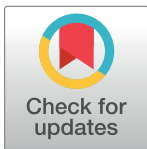# PLOS PATHOGENS

On invariant T cells and measles: A theory of "innate immune amnesia"

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Measles (aka rubeola) is a highly contagious disease caused by a single-stranded RNA virus belonging to the family Paramyxoviridae. Measles virus (MeV) caused major epidemics and claimed an estimated 2.6 million lives annually prior to 1963 when a measles vaccine was introduced. Immunization against measles is estimated to have prevented 23.2 million deaths between 2000 and 2018. Notwithstanding, MeV continues to ravage impoverished regions, especially in the aftermath of natural disasters. In addition, despite the availability of safe, effective and affordable vaccines against MeV, anti-vaccination sentiments have created vulnerable societal pockets, which can be troubling in light of the increasing ease of global travel. It is therefore not surprising that recent years have witnessed a multitude of measles outbreaks and that measles-associated deaths have been alarmingly on the rise.

Measles-induced immunosuppression

Many deaths from measles are due to secondary infections with unrelated pathogens amid a profound state of immunosuppression [1,2]. The three receptors dictating the cellular tropism of MeV are CD46 (aka membrane cofactor protein) [3,4], nectin 4 (aka poliovirus receptor-related 4) [5,6], and CD150 (aka signaling lymphocyte activation molecule family member 1) [7–9]. Wild-type (WT), laboratory-adapted and vaccine strains of MeV utilize or hijack CD150 to interact with or infect permissive immunocytes, and measles-elicited lymphopenia and antigen (Ag)-presenting cell (APC) impairments have been linked to CD150 expression.

The acquired immune deficiency of patients with measles was reported as early as in 1908 when a failure to mount normal tuberculin skin reactions was observed in children following measles [10]. The mechanisms underlying measles-associated immunosuppression, which can last for weeks to months, are wide-ranging and far from fully understood. Macrophages and dendritic cells (DCs) become infected with MeV and serve as Trojan horses transferring the virions to select lymphocyte subpopulations [11–13]. Exposure to or infection with MeV alters signal transduction pathways operating in DCs and interferes with their survival, maturation, and pro-inflammatory cytokine production and naïve T cell priming capacities [14–16]. T/B cell lymphopenia, retarded T cell proliferation in response to nonspecific mitogens [17], a prolonged cytokine imbalance in favor of T helper 2 (T_H2)-type and anti-inflammatory mediators [e.g., interleukin (IL)-4, IL-13 and IL-10] [18,19], and CD4$^+$CD25$^+$ regulatory T cell accumulation in the peripheral blood [20] are among other immunological consequences of measles.

Adaptive immune amnesia

By infecting and eliminating preexisting memory cells that express high levels of CD150, MeV erases the recollection of past exposures to microbes and "resets" the host's defense system back to its default. This is referred to as "immune amnesia" [21], which is thought to contribute to measles immunosuppression (Fig 1A and 1B).

