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COMMENTARY

A Brief Historical Perspective on the Pathological Consequences of Excessive Type I Interferon Exposure In vivo

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Interferon was described by Isaacs and Lindenmann in 1957 [1, 2], and its importance in antiviral host defense was first demonstrated in 1960 [3]. Virelizier and Gresser were the first to show that endogenous interferon type I mediated one example of genetically determined resistance to a viral infection, when they found that injection of an anti-type I interferon IgG overcame the innate resistance of C3H and A/J mice to mouse hepatitis virus [4]. These results were then extended by Haller and colleagues, using the same anti-IFN IgG to render a Mendelian-determined resistant strain of mice fully susceptible to the lethal effects of influenza A virus [5, 6]. Molecular confirmation of these data came through the definition of murine models lacking the type I interferon receptor and relevant downstream signaling molecules [7–9] and the study of human inborn errors of immunity, beginning with the identification of inherited complete STAT1 deficiency in 2003 [10, 11]. The phenotypes of *Ifnar1*, *Ifnar2*, *Stat1*, *Stat2*, *Isg15*, and *Irf9*-deficient mice and the corresponding human mutant states differ somewhat, in regard to the pattern of expression of interferon stimulated genes and susceptibility to viruses, suggesting that each of these components is essential in its own way for a proper interferon response [12]. Beyond the more specialized roles of interferon lambda and gamma in epithelial defense and macrophage activation respectively [13–15], definition of specific functions of individual interferon alpha subtypes and interferon beta has remained elusive, although their mere diversity and different patterns of evolutionary selection [16] suggest discrete and perhaps non-overlapping activities. Overall, 50 years of experimentation has established that type I interferons are globally essential for host defense against a variety of viruses in all species examined.

In parallel, another line of research established the paradoxical situation where excessive interferon production can be detrimental to the host [17]. Studies performed by Gresser and colleagues more than 40 years ago showed that when different strains of newborn mice were injected with potent preparations of partially purified or electrophoretically pure mouse type I interferon, they developed a syndrome characterized by inhibition of growth, delay in maturation of several organs, diffuse liver cell necrosis, and death between the 8th and 14th day of life [18, 19]. Remarkably, when type I interferon treatment was discontinued at 1 week of life, the mice seemed to recover and gain weight, but then died in the ensuing months with a progressive glomerulonephritis [20, 21]. In the A2G mouse strain, type I interferon induced a similar liver cell necrosis. However, in this case, recovery following discontinuation of treatment was followed by the development of large pulmonary cysts in the absence of any renal involvement [22]. Injection of newborn rats with potent preparations of rat type I interferon also resulted in a delay of growth and maturation of different organs, and the subsequent development of nephritis [23].

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The above experiments indicated that exogenously administered type I interferon could have pleiotropic effects in mice, which might be separated temporally, sometimes by several months, from the initial exposure, and show a dependency on background strain. To explore the relevance of these observations in a more physiological setting, it was noted that the injection of newborn mice with lymphocytic choriomeningitis virus (LCMV) induced a phenotype apparently identical to that observed in type I interferon-treated suckling mice, and, similarly, surviving mice subsequently developed a progressive and lethal glomerulonephritis [24, 25]. A difference was observed in the severity of disease in different strains of mice infected with LCMV, which correlated with the amount of interferon produced and the duration of the interferonemia. Inoculation of LCMV-infected mice with a potent, purified sheep IgG anti-mouse type I interferon resulted in a hundred fold increase in the serum viral titer compared to virus-injected mice treated with control IgGs. As expected, control mice had significant serum interferon titers, whereas interferon was not detected in the serum of mice treated with anti-interferon IgG. Strikingly, however, prior inoculation with anti-interferon IgG inhibited the early manifestations of LCMV disease [26], as well as the later development of glomerulonephritis [27]. Furthermore, the same antibody abrogated the liver necrosis of Pichinde virus (another arenavirus) infected suckling mice [28]. It should be noted that, as first described in 1971 [29], in most instances, antibody to interferon exacerbates the manifestations of acute viral disease.

