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REVIEW

Mx genes: host determinants controlling influenza virus infection and trans-species transmission

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Abstract

The human MxA protein, encoded by the interferon-inducible *MX1* gene, is an intracellular influenza A virus (IAV) restriction factor. It can protect transgenic mice from severe IAV-induced disease, indicating a key role of human MxA for host survival and suggesting that natural variations in *MX1* may account for inter-individual differences in disease severity among humans. MxA also provides a robust barrier against zoonotic transmissions of avian and swine IAV strains. Therefore, zoonotic IAV must acquire MxA escape mutations to achieve sustained human-to-human transmission. Here, we discuss recent progress in the field.

Introduction

Infections with seasonal influenza A viruses (IAV) are usually self-limiting, but in rare cases may become life-threatening or even fatal. The striking inter-individual variability in disease outcome is best explained by pre-existing immunity, co-morbidity, or age. In previously healthy non-vaccinated children and young adults, however, the cause for fatal influenza pneumonia is less obvious. Recent studies revealed that alterations in genes controlling innate immunity are involved in such cases (Casanova and Abel 2018; Ciancanelli et al. 2016; Zhang et al. 2019). Interestingly, genetic susceptibility to devastating influenza does not appear to be a polygenic trait, but is determined by defects in single genes that govern non-redundant pathways of type I (α/β) and type III (λ) interferon (IFN) responses. Critical genes identified so far are either involved in induction of type I and type III IFNs (TLR3, IRF7) (Ciancanelli et al. 2015; Lim et al. 2019), IFN production by plasmacytoid dendritic cells (GATA2) (Sologuren et al. 2018) or are part of the IFN signaling pathway required for antiviral action (IRF9) (Hernandez et al. 2018). Surprisingly, however, no clear defects have yet been found in type I and type III IFN-stimulated genes (ISGs). The only alterations in a gene associated with severe seasonal influenza in hospitalized patients were two single nucleotide polymorphisms (SNP) in *IFITM3*. One, rs12252, leads to a truncation (Everitt et al. 2012; Xuan et al. 2015; Zhang et al. 2013), and the other, rs34481144i, to diminished expression and impaired recruitment of immune CD8+ T cells into the infected airways (Allen et al. 2017). Still, the role of *IFITM3* in human influenza infections remains controversial (Mills et al. 2014; Williams et al. 2014; Zani and Yount 2018).

Much experimental evidence indicates that the human *MX1* gene may also play a critical role in the outcome of human IAV infections. *MX1* is located on the long arm of chromosome 21 (map position 21q22.3) and contains 17 exons extending over 33 kb (Horisberger et al. 1988; Tazi-Ahnini et al. 2000). It encodes a large GTPase, MxA, which mediates broad resistance to influenza and other viruses both in cell culture (Aebi et al. 1989; Haller et al. 2015) and transgenic mice (Deeg et al. 2017; Hefti et al. 1999; Pavlovic et al. 1995). Interestingly, there are humans harboring allelic variants in *MX1* (Duc et al. 2012; Graf et al. 2018; Tazi-Ahnini et al. 2000) in heterozygous or homozygous form, but none of these variants have so far been linked to enhanced influenza virus susceptibility (Ciancanelli et al. 2016; Graf et al. 2018). Nevertheless, as outlined in this review, *MX1* remains a strong candidate gene for controlling influenza virus susceptibility in humans.

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From *Mx1*-positive mice to human *MX1*

Early studies on innate *Mx*-mediated resistance in mice paved the way for the characterization of the human *MX1* gene (Aebi et al. 1989). The discovery of the dominant antiviral resistance gene *Mx* (for "myxovirus resistance") in a rare inbred mouse strain (A2G) has recently been described in detail (Haller et al. 2018). *Mx1*-bearing mice survive infection with mouse-adapted IAV at doses that are lethal for standard inbred strains. The *Mx1* gene is located on chromosome 16 in a region that is syntenic with the long arm of human chromosome 21 (Reeves et al. 1988). *Mx1* is functional in wild mouse species (Haller et al. 1987) and wild mouse-derived strains (Ferris et al. 2013; Jin et al. 1998; Maurizio et al. 2018; Nurnberger et al. 2016; Vanlaere et al. 2008) and may protect wild mice from infection with influenza-like viruses transmitted by ticks (Haller et al. 1995) and possibly other pathogens. The *Mx1* gene is defective in all standard laboratory mouse strains due to large deletions or nonsense mutations that destroy Mx1 protein function (Staeheli et al. 1988). Defective alleles also occur in wild mice (Haller et al. 1987) and must have been introduced into laboratory mice during early inbreeding (Guenet and Bonhomme 2003). As a consequence, most studies on influenza viruses are inadvertently performed in *Mx1*-null mice that lack this essential component of innate immunity and may lead to wrong conclusions regarding influenza virus pathogenicity and the anti-influenza activity of IFNs (Haller et al. 2018; Iwasaki 2016).