Using human tonsillar tissue blocks, Condack and colleagues reported that WT MeV strains infect approximately 5 to 6 times more $CD3^+CD45RO^+$ memory T (T_M) cells than $CD3^+CD62L^+CD45RA^+$ naïve T (T_N) cells [22]. These results were recapitulated in an in vivo setting in which intratracheal infection of rhesus macaques and cynomolgus macaques resulted in the preferential infection of $CD4^+$ and $CD8^+$ T_M cells [23]. de Vries and colleagues subsequently demonstrated that MeV infects central memory T (T_{CM}) and effector memory T (T_{EM}) cells present in the peripheral blood, tracheobronchial lymph nodes, tonsils/adenoids, and Peyer's patches of infected macaques [21]. Importantly, a numerical decline in the T_M compartment was followed by massive lymphoproliferation. Accordingly, the authors posited that measles lymphopenia, driven by T_M depletion, can be masked by the expansion of MeV-
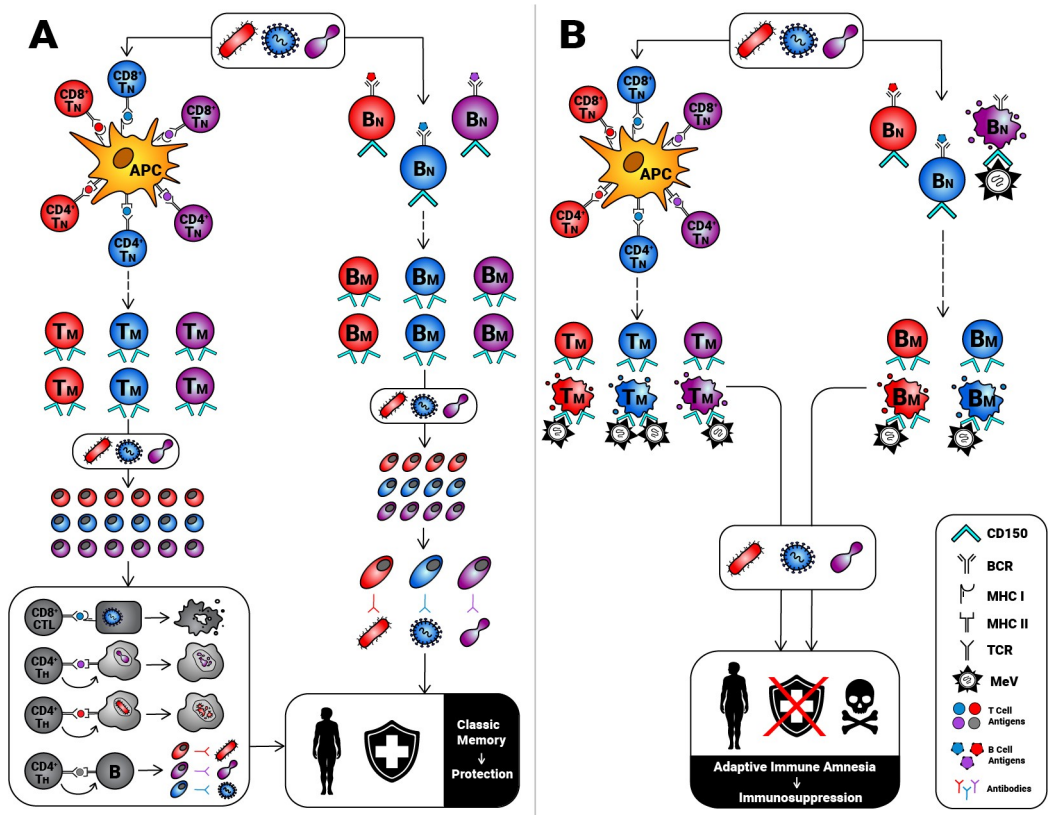
Fig 1. By killing memory cells, MeV causes adaptive immune amnesia. (A) Primary T and B cell responses to various microbial pathogens generate diverse memory cell pools. Once reexposed to cognate antigens, memory cells respond specifically, quickly and strongly to eliminate pathogens through cell-mediated and humoral mechanisms that are often protective. (B) MeV binds CD150 and destroys naïve and memory B cells as well as memory T cells. As a result, memory cell repertoires are depleted of many specificities, and a state of adaptive immune amnesia is established, which is responsible, at least partially, for measles-associated immunosuppression and heightened susceptibility to infections that are unrelated to measles. APC, antigen-presenting cell; BCR, B cell receptor; B_M, memory B [cell]; B_N, naïve B [cell]; CTL, cytotoxic T lymphocyte; MeV, measles virus; MHC, major histocompatibility complex; TCR, T cell receptor; T_H, helper T [cell]; T_M, memory T [cell]; T_N, naïve T [cell].

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specific lymphocytes and bystander cells. This may explain, at least partially, the sustained immunosuppression of measles patients despite their seemingly short-term lymphopenia.

