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REVIEW ARTICLE

Genetic diseases conferring resistance to infectious diseases

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Abstract This review considers available evidence for mechanisms of conferred adaptive advantages in the face of specific infectious diseases. In short, we explore a number of genetic conditions, which carry some benefits in adverse circumstances including exposure to infectious agents. The examples discussed are conditions known to result in resistance to a specific infectious disease, or have been proposed as being associated with resistance to various infectious diseases. These infectious disease—genetic disorder pairings include malaria and hemoglobinopathies, cholera and cystic fibrosis, tuberculosis and Tay-Sachs disease, mycotic abortions and phenylketonuria, infection by enveloped viruses and disorders of glycosylation, infection by filoviruses and Niemann–Pick C1 disease, as well as rabies and myasthenia gravis.

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We also discuss two genetic conditions that lead to infectious disease hypersusceptibility, although we did not cover the large number of immunologic defects leading to infectious disease hypersusceptibilities. Four of the resistance-associated pairings (malaria/hemogloginopathies, cholera/cystic fibrosis, tuberculosis/Tay-Sachs, and mycotic abortions/phenylketonuria) appear to be a result of selection pressures in geographic regions in which the specific infectious agent is endemic. The other pairings do not appear to be based on selection pressure and instead may be serendipitous. Nonetheless, research investigating these relationships may lead to treatment options for the aforementioned diseases by exploiting established mechanisms between genetically affected cells and infectious organisms. This may prove invaluable as a starting point for research in the case of diseases that currently have no reliably curative treatments, *e.g.*, HIV, rabies, and Ebola.

Introduction

Some genetic conditions can confer resistance to specific infectious diseases. It is theorized that these genotypes are preferentially maintained in populations regularly exposed to certain infectious agents, especially those with high virulence. The protection afforded by these conditions has provided the impetus for understanding these genetic mechanisms of resistance that can potentially be exploited for developing novel therapies or improving current therapies. This review describes a number of these resistances, the molecular bases for each resistance, and therapeutic implications from the resistance. We also discuss two relationships that lead to infectious disease hypersusceptiblity, which also provides valuable information that has been used or will be used to develop therapies.

This review is organized based on a description of four genetic conditions/infectious resistance pairings in which there appears to be a selection pressure. The first of which is sickle cell anemia (and other hemoglobinopathies) and malaria in geographic regions in which the malaria-causing parasite and vector is endemic.[1] Interestingly, this disease complex leads to increased susceptibility to respiratory infections through a mechanism independent of hemoglobin.

The second pair involving a putative selection pressure is cystic fibrosis, which involves a mutation encoding a defective chloride channel. In unaffected individuals, this channel can be exploited by diarrhea-producing enteropathogens. The derangement of this channel may result in resistance to the enteric effects of cholera, and the cystic fibrosis genotype has a higher prevalence in regions in which cholera is or was endemic.[2]

The third selection pressure-associated pair involves Tay-Sachs disease, a lysosomal storage disease characterized by deficiency of hexosaminidase A. Historically, Ashkenazi Jews had a high prevalence of the Tay-Sachs allele and a low prevalence of tuberculosis caused by *Mycobacterium tuberculosis*, a relationship that may be related to crowded environments associated with this ethnic population and concentration of *Mycobacterium tuberculosis*.[3]

Yet another relationship with a putative selection pressure is phenylketonuria, a metabolic genetic disorder in which phenylalanine accumulates to toxic levels in the affected individual. Women who are heterozygotes for the disorder are significantly less sensitive to the abortifacient activities of the mycotoxin designated as ochratoxin A. This relationship appears to be relevant in moist regions in which pathogenic fungi are endemic.[4]

Three other relationships do not appear to have a selection pressure, one of which is congenital disorder of glycosylation 2b (CDG-IIb) which leads to impaired glycosylation of proteins and thus confers resistance to viruses that have glycosylated capsids.[5] The second "spurious" relationship involves myasthenia gravis in which autoantibodies attack the acetylcholine receptor that is coincidentally exploited as a docking site for the rabies virus; this competition may lead to resistance to rabies.[6] Finally, Niemann—Pick C1 disease is a lysosomal storage disorder in which a faulty cholesterol transporter leads to abnormal accumulation of cholesterol within lysosomes. The Ebola virus apparently uses this transporter and thus its dysfunction impairs viral pathogenicity in patients with Niemann—Pick C1 disease.[7]

It is of note that a particular genetic disorder leads to infectious disease hypersusceptibility, and this relationship has provided the basis for a preventative. Specifically, the relationship between hemosiderosis and typhoid fever has led to the development of a vaccine that intervenes in this relationship.