It is now well established that the efficacy of both type I and type III IFNs against influenza viruses in mice rely on *Mx1* and that *Mx1*-competent mice should be used to study antiviral responses (Bradley et al. 2019; Iwasaki 2016; Klinkhammer et al. 2018; Mordstein et al. 2008; Nurnberger et al. 2016; Pillai et al. 2016; Tumpey et al. 2007). The importance of the mouse *Mx1* locus in controlling IAV susceptibility has been verified in the unbiased mouse collaborative cross project which displays the breadth of host responses found in outbred populations and best reflects the situation in humans in which a functional *MX1* gene is present on an outbred genetic background (Ferris et al. 2013; Leist et al. 2016; Maurizio et al. 2018).

Genetic defects in IFN signaling and *Mx* gene expression

Mx genes possess IFN-responsive promoter regions (Asano et al. 2003; Gerardin et al. 2004; Hug et al. 1988) and are strongly expressed upon signaling by type I or type III IFNs. Type I IFNs signal through the heterodimeric type I IFN receptor (IFNAR1/IFNAR2), whereas type III IFNs use their cognate IFN-lambda receptor (IFNLR), composed of IFN-lambda receptor 1 and IL-10 receptor subunit-β. Upon ligand binding, both receptors activate the signal transducer and activator of transcription factors (STAT1 and STAT2) that together associate with interferon regulatory factor 9 (IRF9) to form the interferon-stimulated gene factor 3 (ISGF3) which is required for *Mx* gene expression (Schneider et al. 2014). Knockout mice lacking both functional IFN receptors fail to express MX1 protein despite carrying a functional *Mx1* gene and exhibit greatly enhanced susceptibility even to normally non-pathogenic influenza virus variants (Mordstein et al. 2008). Likewise, cells obtained from STAT1-deficient humans are unable to upregulate *MX1* expression upon exposure to type I or type III IFNs (Holzinger et al. 2007). Hence, the few patients with STAT1 deficiencies would be expected to be hypersensitive to influenza virus infection, but they predominantly suffered from other severe infections (mostly by mycobacteria and herpes viruses) and not influenza, perhaps because they were never exposed to influenza viruses (Boisson-Dupuis et al. 2012).

Mouse *Mx1*- and human *MX1*-transgenic mice

Transgenic technology was used to formally prove that *Mx1* was the missing defense gene against IAV in standard inbred mouse strains. Mice were generated that expressed the MX1 protein under control of an IFN-responsive element, mimicking the situation in A2G or feral mice in which *Mx1* gene expression is activated by virus-induced IFNs. Upon infection with IAV, the transgenic mice produced MX1 protein at the local sites of viral replication and survived pathogenic IAV infection. These findings illustrated the power of *Mx1* and demonstrated for the first time that the introduction of an IFN-regulated antiviral transgene into the genome of a susceptible host is sufficient to generate virus resistance (Arnheiter et al. 1990).

To demonstrate the key role of the human homolog MxA for host survival, two types of *MX1*-transgenic mice were generated. When expressed constitutively from an *MX1* cDNA construct, mice showed some protection against IAV (Pavlovic et al. 1995) even when lacking a functional IFNAR (Hefti et al. 1999). Protection was not very pronounced likely because of low MxA expression levels. Nevertheless, these experiments revealed for the first time the autonomous antiviral power of MxA in an otherwise type I IFN-nonresponsive host (Hefti et al. 1999). More recently, a transgenic mouse was produced that carries the entire human *MX* locus spanning approximately 150 kbp of chromosome 21 (Fig. 1). This