Unlike their naïve counterparts, human blood and tonsillar T_{CM} and T_{EM} cells are highly susceptible to MeV infection in vitro [21,24,25]. By comparison, naïve B (B_N) and memory B (B_M) cells are comparable in their permissiveness to MeV [24]. A 2013 measles outbreak that afflicted unvaccinated children from a Dutch Orthodox Protestant community provided Laksono and coworkers with a unique opportunity to analyze serial peripheral blood mononuclear cell (PBMC) samples collected before and after measles [26]. These investigators confirmed T/B lymphopenia during prodromal measles. They also detected MeV-infected CD4$^+$ and CD8$^+$ T_M cells, but not T_N cells, which had reached their peak frequencies approximately 1 day before the onset of the characteristic measles rash. By contrast, infected B_N and B_M cells were detectable at similar levels. Importantly, comparing pre- and post-measles samples revealed significant drops in IgG$^+$ and IgA$^+$ B_M cell percentages [26]. Although B_M cells are not the only B cell population targeted by MeV, their depletion should compromise recall responses of humoral nature to a plethora of pathogens. Consistent with this notion, experimental infection of rhesus macaques and natural infection of unvaccinated children with MeV shrunk the size of preexisting antibody repertoires by up to 60% and 73%, respectively [27], likely due to long-lived plasma cell (LLPC) deletion. Some of the missing specificities should recover upon reexposure to cognate Ags. However, some antibodies may be permanently lost if B_N and B_M cells, along with LLPCs, are drastically eliminated. In fact, B cell receptor (BCR) sequencing of pre- and post-measles PBMCs by Petrova and colleagues showed inadequate reconstitution of B_N cell pools as well as a loss of previously expanded B_M cell clones after MeV infection [28].

Petrova and colleagues also employed a ferret model of influenza A virus (IAV) vaccination to document the functional significance of immune amnesia [28]. Infecting IAV-vaccinated ferrets with canine distemper virus (CDV), a morbillivirus closely related to MeV, lowered IAV-neutralizing antibody titers, indicating the abolishment of "serological memory" otherwise maintained by plasma cells. Moreover, CDV infection curtailed the animals' recall response to a secondary IAV challenge and worsened the severity of their flu symptoms.

Unmasking the innate face of immune amnesia

Immunological memory is commonly viewed as a hallmark feature of adaptive immunity. However, numerous studies in the past decade or so have demonstrated that priming innate and innate-like immune cells with a pathogen may prepare or "train" them for stronger responses to the same, similar or even somewhat dissimilar microbes [29].

Up until recently, immune amnesia was discussed exclusively in the context of adaptive immunity, and whether MeV also targets innate, "memory-like" T cells remained unknown. These include mucosa-associated invariant T (MAIT) and invariant natural killer T (*i*NKT) cells, which are regarded as emergency responders to microbial invaders [30–33].

MAIT cells recognize riboflavin precursor derivatives of bacterial and fungal origin, among other compounds, in the context of MHC-related protein 1 (MR1) [34–37] (Fig 2A). *i*NKT cells detect glycolipid Ags, including those derived from pathogens, presented within the hydrophobic pocket of CD1d [38–40] (Fig 2A). The antimicrobial properties of these invariant T (*i*T) cells are owed to their tremendous immunomodulatory and cytolytic activities [32,41–43].