At around the same time, Lebon and colleagues showed that interferon alpha activity was present in normal amniotic fluid [30, 31] and in the placenta [32] in the absence of any viral infection. Although interferon was detectable at the feto-placental interface in the non-diseased state, it was not recorded in the blood of fetuses of women free from infection. Furthermore, it was shown that interferon alpha administered to pregnant women infected with human immunodeficiency virus did not cross the placenta [33]. In contrast, an acid labile alpha interferon activity was present in the sera of fetuses and children with congenital rubella [34], at as early as 20 weeks of gestation, raising the question as to whether this interferon might play an active role in the sequelae of such infection. Similarly, interferon alpha activity was detected in fetal blood after infection with cytomegalovirus, parvovirus B19 [35, 36], LCMV [37], and enterovirus [38], with the fetal origin of this interferon indicated by its absence from maternal blood sampled at the same time.

Following on from the body of work described above, in 1980, Gresser and colleagues suggested the possibility that as interferon did not cross the placenta, some embryotoxic effects ascribed to viral infection, such as rubella virus, might be related to interferon induced in the embryo itself [17]; that is, as a function of the host response to infection. Furthermore, they predicted that disease states might exist in humans where pathogenesis was directly consequent upon enhanced type I interferon signaling. Remarkably then, only 4 years later, Lebon and colleagues described increased levels of interferon alpha activity in the serum and cerebrospinal fluid of children affected by a presumed genetic disorder [39–41], with such activity detected in fetal blood at as early as 29 weeks of gestation [42, 43]. In doing so, they defined the first Mendelian disease associated with enhanced type I interferon signaling, now referred to as Aicardi-Goutières syndrome (AGS).

These studies coincided with the use of recombinant leukocyte interferon preparations as a therapy, and the first reports of both neurological disease [44–46], particularly confusion and spasticity, and an association with the onset of systemic lupus erythematosus (SLE), and other autoimmune phenotypes, apparently consequent upon iatrogenic exposure [47]. The neurotoxic potential of type I interferon was further emphasized by the work of Campbell and colleagues through the production of transgenic mice that chronically produce interferon alpha from astrocytes, thereby recapitulating the neuropathological features of AGS [48, 49].

Beginning in 2006, the subsequent unraveling of the genetic basis of AGS has underlined the prescience of the earlier pioneer studies. Thus, as originally described, AGS can be considered as a Mendelian mimic of congenital infection due to dysfunction of genes involved in either nucleic acid processing (TREX1, the RNase H2 complex, SAMHD1, ADAR1) or sensing (MDA5). Such defects result in a misinterpretation of self nucleic acids as non-self (viral) and the induction of an (inappropriate) interferon-mediated (antiviral) response. These observations, supported by in vitro and animal experimentation, subsequently led to the introduction of the type I interferonopathy concept in 2011, a set of Mendelian diseases where upregulated type I interferon signaling is considered directly relevant to pathogenesis [50]. Starting in the 1970s, systemic lupus erythematosus was the first human disease to be linked to enhanced type I interferon beyond infection [51–56]. It is of note that variants in a number of genes related to Mendelian type I interferonopathies are associated with lupus [57–59]. Conversely, the co-occurrence of lupus in that context is suggestive of a common pathogenic link [60–63], albeit the frequency of overt lupus is relatively low and clear phenotypic differences exist.

Given the focus here on type I interferon, we do not discuss the clear importance of type II and III interferons in host defense. However, we do note that the so-called interferon signature i.e. the increased expression of a programmed set of interferon stimulated genes, is not specific

to type I interferon [http://interferome.its.monash.edu.au/interferome]. As such, the possibility that enhanced interferon signaling induced by types II and III interferons might also have detrimental effects on cell and organismal health is deserving of further investigation. Indeed, this is possibly the case for interferon gamma in hereditary hemophagocytic lymphohistiocytosis [64], and might be relevant to type III interferons and the gastrointestinal involvement sometimes observed in AGS [65].