This literature review discusses the potential benefits garnered from further study of the pathways associated with these genetic conditions and infectious disease resistance (or hypersusceptibility). A summary of the current state of research is presented in Table 1. The more we understand about the link between these genetic conditions and the infectious disease resistances, the easier it will be to exploit the mechanism for therapeutic uses. When trying to develop therapies, the most difficult part is often finding a starting point for research. The nature of the human condition provides us with these starting points.

Resistance to malaria and the sickle trait

Resistance to malaria has been linked to a number of conditions including hemoglobinopathies, enzymopathies, and the absence of an erythrocyte surface protein. Other

Table 1 Summary of the genetic disorder and infectious disease pairings described herein.

Genetic disorder and infectious disease	Genetic basis for the disorder	Clinical manifestations of the disorder	Potential therapies for the disorder or the infection based on the relationship	Resistance or hypersusceptibility
Sickle cell trait and malaria	Mutations encoding hemoglobin or enzymes vital to erythrocyte metabolism	Anemia	Hydroxyurea to increase the expression of a hemoglobin subtype that is unaffected by malaria[8]	Resistance
Sickle cell trait and pneumococcal pneumonia	*ibid*	*ibid*	*ibid*	Hypersusceptibility
Cystic fibrosis and cholera	Mutations in a gene encoding a chloride channel (CFTR)	Excessive respiratory secretions that provide a hospitable environment for bacterial growth	Inhibiting the CFTR may prevent the gastrointestinal fluid loss associated with cholera[2]	Resistance
Tay-Sachs disease and tuberculosis	Mutations in the gene encoding α-hexosaminidase	Mental and physical disabilities leading to death in infants	Up-regulation or activation of -hexosaminidase may have mycobactericidal effects[18]	Resistance
Phenylketonuria and mycotic abortions	Mutations in the gene encoding phenylalanine hydroxylase	Mental retardation, seizures, *etc*.	Inhibiting phenylalanine hydroxylase, minimizing phenylalanine intake, or glycomacropeptides, (nutritives that curb aromatic amino acids in the plasma of the host[33]) may prevent the abortions although these strategies may be deleterious to the fetus	Resistance
Congenital disorder of glycosylation IIb and viral infections	Mutations in the gene encoding mannosyl-oligosaccaride glucosidase	Developmental disorders, hypotonia, hypoglycemia, protein-losing enteropathy	Treating or preventing viral infections with MOGS inhibitors (castanospermine, N-butyldeoxynojirimycin, and deoxynojirimycin[19–22]) or other glycosylation inhibitors (2-deoxyglucose and tunicamycin[23])	Resistance
Myasthenia gravis and rabies	Auto-antibodies directed at cholinergic receptors	Paralysis and respiratory failure	Cholinergic antagonists may block rabies virus translocation	Resistance
Niemann–Pick C1 disease and filovirus infection	Mutations that lead to NPC1 deficiencies in lysosomes	Hepatospleno-megaly, thrombocytopenia, and neurologic deficits	NPC1 inhibition for preventing filovirus infection	Resistance
Hemosiderosis and typhoid fever	Mutations in genes encoding for proteins that regulate erythrocytic iron	Polycythemia and hemorrhage	Blockade of the siderophore receptor protein to prevent salmonelloses[32]	Hypersusceptibility

genetic conditions can lead to resistance to malaria, but these three specific conditions provide specific insights into anti-malarial strategies.