Several phenotypic markers of NK cells (e.g., CD56 and CD161) and mainstream T cells (e.g., CD3) and their memory subset (e.g., CD45RO) are also expressed by many *i*T cells [44–47]. Therefore, *i*T cells may have been given mistaken identities in previous studies, including but not limited to those conducted on measles. This is particularly important in the case of
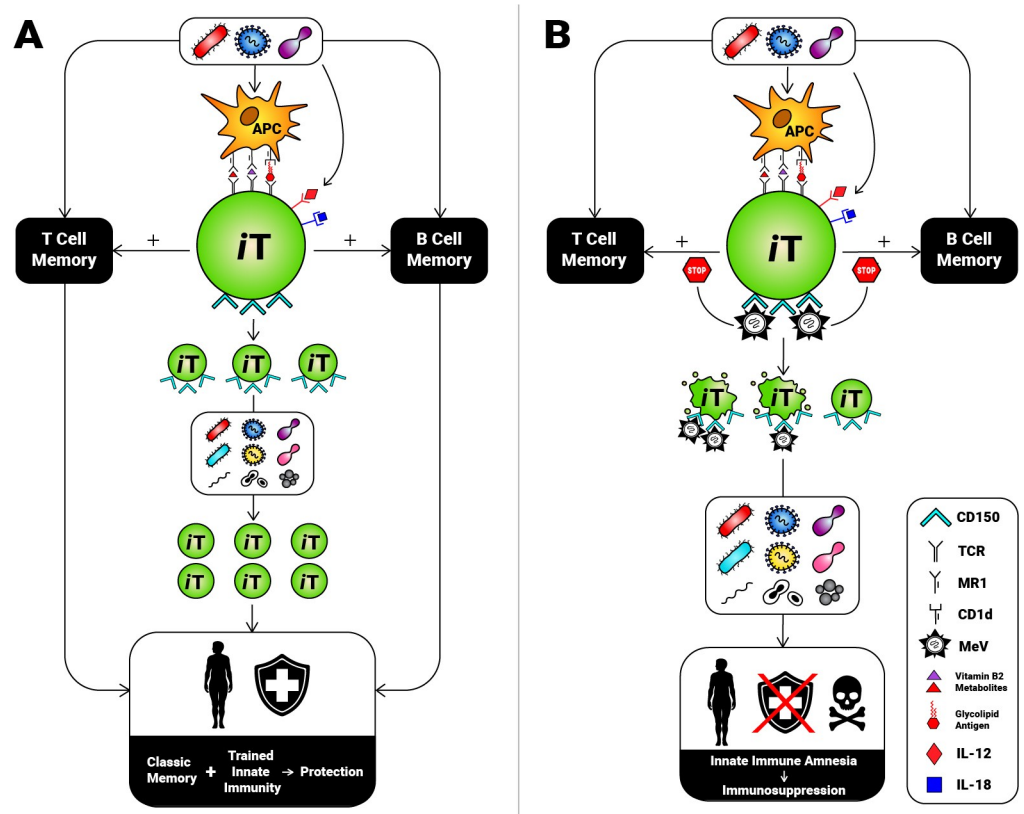
Fig 2. Invariant T cell depletion by MeV results in innate immune amnesia and contributes to adaptive immune amnesia. (A) MAIT and *i*NKT cells recognize certain bacterial and/or fungal components displayed by the monomorphic antigen-presenting molecules MR1 and CD1d, respectively. These *i*T cells can also be activated during viral infections in a cytokine-dependent manner, primarily through IL-12 and IL-18 receptor signaling. *i*T cells may remember their encounter with pathogens or may be "trained" to launch more robust responses to the same, similar, or unrelated microbes in the future. They also promote classic memory cell responses, thus indirectly aiding in cell-mediated and humoral immunity to cognate microbial antigens. (B) *i*T cells express very high levels of CD150 and may be consequently targeted and eliminated by MeV. The net effect is hindered trained immunity and compromised classic memory against a broad spectrum of pathogens, which together cause severe immunosuppression and increased proneness to many infections. APC, antigen-presenting cell; IL, interleukin; *i*NKT, invariant natural killer T [cell]; *i*T, invariant T [cell]; MAIT, mucosa-associated invariant T [cell]; MeV, measles virus; MR1, MHC-related protein 1; TCR, T cell receptor.

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MAIT cells that form a substantial fraction of peripheral blood $CD3^+$, $CD8^+$, and $CD45RO^+$ (or $CD45RA^-$) cells in humans. Of note, human MAIT cells can be loosely divided into interferon (IFN)-γ-producing MAIT-1 and IL-17-producing MAIT-17 subsets with transcriptionally overlapping features [48,49]. Interestingly, of functional T cell subsets, T_H17- and T_H1/T_H17-type cells are reportedly most sensitive to MeV infection in vitro [24] and circulate at reduced frequencies in children with measles [26]. The latter observation lends credence to the possibility of MAIT cell depletion during measles.