Many questions central to a comprehensive understanding of the type I interferonopathy field remain, perhaps the most urgent being the source of the putative endogenous nucleic acid driving an interferon response, with two major possibilities currently favored, i.e., either products of DNA damage/repair or endogenous retro elements. Another interesting question relates to the importance of tonic interferon signaling, which may have roles beyond the maintenance of a baseline level of antiviral protection [66]. In the meanwhile, recent papers have again highlighted the importance of the host interferon-mediated antiviral response in disease, demonstrating a significant contribution to pathology in a mouse model of congenital ZIKV infection [67–69]. Here, we place these exciting new insights into historical perspective by emphasizing certain data generated in the 1970s and 1980s. In brief, either too little or too much type I interferon can be detrimental to the host, including the fetus.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Image. The authors during a working lunch at Chez Fernand, Saint-Germain-des-Près, Paris (where Pierre Lebon's son Remi is the head chef) (left to right: Pierre Lebon, Yanick Crow, Ion Gresser, and Jean-Laurent Casanova).

References

1. Isaacs A, Lindenmann J. Virus interference. I. The interferon. Proc R Soc Lond B Biol Sci. 1957;147(927):258–67.
2. Isaacs A, Lindenmann J, Valentine RC. Virus interference. II. Some properties of interferon. Proc R Soc Lond B Biol Sci. 1957;147(927):268–73.
3. Isaacs A, Hitchcock G. Role of interferon in recovery from virus infections. Lancet. 1960;2(7141):69–71.
4. Virelizier JL, Gresser I. Role of interferon in the pathogenesis of viral diseases of mice as demonstrated by the use of anti-interferon serum. V. Protective role in mouse hepatitis virus type 3 infection of susceptible and resistant strains of mice. J Immunol. 1978;120(5):1616–9.
5. Haller O, Arnheiter H, Gresser I, Lindenmann J. Genetically determined, interferon-dependent resistance to influenza virus in mice. J Exp Med. 1979;149(3):601–12.
6. Haller O, Arnheiter H, Lindenmann J, Gresser I. Host gene influences sensitivity to interferon action selectively for influenza virus. Nature. 1980;283(5748):660–2.
7. Muller U, Steinhoff U, Reis LF, Hemmi S, Pavlovic J, Zinkernagel RM, et al. Functional role of type I and type II interferons in antiviral defense. Science. 1994;264(5167):1918–21.
8. Durbin JE, Hackenmiller R, Simon MC, Levy DE. Targeted disruption of the mouse Stat1 gene results in compromised innate immunity to viral disease. Cell. 1996;84(3):443–50.
9. Meraz MA, White JM, Sheehan KC, Bach EA, Rodig SJ, Dighe AS, et al. Targeted disruption of the Stat1 gene in mice reveals unexpected physiologic specificity in the JAK-STAT signaling pathway. Cell. 1996;84(3):431–42.
10. Casanova JL. Severe infectious diseases of childhood as monogenic inborn errors of immunity. Proc Natl Acad Sci U S A. 2015;112(51):E7128–37.
11. Dupuis S, Jouanguy E, Al-Hajjar S, Fieschi C, Al-Mohsen IZ, Al-Jumaah S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. Nat Genet. 2003;33(3):388–91.
12. de Weerd NA, Vivian JP, Nguyen TK, Mangan NE, Gould JA, Braniff SJ, et al. Structural basis of a unique interferon-beta signaling axis mediated via the receptor IFNAR1. Nat Immunol. 2013;14(9):901–7.
13. Nathan CF, Murray HW, Wiebe ME, Rubin BY. Identification of interferon-gamma as the lymphokine that activates human macrophage oxidative metabolism and antimicrobial activity. J Exp Med. 1983;158(3):670–89.
14. Kotenko SV, Gallagher G, Baurin VV, Lewis-Antes A, Shen M, Shah NK, et al. IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. Nat Immunol. 2003;4(1):69–77.
15. Sheppard P, Kindsvogel W, Xu W, Henderson K, Schlutsmeyer S, Whitmore TE, et al. IL-28, IL-29 and their class II cytokine receptor IL-28R. Nat Immunol. 2003;4(1):63–8.
16. Manry J, Laval G, Patin E, Fornarino S, Itan Y, Fumagalli M, et al. Evolutionary genetic dissection of human interferons. J Exp Med. 2011;208(13):2747–59. https://doi.org/10.1084/jem.20111680.