Hemoglobinopathies

Thalassemias and other hemoglobinopathies, including sickle cell disease, are among the most common single-gene disorders in humans. Thalassemia disorders arise from alterations in either the α or β globin chain of hemoglobin. In the case of sickle cell disease, hemoglobin S is dysfunctional while fetal hemoglobin (hemoglobin F) is spared. Malaria susceptibility and hemoglobin S are directly linked; the dysfunctional hemoglobin S ultimately prevents further erythrocyte invasion and intra-erythrocyte growth of *Plasmodium*. That is, infection still occurs but the disease does not progress. Based on these findings, hydroxyurea has been explored as a chemotherapeutic agent that induces the production of wild-type fetal hemoglobin (hemoglobin F), which serves as a fully functional oxygen-carrying protein. The hydroxyurea-mediated increased expression of hemoglobin F leads to decreased expression of hemoglobin S, ultimately minimizing malarial susceptibility.[8]

Enzymopathies

Glucose-6-phosphate dehydrogenase (G6PD) deficiency results in erythrocytes that are more prone to suffering damage. The invasion of malarial parasites exacerbates this condition, making the cells highly susceptible to phagocytosis. Infected G6PD-deficient erythrocytes are morphologically different compared to non-infected ones and are thus hypersusceptible to phagocytosis. Another enzymopathy involves pyruvate kinase deficiency leading to altered membrane rigidity of erythrocytes, thus preventing *Plasmodium* invasion. Moreover, pyruvate kinase deficiency significantly reduces the intracellular concentration of glucose, a vital source of energy for the intra-cellular life cycle of *Plasmodium*. As such, both G6PD and pyruvate kinase have been recognized as important drug targets against *P. falciparum*.[9]

Erythrocyte polymorphisms

In contrast to thalassemais and enzymopathies, the Duffy antigen represents an extracellular-based resistance mechanism. The Duffy antigen, a receptor for chemokines, is present on the surface of erythrocytes. This antigen is also an obligatory binding site for the malarial toxin secreted by *P. vivax*. A point mutation in the Duffy gene leads to lack of expression of the encoded receptor and thus negates *P. vivax* toxin attachment. This innocuous polymorphism is the most common in Papua New Guinea and Western Africa, which may explain why infection of *P. vivax* is uncommon in these areas of the world.[10]

Sickle cell anemia and pneumococcal infections

While sickle anemia confers resistance to malaria, the condition renders the patient hypersusceptible to pneumococcal infections. Because of the hypoxia associated with the anemia, the respiratory endothelium is hyperactive and overexpresses the receptor for platelet-activating factor.[11] This receptor is a docking site for *Streptococcus pneumoniae*,[12] and thus the receptor hyperexpression provides ample attachment sites for the infection by this bacterial pathogen.

In summary, the molecular bases of malarial resistance vary but a common theme involves the structure of the erythrocyte. These mechanisms of resistance have provided insight into pharmacologic targeting of the malarial infection. It is fortuitous that the innocuous absence of the Duffy antigen leads to resistance to a certain type of malaria. Targeting the Duffy antigen is therefore a meritorious strategy for treatment, and it will be advantageous to find an orthologous protein for *P. falciparum* infection. Indeed, this type of resistance mechanism is the most useful since the lack of this particular protein has no apparent consequence to the individual, and thus targeting the protein should have little adverse effect.

Cystic fibrosis and resistance to cholera

Cystic fibrosis (CF) is caused by an autosomal recessive mutation in a gene that codes for a chloride channel designated as the cystic fibrosis transmembrane conductance regulator (CFTR).[13,14] Homozygous recessive individuals express a defective chloride channel, and as a result are unable to osmotically decrease viscosity of mucous secretions. This increased viscosity leads to decreased ciliary mucus clearance in the lungs and a rise in susceptibility to pulmonary infections, ultimately leading to respiratory failure. Enterocyte secretions are similarly effected as a result of the defective chloride transport in the gut. Current treatment of CF involves intensive regimens that improve the hydration of secretions (promoting ciliary clearance), as well as nutritional support, prevention of pulmonary infections, and management of chronic airway inflammation.[14]

CF has a high fatality rate[13] yet there is an increased prevalence in those of Caucasian/European ancestry, relative to those of African descent.[14] The prevalence of heterozygous CF carriers is even higher and the current differences in allele frequencies have been attributed to cholera outbreaks in the 19th century. This is due to the supporting evidence that suggests CF heterozygousity conferred a survival advantage during the outbreak periods.[14]