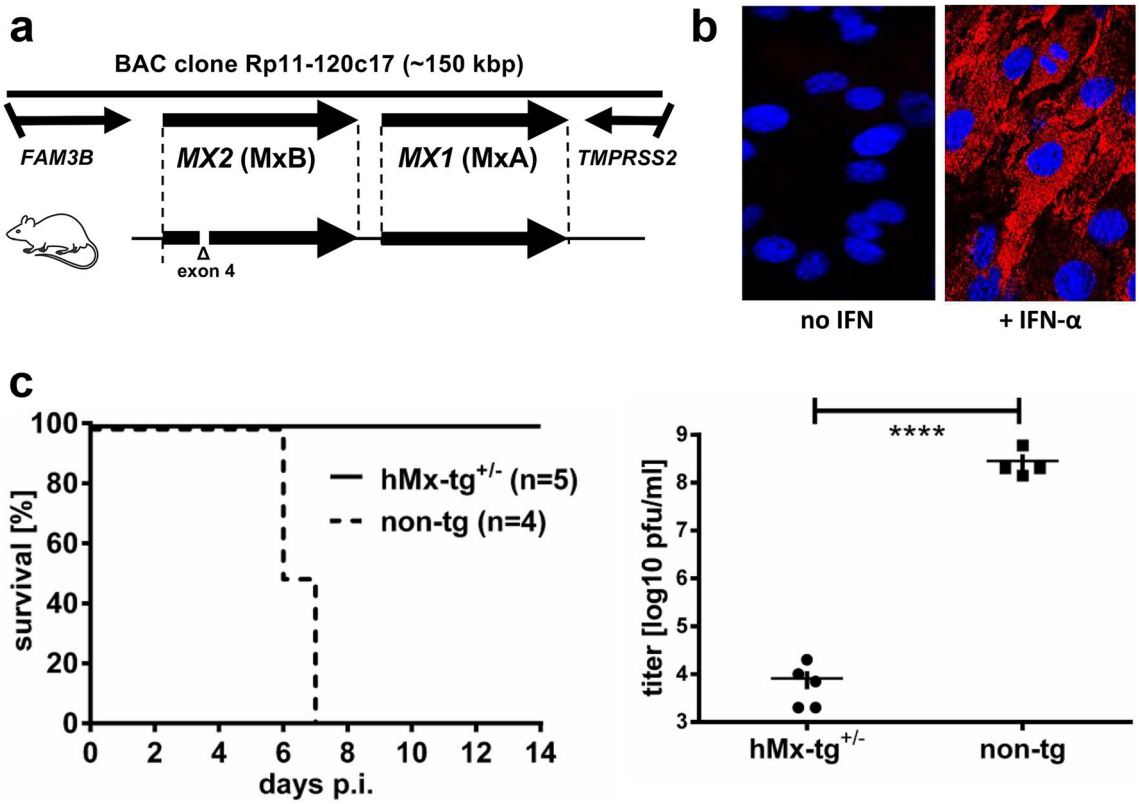

Fig. 1 MxA-transgenic mice resist lethal influenza virus infection. **a** Fragment of human chromosome 21 present in BAC clone Rp11-120c17 (top) and transgenic mice (bottom). The transgenic *MX2* gene carries a deletion of exon 4 and is non-functional. **b** MxA protein (red) is expressed in the cytoplasm of interferon-treated transgenic embryo fibroblasts, as revealed by immunofluorescence. **c** Resistance of transgenic (hMx-tg$^{+/-}$) versus susceptibility of non-transgenic (non-tg) mice to infection with a highly pathogenic avian IAV (H7N7). Survival (left panel) and virus load in infected lungs at day 5 post-infection (right panel) are shown [reprinted from reference (Haller et al. 2018), with permission]

locus contains the two MX paralogs, *MX1* (coding for MxA) and *MX2* (coding for MxB), but *MX2* was crippled in the transgenic mouse line due to an unintended deletion of the corresponding exon 4 (Deeg et al. 2017). The *MX1*-transgenic mice readily expressed human MxA in response to IFN exposure in all major organs, including the respiratory tract, and they showed a high degree of resistance to pathogenic avian IAVs (Fig. 1). Interestingly, however, their resistance to seasonal IAV strains circulating in humans was moderate (Deeg et al. 2017). This mouse represents the first small animal model that faithfully mimics an important facet of human innate immunity toward influenza viruses and provides solid evidence that MxA is a key influenza restriction factor in experimental animals and most likely humans.

