**S1 Table. Genes involved in the innate immune response to bacterial pathogens.**

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| --- | --- | --- | --- |
| **Gene name** | **Protein name; description** | **Function** | **Reference** |
| ***Cp*** | Ceruloplasmin | Binds serum copper, loads transferrin with iron. | [1] |
| ***Bdh2*** | 3-Hydroxybutyrate dehydrogenase 2 | Facilitates the production of 2,5-dihydroxybenzoic acid (2,5-DHBA), a mammalian siderophore that is structurally similar to enterobactin and binds LCN2. | [2,3] |
| ***Hamp*** | Hepcidin | Binds to and internalizes ferroportin, sequestering iron within macrophages and hepatocytes. Decreases intestinal absorption of iron. | [4] |
| ***Lcn2*** | Lipocalin-2 | Sequesters catechol siderophores, including the mammalian siderophore 2,5-DHBA. Binding of 2,5-DHBA reduces the availability of free intracellular iron. | [2,5–8] |
| ***Ltf*** | Lactoferrin | Iron-binding glycoprotein responsible for sequestering the metal at mucosal surfaces.  | [9–12] |
| ***Slc40a1*** | Solute carrier family 40 member 1; ferroportin | Only known iron exporter, transports iron from the cytosol. Required for iron homeostasis. Expression is regulated by hepcidin. Also exports zinc, cobalt, nickel, and manganese.  | [13–19] |
| ***Slc11a2*** | Solute carrier family 11 member 2; divalent metal transporter 1 ((DMT1) also known as natural-resistance associated macrophage protein 2 (NRAMP2)) | Promotes uptake of dietary iron from the duodenal lumen by enterocytes. Facilitates transport of other divalent metals including manganese, cobalt, copper, zinc, nickel, lead, and cadmium.  | [20,21]  |
| ***S100a8*** | S100 calcium-binding protein A8; subunit of calprotectin | As a heterodimer with S100A9 it sequesters transition metals including iron, manganese, and zinc to inhibit bacterial growth. | [22,23] |
| ***S100a9*** | S100 calcium-binding protein A9; subunit of calprotectin | As a heterodimer with S100A8 it sequesters transition metals including iron, manganese, and zinc to inhibit bacterial growth. | [22,23] |
| ***Slc30a10*** | Solute carrier family 30 member 10; ZNT10 | Exports manganese from enterocytes and hepatocytes. Contributes to manganese homeostasis and alleviates manganese toxicity.  | [24–26] |
| ***Slc39a14*** | Solute carrier family 39 member 14; ZIP14 | Involved in manganese homeostasis. Promotes uptake of manganese, and subsequent excretion, from the liver and pancreas. Facilitates cellular uptake of divalent metals such as iron and zinc.  | [27–29] |

