involved in neutrophil/monocyte recruitment, corneal neovascularization, and intraocular inflammatory relapses. central regulators of neutrophil chemotaxis and inflammation in dry eye, meibomian gland dysfunction (MGD), pterygium, and corneal neovascularization.[36]
Q13421 Mesothelin	Mesothelin is expressed in the normal human corneal epithelium and endothelium, where it is thought to contribute to cell-cell adhesion and ocular surface barrier integrity, but no eye-specific pathology linked directly to it has been defined yet.[37]
O95678 Keratin, type II	A recent proteomic investigation of human lens epithelium exposed to warming conditions identified the presence of K2C75_HUMAN (O95678; keratin, type II cytoskeletal 75), however, no specific functional role was attributed.It is primarily recognized as a hair and nail associated and currently has no defined physiological function in ocular tissues. Existing evidence indicates that its detection in eye-related

cytoskeletal 75	tissues, such as lens epithelium proteomic datasets, is incidental or occurs at low levels, with no established involvement in normal corneal physiology or ocular disease pathogenesis to date.[38]
P01871 Immunoglobulin heavy constant mu	In ophthalmology, secreted IgM is present in vitreous and aqueous humor and contributes to retinal homeostasis and anti-inflammatory control during aging, while systemic IgM deficiency increases susceptibility to ocular infections and retinal degeneration.[39]

Table S4. Functional category of proteins identified in tear extract based on Gene Ontology analysis.

GO_term	Description	Count_in_network	Strength	Signal	FDR
GO:0001895	Retina homeostasis	18 of 78	1.81	5.36	1.66e-22
GO:0001894	Tissue homeostasis	22 of 238	1.41	3.73	9.28e-21

GO:0045104	Intermediate filament cytoskeleton organization	11 of 88	1.54	2.52	1.46e-10
GO:0045109	Intermediate filament organization	10 of 69	1.6	2.5	4.28e-10
GO:0001580	Detection of chemical stimulus involved in sensory perception	7 of 37	1.72	1.93	2.37e-07
GO:0050909	Sensory perception of taste	8 of 69	1.51	1.79	2.82e-07
GO:1990748	Cellular detoxification	9 of 106	1.37	1.69	2.82e-07
GO:0042742	Defense response to bacterium	14 of 306	1.1	1.62	1.17e-08
GO:0006959	Humoral immune response	12 of 268	1.09	1.42	2.82e-07
GO:0031424	Keratinization	7 of 83	1.37	1.31	1.59e-05
GO:0052548	Regulation of endopeptidase activity	14 of 414	0.97	1.28	2.82e-07
GO:0042592	Homeostatic process	28 of 1406	0.74	1.2	6.61e-11
GO:0030216	Keratinocyte differentiation	8 of 138	1.21	1.18	2.42e-05
GO:2000116	Regulation of cysteine-type endopeptidase activity	10 of 236	1.07	1.16	9.52e-06
GO:0019730	Antimicrobial humoral response	8 of 149	1.17	1.12	3.90e-05
GO:0030162	Regulation of proteolysis	17 of 739	0.8	1.04	6.28e-07
GO:0098542	Defense response to other organism	20 of 989	0.75	1.01	2.44e-07
GO:0051346	Negative regulation of hydrolase activity	11 of 354	0.94	0.98	3.11e-05
GO:2000117	Negative regulation of cysteine-type endopeptidase activity	6 of 88	1.28	0.97	0.00031
GO:0006952	Defense response	24 of 1394	0.68	0.95	8.85e-08
GO:0051707	Response to other organism	23 of 1328	0.68	0.93	2.05e-07
GO:0009617	Response to bacterium	15 of 663	0.8	0.93	7.89e-06
GO:0008544	Epidermis development	10 of 320	0.94	0.9	0.00010
GO:0044419	Biological process involved in interspecies interaction	24 of 1490	0.65	0.89	2.44e-07
GO:0043588	Skin development	9 of 266	0.97	0.88	0.00020
GO:0097435	Supramolecular fiber organization	13 of 570	0.8	0.84	5.44e-05
GO:0061844	Antimicrobial humoral immune response	6 of 113	1.17	0.81	0.0011