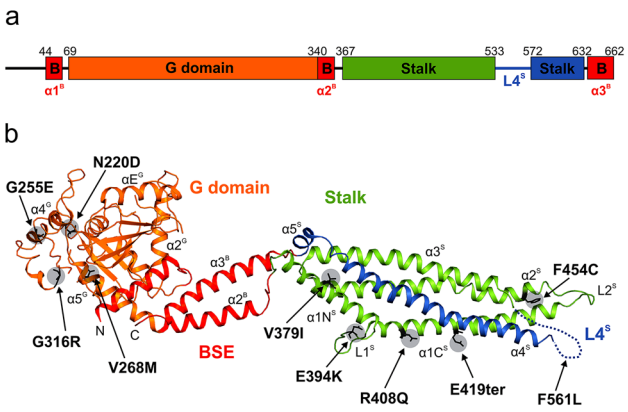

Fig. 2 Structure of MxA. **a** Linear representation of the MxA domains consisting of the G domain (orange), the stalk (green/blue) and the three helices of the bundle-signaling element, BSE (B, red). **b** Structure of an MxA monomer (colored as in **a**), with the unstructured loop L4 (L4^S) in the stalk indicated by a dashed blue line. The three helices of the BSE are assembled to a connective element between G domain and stalk [adapted from reference (Gao et al. 2011), with permission]. The allelic variations discussed in the text are indicated

How does the antiviral MxA protein inhibit influenza viruses?

MxA belongs to the dynamin superfamily of large GTPases (Jimah and Hinshaw 2019) and consists of a globular GTPase (G) domain that is connected via a flexible bundle-signaling element (BSE) to an alpha helical stalk (Fig. 2) (Gao et al. 2010, 2011; Haller et al. 2015). GTPase activity and oligomerization (via stalk and additional interfaces) are both required for antiviral function (Dick et al. 2015; Gao et al. 2010, 2011; von der Malsburg et al. 2011). In particular, GTP hydrolysis and antiviral activity are stimulated by intermolecular G–G domain interactions between MxA oligomers via a highly conserved G interface (Chen et al. 2017; Dick et al. 2015; Rennie et al. 2014). In fact, G domain mutations affecting GTP-binding and/or -hydrolysis and stalk interface mutations that eliminate dimer and oligomer formation abolish anti-IAV activity (Dick et al. 2015; Gao et al. 2011). A disordered loop (L4) at the tip of the stalk determines antiviral specificity and provides a viral target interface (Mitchell et al. 2012; Patzina et al. 2014) (Fig. 2). This loop binds to the viral nucleoprotein (NP), the major component of the viral ribonucleoprotein complex (vRNP) or nucleocapsid of IAV (Nigg and Pavlovic 2015). Hence, MxA recognizes incoming vRNPs as well as newly synthesized NP in the cytoplasm of infected cells and thus inhibits transport of vRNPs and NP into the nucleus, thereby blocking early steps in the viral life cycle (Haller et al. 2015; Kochs and Haller 1999; Pavlovic et al. 1990; Xiao et al. 2013). Despite considerable insights into the biochemistry and molecular biology of MxA, the precise mechanism by which the MxA GTPase inhibits IAV infection is presently not known. MxA forms large self-assemblies that condensate to granular and punctate structures in the cytosol (Haller et al. 2007; Pavlovic et al. 1990) and a fraction of MxA is also found associated with intracellular membranes (Accola et al. 2002; Reichelt et al. 2004; Stertz et al. 2006), in agreement with the propensity of purified MxA to bind to and tubulate lipid vesicles in vitro (Accola et al. 2002; von der Malsburg et al. 2011). A recent report demonstrates that cytoplasmic condensates of MxA are metastable and undergo rapid and reversible tonicity-driven phase transitions (Davis et al. 2019). In cells infected with vesicular stomatitis virus (VSV), the viral nucleoprotein is recruited into these dot-like condensates (Davis et al. 2019), a process that may contribute to the known anti-VSV effect of MxA (Pavlovic et al. 1990). Moreover, antivirally active wild-type MxA (but not an inactive MxA mutant) is able to sequester the nucleoprotein N of LaCrosse and other bunyaviruses into membrane-less perinuclear complexes, whereby wild-type but not mutant MxA is relocated from the characteristic cytoplasmic dots into the newly formed MxA/N assemblies surrounding the nucleus (Kochs et al. 2002). At present, the relevance of these findings for the antiviral mechanism of MxA against influenza virus is not clear. Mouse Mx1 (the ortholog of human MxA) accumulates in distinct dots close to PML bodies in the nucleus (Engelhardt et al. 2004), due to a nuclear localization signal (NLS) that is not present in MxA. When human MxA is equipped with a foreign NLS and forced to enter the nucleus, it forms comparable dots and inhibits primary transcription like mouse Mx1, suggesting a common mode of action (Engelhardt et al. 2004; Zurcher et al. 1992). Mouse Mx1 has been proposed to disrupt the interaction of the influenza viral polymerase subunit PB2 with NP leading to a block in viral transcription (Verhelst et al. 2012), but experimental evidence for such a mechanism is missing for MxA. There is, however, good evidence that MxA relies on the help of other cellular factor(s) for its anti-influenza activity. Candidate proteins are the RNA helicase UAP 56 and URH49 which interact with NP and MxA (Wisskirchen et al. 2011a, b) or the SMARCA2 chromatin remodeling factor (Dornfeld et al. 2018). Moreover, cytoplasmic MxA appears to require additional, and as yet unknown, interferon-inducible factor(s) to prevent incoming vRNPs from entering the nucleus (Xiao et al. 2013). It is conceivable that such cofactors are variably expressed in different tissues and govern the antiviral activity of MxA in an organ-specific way. Indeed, a recent report highlights a novel antiviral mechanism of human MxA in the respiratory epithelium. It demonstrates that MxA serves as an inflammasome sensor that recognizes NP of IAV in respiratory epithelial cells and triggers a rapid inflammatory response contributing to the antiviral control (Lee et al. 2019).