One proposed mechanism for an evolutionary advantage afforded by CFTR mutations relates to the virulence of cholera in affected individuals. The etiologic agent, *Vibrio cholerae*, produces a toxin that constitutively activates guanine nucleotide-binding proteins that in turn hyperactivate the same chloride channels affected by mutations in the CFTR gene.[13] This hyperactivation causes a profound secretory diarrhea (see Fig. 1). In murine model studies, heterozygous mice were less susceptible to the cholera toxin and consequently did not suffer from symptoms as severe as seen in mice with normal CFTR function. It is postulated that this result was due to heterozygous mice having only 50% of the functioning chloride channels compared with a wild-type mouse. The decrease in functioning chloride channels

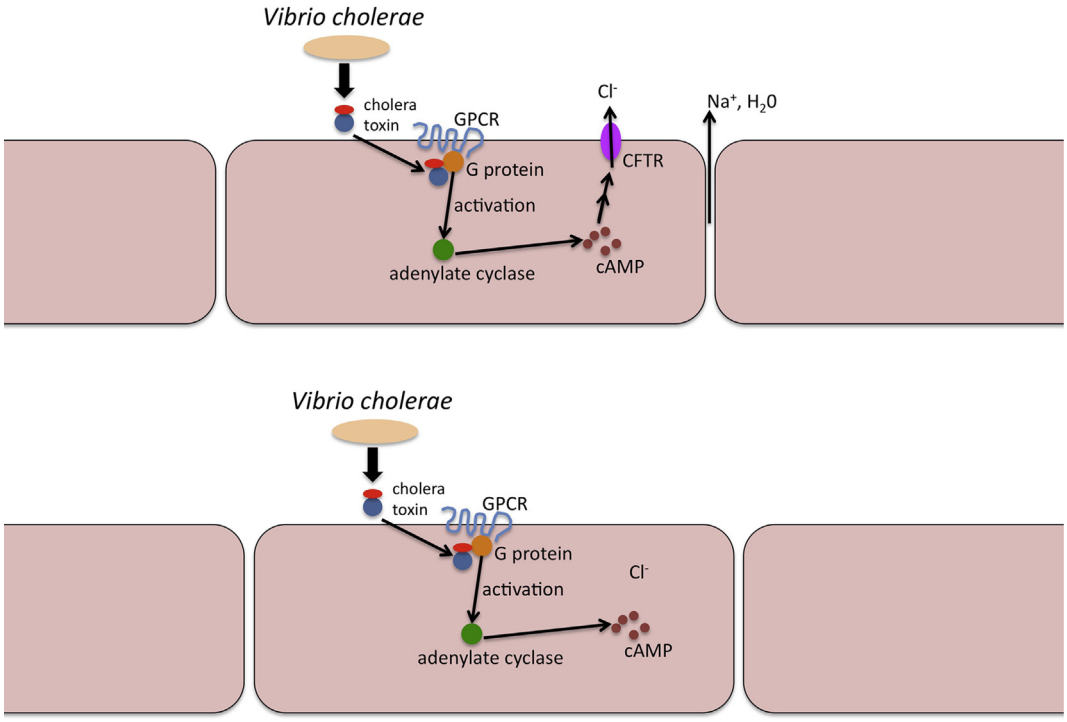

Figure 1 Top, cartoon of the mechanism of diarrhea mediated by *Vibrio cholerae* in intestinal cells from an individual with an intact and fully functional CFTR. The bacteria releases a toxin that constitutively activates an intracellular G protein, which consequently activates adenylate cyclase. Adenylate cyclase catalyzes an ATP→cAMP reaction and the product of this reaction eventually activates CFTR. The activated CFTR facilitates a chloride ion movement into the gut lumen, which causes an osmotic loss of sodium ions and water into the lumen. The net result is a watery diarrhea. Bottom, cartoon of the mechanism of resistance to *Vibrio cholerae* in intestinal cells from an individual with one or two alleles for the cystic fibrosis phenotype. As per the top panel, the bacteria releases a toxin, the G protein is activated, adenylate cyclase is activated and cAMP is produced. Because of the mutant allele(s) encoding the CFTR, there are either inadequate numbers or a complete absence of fully functional CFTRs to facilitate the chloride loss into the lumen.