GO:0051238	Sequestering of metal ion	3 of 11	1.88	0.77	0.0038
GO:0051336	Regulation of hydrolase activity	17 of 1011	0.67	0.75	3.90e-05
GO:0018149	Peptide cross-linking	4 of 37	1.48	0.74	0.0035
GO:0045087	Innate immune response	14 of 754	0.71	0.72	0.00017
GO:0001906	Cell killing	6 of 129	1.11	0.72	0.0023
GO:0043086	Negative regulation of catalytic activity	14 of 771	0.7	0.71	0.00020
GO:0006955	Immune response	19 of 1321	0.6	0.68	6.21e-05
GO:0030855	Epithelial cell differentiation	12 of 617	0.73	0.67	0.00061
GO:0051651	Maintenance of location in cell	5 of 97	1.16	0.61	0.0075
GO:0009605	Response to external stimulus	26 of 2355	0.49	0.6	3.60e-05
GO:0042981	Regulation of apoptotic process	19 of 1462	0.56	0.6	0.00023
GO:0044092	Negative regulation of molecular function	16 of 1143	0.59	0.58	0.00071
GO:0070488	Neutrophil aggregation	2 of 2	2.44	0.58	0.0159
GO:0065008	Regulation of biological quality	34 of 3654	0.41	0.57	1.04e-05
GO:0010941	Regulation of cell death	20 of 1651	0.53	0.57	0.00030
GO:0051248	Negative regulation of protein metabolic process	15 of 1038	0.6	0.57	0.0010
GO:2001242	Regulation of intrinsic apoptotic signaling pathway	6 of 169	0.99	0.56	0.0088
GO:0060429	Epithelium development	15 of 1069	0.59	0.55	0.0014
GO:0002376	Immune system process	23 of 2121	0.48	0.54	0.00026
GO:0006956	Complement activation	4 of 60	1.27	0.53	0.0170
GO:0050832	Defense response to fungus	4 of 62	1.25	0.52	0.0185
GO:0050790	Regulation of catalytic activity	24 of 2370	0.45	0.51	0.00043
GO:0006950	Response to stress	30 of 3358	0.39	0.5	0.00019
GO:0043066	Negative regulation of apoptotic process	13 of 891	0.61	0.5	0.0041
GO:0019731	Antibacterial humoral response	4 of 64	1.24	0.5	0.0205
GO:0042744	Hydrogen peroxide catabolic process	3 of 25	1.52	0.5	0.0258
GO:0042026	Protein refolding	3 of 25	1.52	0.5	0.0258
GO:2001233	Regulation of apoptotic signaling pathway	8 of 365	0.78	0.48	0.0124

GO:0032119	Sequestering of zinc ion	2 of 4	2.14	0.48	0.0337
GO:0006979	Response to oxidative stress	8 of 368	0.78	0.47	0.0130
GO:0050830	Defense response to Gram-positive bacterium	5 of 130	1.03	0.46	0.0239
GO:0031640	Killing of cells of another organism	4 of 71	1.19	0.46	0.0283
GO:0055076	Transition metal ion homeostasis	5 of 137	1.01	0.44	0.0289
GO:0070606	Sensory perception of chemical stimulus	9 of 503	0.7	0.43	0.0177
GO:0050896	Response to stimulus	50 of 7835	0.25	0.42	6.80e-05
GO:0032501	Multicellular organismal process	44 of 6490	0.27	0.42	0.00019
GO:0065009	Regulation of molecular function	26 of 3085	0.37	0.4	0.0035
GO:2001234	Negative regulation of apoptotic signaling pathway	6 of 230	0.86	0.4	0.0359
GO:0051246	Regulation of protein metabolic process	23 of 2622	0.39	0.38	0.0069
GO:0007010	Cytoskeleton organization	14 of 1229	0.5	0.36	0.0223
GO:0070887	Cellular response to chemical stimulus	22 of 2609	0.37	0.33	0.0177
GO:0042221	Response to chemical	29 of 4010	0.3	0.32	0.0146

Table S5. Functional category of proteins identified in IONP@TPC based on Gene Ontology analysis.

GO-term	Description	Count in network	Strength	Signal	FDR
GO:0001895	Retina homeostasis	12 of 78	2.16	6.62	1.70E-19
GO:0001894	Tissue homeostasis	13 of 238	1.71	4.22	2.46E-16
GO:0042592	Homeostatic process	15 of 1406	1	1.36	7.69E-10
GO:0050909	Sensory perception of taste	4 of 69	1.74	1.13	0.0018
GO:0045109	Intermediate filament organization	4 of 69	1.74	1.13	0.0018
GO:0042742	Defense response to bacterium	6 of 306	1.26	0.96	0.0015
GO:0070488	Neutrophil aggregation	2 of 2	2.97	0.96	0.0078
GO:0001580	Detection of chemical stimulus involved in sensory perception of bitter taste	3 of 37	1.88	0.85	0.0105
GO:0032119	Sequestering of zinc ion	2 of 4	2.67	0.84	0.0142
GO:0006959	Humoral immune response	5 of 268	1.24	0.73	0.0093
GO:0018119	Peptidyl-cysteine S-nitrosylation	2 of 6	2.5	0.73	0.0236
GO:0019730	Antimicrobial humoral response	4 of 149	1.4	0.71	0.0155
GO:0035425	Autocrine signaling	2 of 7	2.43	0.7	0.0276
GO:0050832	Defense response to fungus	3 of 62	1.66	0.66	0.0276
GO:0002544	Chronic inflammatory response	2 of 13	2.16	0.59	0.0490
GO:0031424	Keratinization	3 of 83	1.53	0.56	0.0451
GO:0052548	Regulation of endopeptidase activity	5 of 414	1.05	0.51	0.0351
GO:0098542	Defense response to other organism	7 of 989	0.82	0.46	0.0308

GO:0051707	Response to other organism	8 of 1328	0.75	0.44	0.0276
GO:0032501	Multicellular organismal process	18 of 6490	0.42	0.37	0.0018

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