MxA-mediated IAV restriction and escape are dictated by a few critical amino acids in either MxA or the viral NP

MX genes in mammals are subject to both rapid evolution and recurrent gene conversion, as expected for antiviral genes engaged in a continuous battle with ever-changing pathogens (Mitchell et al. 2013, 2015; Qi et al. 2019). Comparisons of MxA sequences in primates identified loop L4 as a "hotspot" of diversifying selection, in agreement with its function as an antiviral module (Mitchell et al. 2012; Patzina et al. 2014). Interestingly, human MxA inhibits a wide range of RNA and DNA viruses by targeting a diverse set of viral proteins (Haller et al. 2015), suggesting that in the past, *MX1* evolved to directly combat multiple infections (Mitchell et al. 2013). The specificity of MxA for IAV and other *orthomyxoviruses* is largely determined by a few

amino acid residues (in particular F561) in L4 (Fig. 2b) that have repeatedly been mutated throughout primate MxA evolution (Mitchell et al. 2012; Patzina et al. 2014). A recent approach using combinatorial mutagenesis of the positively selected L4 residues generated "super-restrictor" variants that showed increased binding to viral NP and heightened antiviral activity against Thogoto (THOV) orthomyxovirus. Interestingly, however, these "super-restrictors" for THOV showed reduced IAV restriction, suggesting a classical trade-off between antiviral breadth and specificity (Colon-Thillet et al. 2019).

In contrast to L4, the sequences of the G domain, BSE, and stalk appear to be under purifying selection, indicating that changes affecting enzymatic or self-assembly properties of the GTPase are not tolerated (Mitchell et al. 2012). On the other hand, IAV have high mutation rates due to the infidelity of the viral RNA-dependent RNA polymerase required for genome amplification. This mutational flexibility allows for occasional adaptation of the virus to new hosts and efficient immune evasion. Indeed, seasonal IAV circulating in the human population have acquired and maintained MxA escape mutations in NP and are less efficiently controlled by MxA compared to avian IAV strains (Deeg et al. 2017; Dittmann et al. 2008; Zimmermann et al. 2011). Selection for MxA escape does not occur in avian species, because avian MX proteins lack anti-IAV activity (Benfield et al. 2008; Bernasconi et al. 1995; Schusser et al. 2011). Interestingly, avian H7N9 viruses that emerged in 2013 in China (Gao et al. 2013) and have since caused severe human infections show reduced MxA sensitivity due to a single amino acid change (N52Y) in NP (Riegger et al. 2015). Partial MxA escape might be acquired in pigs which serve as intermediate hosts and possess an antivirally active MX1 protein (Van Dam et al. 2019). In fact, the 2009 pandemic H1N1 virus features an MxA escape signature that is suggestive of porcine MX1 evasion (Manz et al. 2013). Recent phylogenetic analyses revealed that the viral NP of the Eurasian avian-like swine lineage successively gained MxA escape mutations that increase the zoonotic potential of these viruses (Dornfeld et al. 2019). It is conceivable that new MxA escape mutations in NP may arise in the future, be they located in the well-defined MxA sensitivity region (Manz et al. 2013) or at novel sites as recently suggested by a deep mutational scanning approach (Ashenberg et al. 2017). It has to be noted, however, that it is not easy for any IAV to overcome the MxA barrier, as acquisition of MxA escape mutations in NP leads to severely impaired viral growth both in human and avian cells. Indeed, restoration of viral fitness requires compensatory mutations in NP and perhaps other viral proteins (Gotz et al. 2016; Manz et al. 2013) (Fig. 3).