reduced the mass influx of ions, thus ameliorating diarrhea.[13] Research concerning the CFTR chloride channel and its role in intestinal secretions resulted in potentially novel therapies for cholera. The volume of fluid losses seen in cholera cases could be reduced by pharmacologic inhibition of CFTR and chloride secretions.[2]

Tay-Sachs disease and resistance to tuberculosis

Tay-Sachs is a rare genetic disease that results in an abnormal accumulation of neuronal lipids caused by a defective lysosomal enzyme, α-hexosaminidase. Alleles for this disease are more prevalent in certain populations, the most well-known being the Ashkenazi Jews. Although controversial, it has been hypothesized that perpetuation of this allele is associated with the selective advantage it provides protection against *Mycobacteria tuberculosis*, the causative agent for the highly infectious disease tuberculosis. Rotter et al[15] suggest that Ashkenazi Jews were subjected to a stronger selective force than other ethnic groups due to segregation, crowded town environments, and a lack of immigration. Observations of descendent populations revealed a lower frequency of tuberculosis-related deaths in Ashkenazi Jews when compared to non-Jewish populations from similar areas.[15] Another study showed that the frequency of the Tay-Sachs gene in Ashkenazi Jews correlated with areas of the highest tuberculosis incidence,[16] suggesting a protective effect.

It is now known that carriers of the Tay-Sachs gene have increased production of the β-subunit of hexosaminidase[17] and that the β-subunit is closely associated with increased host defense against mycobacteria.[18] Additionally, cell surface bactericidal activity declined in the absence of β-hexosaminidase. It is therefore possible that β-hexosaminidase is cytotoxic to *Mycobacteria tuberculosis*, making the organism more susceptible to macrophage attack.[18] In the advent of drug-resistant tuberculosis, developing drugs that up-regulate or maintain β-hexosaminidase may prove beneficial for the treatment of tuberculosis while circumventing concerns of antibiotic resistance.

Phenylketonuria and resistance to fungal-mediated abortions

Phenylketonuria (PKU) is an autosomal recessive metabolic disorder in which toxic levels of phenylalanine accumulate due to a non-functional hepatic enzyme, phenylalanine hydroxylase. Historically, physicians observed that women who were PKU carriers had a much lower than average incidence of miscarriages. Woolf et al[4] published data showing that women who were heterozygous for the PKU

disorder displayed a significantly reduced rate of spontaneous abortions, when compared to wild-type homozygous individuals. This was the most prevalent in Scotland and Ireland, where the consistent damp climate promotes the growth of mold and fungi on grains and beans. *Aspergillus* spp. produces a mycotoxin known as ochratoxin A which is teratogenic at low doses and potentially lethal at high doses. In the case of pregnant women, ochratoxin A can cross the placenta and cause spontaneous abortions. This toxin, being an N-acyl derivative of phenylalanine, is a competitive inhibitor of phenylalanine in the phenylalanyl-tRNA synthetase-catalyzed reaction thus preventing protein synthesis, which can be reversed by introducing phenylalanine which is in excess in PKU individuals. The high frequency of the PKU gene present in women from this particular section of Europe, as well as that observed in Yemenite Jews, may help to protect against sudden miscarriages, thus ensuring a normal pregnancy.[4]

Congenital disorder of glycosylation 2b and resistance to viral infections

Resistance to glycosylation-dependent viral infections (*e.g.*, HIV-1, dengue, herpes simplex 2, hepatitis C, and influenza) has been linked to congenital disorder of CDG-IIb. This condition is caused by defective mannosyl-oligosaccaride glucosidase (MOGS), which is the initial enzyme in the processing phase of N-linked oligosaccharides. In this extremely rare condition, the process of attaching N-glycans to proteins is disrupted, resulting in dysfunctional glycoprotein synthesis.