17. Gresser I, Morel-Maroger L, Riviere Y, Guillon JC, Tovey MG, Woodrow D, et al. Interferon-induced disease in mice and rats. Ann N Y Acad Sci. 1980;350:12–20.
18. Gresser I, Tovey MG, Maury C, Chouroulinkov I. Lethality of interferon preparations for newborn mice. Nature. 1975;258(5530):76–8.
19. Gresser I, Aguet M, Morel-Maroger L, Woodrow D, Puvion-Dutilleul F, Guillon JC, et al. Electrophoretically pure mouse interferon inhibits growth, induces liver and kidney lesions, and kills suckling mice. Am J Pathol. 1981;102(3):396–402.
20. Gresser I, Maury C, Tovey M, Morel-Maroger L, Pontillon F. Progressive glomerulonephritis in mice treated with interferon preparations at birth. Nature. 1976;263(5576):420–2.
21. Morel-Maroger L, Sloper JC, Vinter J, Woodrow D, Gresser I. An ultrastructural study of the development of nephritis in mice treated with interferon in the neonatal period. Lab Investig; J Technical Methods and Pathology. 1978;39(5):513–22.
22. Woodrow D, Moss J, Gresser I. Interferon induces pulmonary cysts in A2G mice. Proc Natl Acad Sci U S A. 1984;81(24):7937–40.
23. Gresser I, Morel-Maroger L, Chatelet F, Maury C, Tovey M, Bandu MT, et al. Delay in growth and the development of nephritis in rats treated with interferon preparations in the neonatal period. Am J Pathol. 1979;95(2):329–46.
24. Riviere Y, Gresser I, Guillon JC, Bandu MT, Ronco P, Morel-Maroger L, et al. Severity of lymphocytic choriomeningitis virus disease in different strains of suckling mice correlates with increasing amounts of endogenous interferon. J Exp Med. 1980;152(3):633–40.
25. Woodrow D, Ronco P, Riviere Y, Moss J, Gresser I, Guillon JC, et al. Severity of glomerulonephritis induced in different strains of suckling mice by infection with lymphocytic choriomeningitis virus: correlation with amounts of endogenous interferon and circulating immune complexes. J Pathol. 1982;138(4):325–36. https://doi.org/10.1002/path.1711380404.
26. Riviere Y, Gresser I, Guillon JC, Tovey MG. Inhibition by anti-interferon serum of lymphocytic choriomeningitis virus disease in suckling mice. Proc Natl Acad Sci U S A. 1977;74(5):2135–9.
27. Gresser J, Morel-Maroger L, Verroust P, Riviere Y, Guillon JC. Anti-interferon globulin inhibits the development of glomerulonephritis in mice infected at birth with lymphocytic choriomeningitis virus. Proc Natl Acad Sci U S A. 1978;75(7):3413–6.
28. Clark T, Gresser I, Pfau C, Moss J, Woodrow D. Antibody to mouse alpha/beta interferon abrogates Pichinde virus-induced liver lesions in suckling mice. J Virol. 1986;59(3):728–30.
29. Fauconnier B. Effect of an anti-interferon serum on experimental viral pathogenicity in vivo. Pathol Biol. 1971;19(11):575–8.
30. Lebon P, Girard S, Thepot F, Chany C. Constant presence of alpha interferon in human amniotic fluid. CR Acad Sci Paris, Sciences de la vie. 1981;293(1):69–71.
31. Lebon P, Girard S, Thepot F, Chany C. The presence of alpha-interferon in human amniotic fluid. J Gen Virol. 1982;59(Pt 2):393–6.
32. Duc-Goiran P, Lebon P, Chany C. Measurement of interferon in human amniotic fluid and placental blood extract. Methods Enzymol. 1986;119:541–51.
33. Pons JC, Lebon P, Frydman R, Delfraissy JF. Pharmacokinetics of interferon-alpha in pregnant women and fetoplacental passage. Fetal Diagn Ther. 1995;10(1):7–10.
34. Lebon P, Daffos F, Checoury A, Grangeot-Keros L, Forestier F, Toublanc JE. Presence of an acid-labile alpha-interferon in sera from fetuses and children with congenital rubella. J Clin Microbiol. 1985;21(5):775–8.
35. Lebon P MJ, Krivine A, Rozenberg F, Daffos F, Dommergues M, Dumez Y, Forestier F, Mandelbrot L, Poissonnier MH, Pons JC. Infections virales in utero: interet du dosage de l interferon alpha dans le serum fœtal. l7ème séminaire Guigoz GENEUP; Deauville 1992. p. 81–93.
36. Dommergues M, Mahieu-Caputo D, Fallet-Bianco C, Mirlesse V, Aubry MC, Delezoide AL, et al. Fetal serum interferon-alpha suggests viral infection as the aetiology of unexplained lateral cerebral ventriculomegaly. Prenat Diagn. 1996;16(10):883–92.
37. Meritet JF, Krivine A, Lewin F, Poissonnier MH, Poizat R, Loget P, et al. A case of congenital lymphocytic choriomeningitis virus (LCMV) infection revealed by hydrops fetalis. Prenat Diagn. 2009;29(6):626–7.