**S1 Table. Genes involved in the innate immune response to bacterial pathogens (cont’d).**

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| --- | --- | --- | --- |
| **Gene name** | **Protein name; description** | **Function** | **References** |
| ***Slc39a8*** | Solute carrier family 39 member 8; ZIP8 | Cellular uptake of divalent metals including zinc, iron, manganese, and cadmium from the extracellular space into the cytoplasm.  | [30–32] |
| ***Slc11a1*** | Solute carrier family 11 member 1; NRAMP1 | Transports divalent metals, primarily iron and manganese, out of the phagosome. Provides resistance to intracellular pathogens.  | [33–37] |
| ***Mt1*** | Metallothionein 1 | Small cysteine-rich protein involved in heavy metal storage, detoxification, and transport. Can coordinate up to seven molecules of zinc or cadmium. | [38,39] |
| ***Mt2*** | Metallothionein 2  | Small cysteine-rich protein involved in heavy metal storage, detoxification, and transport. Can coordinate up to seven molecules of zinc or cadmium. | [39,40] |
| ***Slc30a2*** | Solute carrier family 30 member 2; ZNT2 | Zinc transporter that may protect cells from cellular toxicity by facilitating zinc import into vesicular compartments, secretes zinc from mammary glands. | [41,42] |
| ***Slc30a5*** | Solute carrier family 30 member 5; ZNT5 | May transport zinc into secretory granules of pancreatic beta cells, involved in activation of alkaline phosphatases. | [43,44] |
| ***Slc30a1*** | Solute carrier family 30 member 1; ZNT1 | Exports cellular zinc into extracellular space. Attenuates growth of intracellular pathogens.  | [45] |
| ***Slc39a11*** | Solute carrier family 39 member 11; ZIP11 | Cellular zinc importer. Facilitates zinc uptake from the stomach and colon.  | [46,47] |
| ***Slc39a4*** | Solute carrier family 39 member 4; ZIP4 | Required for zinc homeostasis. Localized to apical surface of enterocytes and facilitates uptake of dietary zinc.  | [48,49] |
| ***Slc39a7*** | Solute carrier family 39 member 7; ZIP7 | Transports zinc from the Golgi apparatus and endoplasmic reticulum into the cell.  | [50,51] |
| ***Slc30a4*** | Solute carrier family 30 member 4; ZNT4 | Provides zinc to zinc-dependent proteins in the Golgi apparatus. Required for zinc export in mammary cells, deficiency results in lethal milk mouse.  | [52,53] |
| ***Slc30a7*** | Solute carrier family 30 member 7; ZNT7 | Transports cytoplasmic zinc into the Golgi apparatus for zinc storage. Involved in activation of alkaline phosphatases. | [43,54] |
| ***Flvcr1b*** | Feline leukemia virus subgroup C receptor 1 | Exports heme from mitochondria into cytosol. | [55] |
| ***Hba1*** | Alpha hemoglobin; subunit of hemoglobin | Subunit of hemoglobin, the iron-containing, oxygen-transporting component of red blood cells.  | [56] |
| ***Hmox1*** | Heme oxygenase 1 | Catalyzes the degradation of heme to release biliverdin, free ferrous iron, and carbon dioxide. Inducible and thought to confer resistance to oxidative stress. | [57,58] |

**S1 Table. Genes involved in the innate immune response to bacterial pathogens (cont’d).**

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| --- | --- | --- | --- |
| **Gene name** | **Protein name; description** | **Function** | **References** |
| ***Cybb*** | Cytochrome B-245 beta chain; subunit of Cytochrome B-245 and NADPH oxidase | Together with cytochrome B-245 alpha chain forms the main catalytic subunit of NADPH oxidase (Nox2), which is the major microbicidal oxidase of phagocytes. | [59,60] |
| ***Mpo*** | Myeloperoxidase | Peroxidase enzyme that produces hypohalous acids which kill bacteria and other pathogens. Released upon neutrophil degranulation.  | [61] |
| ***Nos2*** | Nitric oxide synthase 2 | Enzyme catalyzing the conversion of L-arginine to nitric oxide, a reactive free radical. NOS2 is inducible and in mice contributes to the defense against intracellular pathogens.  | [62–64] |
| ***Sod1*** | Superoxide dismutase 1; [Cu-Zn]-SOD | Copper and zinc requiring enzyme that catalyzes the conversion of superoxide radicals to hydrogen peroxide and oxygen. Localized to cytosol. Involved in protection against oxidative stress. | [65] |
| ***Sod2*** | Superoxide dismutase 2; [Mn]-SOD | Manganese requiring enzyme that catalyzes the conversion of superoxide radicals to hydrogen peroxide and oxygen. Localized to mitochondria. Involved in protection against oxidative stress.  | [65] |
| ***S100a7*** | Psoriasin  | Secreted by skin epithelial cells, sequesters zinc, activates neutrophils, and exhibits antibacterial activity. | [66–68] |
| ***Il22*** | Interleukin 22 | Maintains barrier function, promotes recruitment of immune cells, promotes defense mechanisms. | [69] |
| ***Gapdh*** | Glyceraldehyde-3-phosphate dehydrogenase | Housekeeping. Enzyme catalyzing the conversion of glyceraldehyde-3-phosphate to D-glycerate 1,3-bisphosphate | [70] |
| ***Hprt1*** | Hypoxanthine Phosphoribosyltransferase 1. | Housekeeping. Enzyme that catalyzes the conversion of hypoxanthine to inosine monophosphate and guanine to guanosine monophosphate. | [70] |
| ***Pgk1*** | Phosphoglycerate kinase 1  | Housekeeping. Enzyme that catalyzes the conversion of 1,3-diphosphoglycerate to 3-phosphoglycerate. | [70] |
| ***Tubb5*** | Tubulin beta-5 chain | Housekeeping. Major component of microtubules.  | [70] |

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