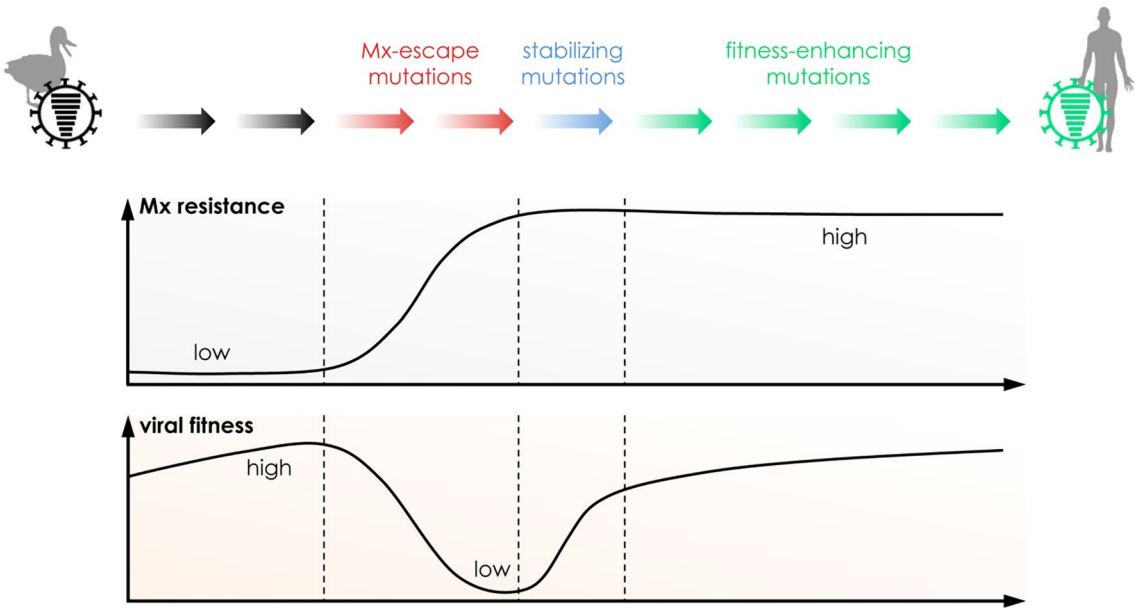

Fig. 3 From birds to humans. Avian IAV have to acquire MxA escape mutations in NP (upper panel, red) to propagate in humans. Accumulation of escape mutations causes a loss in viral fitness (lower panel) that must be compensated by secondary stabilizing NP mutations (upper panel, blue) and gain of fitness mutations (upper panel, green) in additional viral genes [reprinted from (Gotz et al. 2016), with permission]

Table 1 Selected allelic variations in the human *MX1* gene

Variant	Functional region	African (10,406)	Asian (25,166)	Latino (11,578)	European (66,740)	Homozygotes
G domain						
N220D	G interface	–	7	–	–	–
G255E	G interface	–	5	–	–	–
V268 M	G interface	–	36	49	9	1
G316R	G domain	292	6	14	24	9
Stalk						
V379I	$\alpha1N^{s}$, IF1	4654	10,999	4341	38,759	16,893
E394 K	$L1^{S}$, IF3	–	6	–	–	–
R408Q	$\alpha1C^{S}$, IF3	5	–	1	–	–
E419ter	$\alpha1C^{S}$ (stop)	31	–	2	–	–
Q423 K	$\alpha1C^{S}$	8	–	–	–	–
F454C	$\alpha2^{S}$	–	–	–	4	–
V470G	$\alpha2^{S}$, BSE-stalk IF	–	–	–	–	–
E516del	$\alpha3^{S}$ (deletion)	–	6	–	–	–
F561L	$L4^{S}$	–	1	–	4	–
S566Y	$L4^{S}$	–	–	10	–	–
Q611H	$\alpha4^{S}$, IF1	61	–	7	1	–