Due to the dependence of enveloped viruses on proper host cell glycosylation for the assembly of their capsid proteins, it appears that the defective glycosylation in patients with CDG-IIb hinders cellular entry, cellular egress, and viral replication for glycosylation-dependent enveloped viruses. Evidence to support the theory of lowered susceptibility in those with defective glycosylation has been documented through a case study of two siblings with CDG-IIb. These individuals had appropriate immune responses to non-replicating viruses, but failed to mount a humoral response to live glycosylation-dependent virus vaccines MMR and varicella.[5] Furthermore, the MOGS inhibitors castanospermine, N-butyldeoxynojirimycin, and deoxynojirimycin have been shown to lower replication in cells infected with enveloped viruses such as HIV, dengue, hepatitis B and C, and herpes simplex virus-2.[19–22] These findings are additionally supported by the antiviral use of 2-deoxyglucose and tunicamycin, both of which truncate glycan polymers and attenuates the replication of certain viruses.[23] In summary, the antiviral effects of defective glycosylation provide a strong basis for continued research on the next generation of MOGS inhibitors.

Myasthenia gravis and resistance to rabies

Myasthenia gravis (MG) is an autoimmune disorder that involves the destruction of acetylcholine receptors (AChR) by AChR-specific antibodies. The antibodies produced in MG patients effectively inhibit neural transmission at the neuromuscular junction by accelerated degradation of receptors, blocking of acetylcholine-binding sites, and degradation and simplification of synaptic folds.[24] AChRs are abundant in the post-synaptic nerve endings of the neuromuscular junction, and the loss of these receptors leads to pronounced muscle weakness due to inhibited neural signal transmission.

The rabies virus is a neurotropic rhabdovirus that causes inflammation in the nervous systems of warm-blooded animals. Although it is known that the rabies virus may enter the CNS through several routes other than muscle tissue,[25,26] research indicates that entry of the virus into the peripheral nervous system (PNS) may benefit significantly from replication in skeletal muscles. Furthermore, the rabies virus preferentially enters through the neuromuscular junctions of both the intrafusal and extrafusal muscles.[27,28] Infiltration of these muscles is thought to be augmented by the ability of the rabies virus to bind to nicotinic AChRs, whereupon the virus enters via receptor-mediated endocytosis.[28] Following initial infection, the virus enters the PNS where it undergoes replication in the dorsal-root ganglion and travels to the CNS through retrograde transport mechanisms.[29] While we are unaware of documented cases in the literature, to the extent that MG exerts its effects on musculature by either occupying or attacking nicotinic AChRs, it is reasonable to suppose that MG patients will show a diminished likelihood of rabies infection. Even if MG resulted only in a delay in the spread of the rabies virus to the PNS, this interval may create the possibility for immune clearance and additional medical intervention following initial virus introduction.[30] Further research on the different mechanisms behind AChR degradation in MG patients may offer insight in to new medications to better prevent rabies virus pathogenicity.

Niemann—Pick C1 disease and resistance to filoviruses such as Ebola and Marburg

Niemann—Pick C1 disease is a lysosomal storage disorder in which cholesterol abnormally accumulates within lysosomes. This accumulation occurs due to a shortage of the NPC1 protein that normally transports cholesterol out of the lysosome.[7] Carette et al[7] used an *ex vivo* assay and associated NPC1 with the Ebola virus infection process. Further studies revealed that the Ebola virus poorly infected Niemann—Pick C1 disease patient fibroblasts, while normal infection was observed when expression of wild-type NPC1 was restored. NPC1-mediated infection was also observed with another filovirus, the Marburg virus. The discovery of the NPC1-filovirus relationship has raised the possibility that Ebola and Marburg virus outbreaks could be prevented by drugs that block the action of NPC1.

Hemosiderosis and hypersusceptibility to typhoid fever

Hemosiderosis is a genetic condition leading to excess hemosiderin and thus excess iron in the blood. *Salmonella enterica* is an enteric pathogen that can cause a systemic infection designated as typhoid fever. *Salmonella* are