38. Dommergues M, Petitjean J, Aubry MC, Delezoide AL, Narcy F, Fallet-Bianco C, et al. Fetal enteroviral infection with cerebral ventriculomegaly and cardiomyopathy. Fetal Diagn Ther. 1994;9(2):77–8.
39. Aicardi J, Goutieres F. A progressive familial encephalopathy in infancy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. Ann Neurol. 1984;15(1):49–54.
40. Lebon P, Badoual J, Ponsot G, Goutieres F, Hemeury-Cukier F, Aicardi J. Intrathecal synthesis of interferon-alpha in infants with progressive familial encephalopathy. J Neurol Sci. 1988;84(2–3):201–8.
41. Goutieres F, Aicardi J, Barth PG, Lebon P. Aicardi-Goutieres syndrome: an update and results of interferon-alpha studies. Ann Neurol. 1998;44(6):900–7.
42. Le Garrec M, Doret M, Pasquier JC, Till M, Lebon P, Buenerd A, et al. Prenatal diagnosis of Aicardi-Goutieres syndrome. Prenat Diagn. 2005;25(1):28–30.
43. Desanges C, Lebon P, Bauman C, Vuillard E, Garel C, Cordesse A, et al. Elevated interferon-alpha in fetal blood in the prenatal diagnosis of Aicardi-Goutieres syndrome. Fetal Diagn Ther. 2006;21(1):153–5.
44. Honigsberger L, Fielding JW, Priestman TJ. Neurological effects of recombinant human interferon. Br Med J (Clin Res Ed). 1983;286(6366):719.
45. Smedley H, Katrak M, Sikora K, Wheeler T. Neurological effects of recombinant human interferon. Br Med J (Clin Res Ed). 1983;286(6361):262–4.
46. Vesikari T, Nuutila A, Cantell K. Neurologic sequelae following interferon therapy of juvenile laryngeal papilloma. Acta Paediatr Scand. 1988;77(4):619–22.
47. Ronnblom LE, Alm GV, Oberg KE. Possible induction of systemic lupus erythematosus by interferon-alpha treatment in a patient with a malignant carcinoid tumour. J Intern Med. 1990;227(3):207–10.
48. Akwa Y, Hassett DE, Eloranta ML, Sandberg K, Masliah E, Powell H, et al. Transgenic expression of IFN-alpha in the central nervous system of mice protects against lethal neurotropic viral infection but induces inflammation and neurodegeneration. J Immunol. 1998;161(9):5016–26.
49. Campbell IL, Krucker T, Steffensen S, Akwa Y, Powell HC, Lane T, et al. Structural and functional neuropathology in transgenic mice with CNS expression of IFN-alpha. Brain Res. 1999;835(1):46–61.
50. Crow YJ. Type I interferonopathies: a novel set of inborn errors of immunity. Ann N Y Acad Sci. 2011;1238:91–8.
51. Gergely L, Szegedi G, Hadhazy G, Toth FD. Interferon production in vitro by leukocytes in lupus erythematodes disseminatus. Klin Wochenschr. 1970;48(8):498–9.
52. Alarcon-Segovia D, Ruiz-Gomez J, Fishbein E, Bustamante ME. Interferon production by lymphocytes from patients with systemic lupus erythematosus. Arthritis Rheum. 1974;17(5):590–2.
53. Skurkovich SV, Eremkina EI. The probable role of interferon in allergy. Ann Allergy. 1975;35(6):356–60.
54. Hooks JJ, Moutsopoulos HM, Geis SA, Stahl NI, Decker JL, Notkins AL. Immune interferon in the circulation of patients with autoimmune disease. N Engl J Med. 1979;301(1):5–8.