MX1 allelic variants that lead to alterations in functional regions of the G domain or the stalk of MxA were identified, using the ExAC database (Cambridge, MA) (http://exac.broadinstitute.org). Allele counts of the individual *MX1* variations found in different ethnic groups as well as the number of homozygous carriers are indicated. [Adapted from reference (Graf et al. 2018)]

Allelic variations in the human *MX1* gene

A search for human *MX1* alleles in the Exome Aggregation Consortium (ExAC) database (Lek et al. 2016) revealed a small number of synonymous, missense and nonsense variants, in addition to a low frequency of alleles with in-frame deletions or alterations leading to frameshifts or aberrant splicing patterns (Duc et al. 2012; Graf et al. 2018; Tazi-Ahnini et al. 2000). These variations were located all over the coding sequence of *MX1*. Non-synonymous allelic variations at structurally interesting sites were further analyzed (Table 1; Fig. 2b). G316R was the most frequent G domain variant that was also found in homozygous carriers, but did not affect antiviral activity in in vitro assays, as also V268 M (Graf et al. 2018). In contrast, G255E (Duc et al. 2012) and N220D both disturbed proper formation of the G–G interface and resulted in defective GTPase activity and antiviral action (Graf et al. 2018). These G–G interface variants were found in heterozygotes but had no dominant-negative effect on wild-type MxA. Four out of eleven variants (E394 K, R408Q, E419ter, and F454C) in the stalk caused a complete loss of antiviral activity. Except for E419ter, which truncates the stalk and hence renders the protein unable to oligomerize, the other inactive stalk alterations all showed dominant-negative activities against wild-type MxA (Graf et al. 2018), suggesting that heterozygous carriers might have an impaired anti-influenza response. However, the infection history of such heterozygous carriers is not known. The stalk variant V379I that is widely distributed and shows the highest number of homozygous carriers (Table 1) was previously associated with severe respiratory syncytial virus infection (Ciencewicki et al. 2014). However, this variant had undisturbed wild-type activity against IAV and VSV (Graf et al. 2018). On the other hand, the F561L variation at the critical position 561 in loop L4 caused reduced antiviral activity against THOV and IAV though not against VSV, illustrating the flexibility of this antiviral module.

Much previous work has also been focused on non-coding regions of *MX1*. Variations in the promoter region − 123(C/A) and − 88(G7T) affecting MxA expression levels seem to influence disease outcomes of patients with hepatitis B and C as well as SARS and enterovirus 71 (Cao et al. 2009; Ching et al. 2010; Hamano et al. 2005; He et al. 2006; Hijikata et al. 2000; Knapp et al. 2003; Kong et al. 2007; Suzuki et al. 2004; Zhang et al. 2014). Furthermore, an SNP in intron 3 was linked to increased risk for symptomatic West Nile virus infection (Bigham et al. 2011). Presently, no information is available on the effect of these genetic variants on the outcome of IAV infections. Nevertheless, these recent findings underscore the importance of *MX1* for antiviral host defense and hence call for an intensified search for the effects of *MX1* variants on the individual course of severe influenza and possibly other viral infections.

Outlook

Single-gene errors of innate immunity can cause deadly influenza in humans. Most deficiencies implicate the type I and type III IFN pathways that may involve human *MX1*, but severe *MX1* loss-of-function alterations have yet to be reported. Either severe *MX1* defects are exceedingly rare and remain undetected or else they are fully compensated by other host defense mechanisms. Given the present evidence for a major protective role of human MxA in transgenic mice, we expect that deleterious mutations in *MX1* pose a clear and discernible risk for severe influenza in humans. The MxA effect may be partly masked in seasonal epidemics due to MxA escape mutations acquired by circulating IAV strains. We, therefore, anticipate that null or dominant-negative alleles of *MX1* will first be found in severely sick individuals exposed to avian IAV or other emerging zoonotic influenza viruses, or indeed other viral pathogens.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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