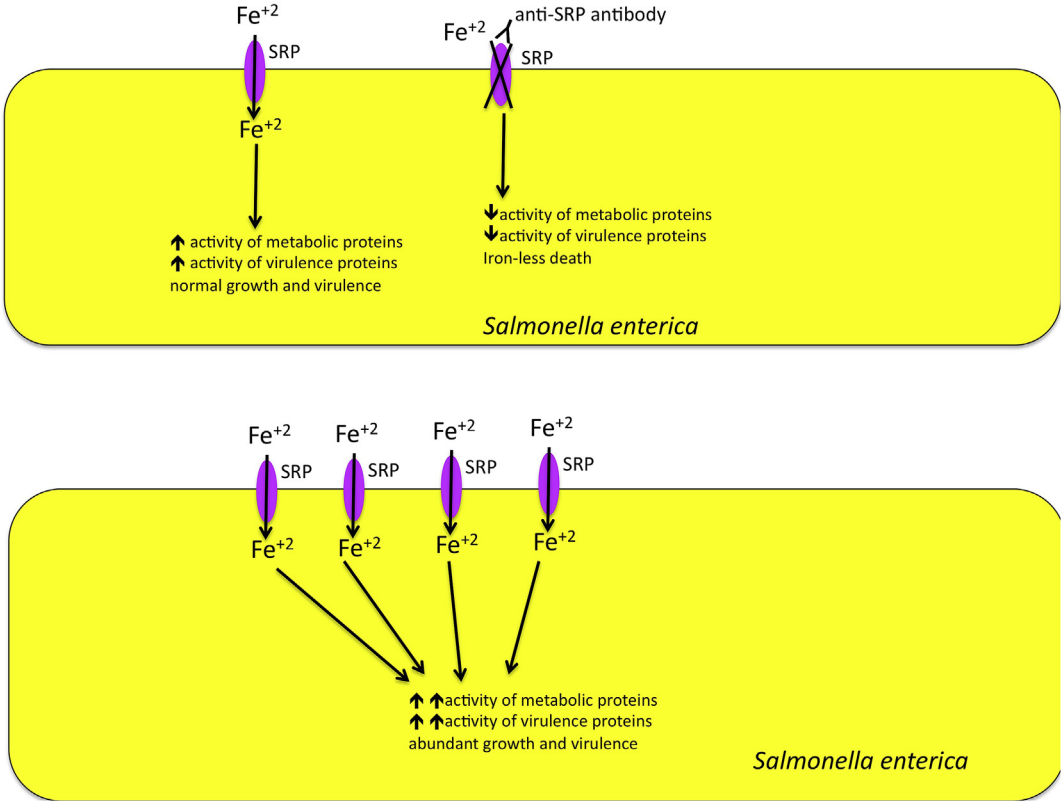

Figure 2 Top, cartoon of the siderophore receptor protein (SRP) and its importance for the survival and growth of *Salmonella*. The SRP serves as an iron sieve that is needed for the activation of iron-dependent metabolic and virulence proteins as part of normal *Salmonella* physiology. The SRP vaccine yields an anamnestic response resulting in anti-SRP antibodies that block the iron transport through the SRP. The iron depletion ultimately leads to death of the microbe. Bottom, hemosiderosis and hypersusceptibility to typhoid fever depicted by the activation of *Salmonella* survival and virulence in the abundance of iron in an individual with hemosiderosis. The SRP serves as an iron sieve that is needed for the activation of iron-dependent metabolic and virulence proteins as part of normal *Salmonella* physiology. The excess of iron in the blood leads to ample activation of *Salmonella* metabolic and virulence proteins, culminating in salmonellosis (*a.k.a.* typhoid fever).

dependent upon the intake of iron and thus the abundance of iron can lead to enhanced susceptibility to typhoid fever in patients afflicted with hemosiderosis.[31] This information has been used to develop an anti-*Salmonella* vaccine that blocks iron intake by the bacteria.[32] Details of these processes are presented in Fig. 2.

Conclusions

The examination of genetic conditions that confer resistance to infectious diseases presented in this article highlights mechanisms that could be exploited for potential therapies. We first discussed genetic conditions that have persisted to protect populations from considerable calamity due to widespread prevalence of an infectious agent. Epidemiological data evaluating the spread of infectious agents in societies with resistant subpopulations provided the impetus for the further study of resistance against malaria, cholera, tuberculosis, and fungal mediated abortions. It is now agreed that genetic conditions persisted to offer resistance, which in turn enables the discovery of potential therapeutic mechanisms. In light of this, other genetic conditions are being explored to discover ways in which we can combat some of the most dangerous infectious diseases such as HIV, rabies, and Ebola, for which there are no known cures. We have presented these relationships to serve as an entry point for discussions regarding therapy development, not only for the resistance mechanisms discussed in this article, but also for other discoverable mechanisms that could prove beneficial against infectious diseases.

Conflicts of interest

All authors have none to declare.

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