55. Baechler EC, Batliwalla FM, Karypis G, Gaffney PM, Ortmann WA, Espe KJ, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci U S A. 2003;100(5):2610–5.
56. Bennett L, Palucka AK, Arce E, Cantrell V, Borvak J, Banchereau J, et al. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. J Exp Med. 2003;197(6):711–23.
57. Lee-Kirsch MA, Gong M, Chowdhury D, Senenko L, Engel K, Lee YA, et al. Mutations in the gene encoding the 3′-5′ DNA exonuclease TREX1 are associated with systemic lupus erythematosus. Nat Genet. 2007;39(9):1065–7.
58. Gunther C, Kind B, Reijns MA, Berndt N, Martinez-Bueno M, Wolf C, et al. Defective removal of ribonucleotides from DNA promotes systemic autoimmunity. J Clin Invest. 2015;125(1):413–24.
59. An J, Briggs TA, Dumax-Vorzet A, Alarcon-Riquelme ME, Belot A, Beresford M et al. Tartrate-resistant acid phosphatase deficiency in the predisposition to systemic lupus erythematosus. Arthritis Rheum (Hoboken, NJ). 2017;69(1):131–42.
60. Dale RC, Tang SP, Heckmatt JZ, Tatnall FM. Familial systemic lupus erythematosus and congenital infection-like syndrome. Neuropediatrics. 2000;31(3):155–8.
61. De Laet C, Goyens P, Christophe C, Ferster A, Mascart F, Dan B. Phenotypic overlap between infantile systemic lupus erythematosus and Aicardi-Goutieres syndrome. Neuropediatrics. 2005;36(6):399–402.
62. Briggs TA, Rice GI, Daly S, Urquhart J, Gornall H, Bader-Meunier B, et al. Tartrate-resistant acid phosphatase deficiency causes a bone dysplasia with autoimmunity and a type I interferon expression signature. Nat Genet. 2011;43(2):127–31.
63. Van Eyck L, De Somer L, Pombal D, Bornschein S, Frans G, Humblet-Baron S et al. IFIH1 mutation causes systemic lupus erythematosus with selective IgA-deficiency. Arthritis & rheumatology (Hoboken, NJ). 2015.
64. Pachlopnik Schmid J, Ho CH, Chrétien F, Lefebvre JM, Pivert G, Kosco-Vilbois M, et al. Neutralization of IFNgamma defeats haemophagocytosis in LCMV-infected perforin- and Rab27a-deficient mice. EMBO Mol Med. 2009 May;1(2):112–24.
65. Hall D, Rice GI, Akbar N, Meager A, Crow YJ, Lim MJ. Aicardi-Goutières syndrome presenting with haematemesis in infancy. Acta Paediatr. 2009 Dec;98(12):2005–8.
66. Ejlerskov P, Hultberg JG, Wang J, Carlsson R, Ambjørn M, Kuss M, et al. Lack of neuronal IFN-β-IFNAR causes Lewy body- and Parkinson's disease-like dementia. Cell. 2015 Oct 8;163(2):324–39.
67. Casazza RL, Lazear HM. Antiviral immunity backfires: Pathogenic effects of type I interferon signaling in fetal development. Science Immunology. 2018;3(19).
68. Szaba FM, Tighe M, Kummer LW, Lanzer KG, Ward JM, Lanthier P, et al. Zika virus infection in immunocompetent pregnant mice causes fetal damage and placental pathology in the absence of fetal infection. PLoS Pathog. 2018;14(4):e1006994.
69. Yockey LJ, Jurado KA, Arora N, Millet A, Rakib T, Milano KM et al. Type I interferons instigate fetal demise after Zika virus infection. Science Immunology. 2018;3(19).