Using tetramer reagents to precisely identify human MAIT [36,50] and *i*NKT cells [51,52], we recently demonstrated that CD150 is more highly expressed by *i*T cells than by any other lymphocyte subsets, including T_{CM} and T_{EM} cells [25]. We found MeV to effectively infect *i*T cells and to quickly program MAIT cells for apoptotic death. Based on these results, it is plausible to assume that MeV tracks and destroys *i*T cells, thus putting an important component of innate antimicrobial defense out of commission. This, in turn, renders measles patients prone to a wide range of unrelated infections (Fig 2B). This phenomenon may be referred to as

"innate immune amnesia" for several reasons. First, most iT cells have a T_{EM}-like phenotype [45–47]. Second, genuine memory iT cell pools may exist [53–55]. Third, exposing MAIT cells to infectious agents or vaccine adjuvants may result in their clonal expansion and sustained activation and may also "train" them to respond more vigorously when they encounter the same agent, other stimuli, or even heterologous infections [56–59] (Fig 2A). This is distinct from the fine specificity of adaptive memory. Fourth and perhaps most definitively at this point, iT cells promote conventional memory cell responses [53,59–64]. As such, their depletion by MeV should also negatively impact classic immunological memory (Fig 2B).

The concept of innate immune amnesia is supported by additional findings. First, some of the bacterial culprits of post-measles infections are recognized and responded to by MAIT cells in vitro [65,66]. Second, reactivation of infection with *Mycobacterium tuberculosis*, which is known to elicit MAIT cell responses [55], has been reported after measles [67]. Third, measles-induced mortality due to immunosuppression is typically caused by secondary infections in the respiratory tract, MeV's main port of entry, and also in the gut [68–70]. These are among locations in which MAIT cells strategically reside and operate.

Implications and future directions

MAIT cells comprise up to approximately 10% of all T cells in the human peripheral blood and a substantial fraction of immune cells in mucosal layers—hence their denomination. They fulfill critical roles early in the course of antibacterial and antifungal host responses. They may detect and kill infected cells displaying MR1-bound Ags [42,71–74], transactivate other anti-pathogen effectors such as NK cells, iNKT cells, and cytotoxic T lymphocytes (CTLs) [75–77], and facilitate memory B cell responses [59,64]. They may also participate in tissue repair [78–81], thus indirectly assisting with the maintenance of tissue-resident memory compartments. Therefore, MAIT cell depletion should have serious repercussions for host defense.

The final extrathymic stage of MAIT cell maturation and their homeostasis in the periphery require the presence of commensal bacteria and B cells [82,83]. One may thus speculate that measles-induced peripheral B cell depletion may affect the numerical reconstitution of MAIT cells after measles. To this end, MAIT cells and B cells, among other MeV targets, need to be compared for their reconstitution kinetics. From a qualitative standpoint, it will be important to ascertain whether returning MAIT cells will exhibit bias, for instance in their cytokine production capacity, as they will be gradually reoccupying their niches. This may be studied longitudinally after MeV is cleared and no longer considered an existential threat to either MAIT cells or B cells.

Unlike in mice, iNKT cells are rare in the human peripheral blood and in human tissues. This is with the exception of the omentum [84], historically dubbed as the "abdominal policeman" [85], which serves to promote peritoneal immune responses [86]. Therefore, iNKT cell elimination by MeV may be detrimental to protective immunity in specialized sites.

Viruses are devoid of the riboflavin biosynthesis machinery that supplies prototypic MAIT Ags [35–37] and of glycolipids that stimulate iNKT cells. However, they can still activate iT cells in an MR1/CD1d-independent fashion, predominantly through cytokines like IL-12 and IL-18 [87–89] (Fig 2). As such, innate immune amnesia should also weaken host responses to viral pathogens other than MeV.

To conclude, iT cell depletion by MeV represents a novel immune evasion strategy that impedes memory responses to bacteria, yeasts, and viruses, either directly or indirectly. Therefore, MAIT and iNKT cells may be considered the missing link for measles immunosuppression at the interface between the innate and adaptive arms of immunity. Future studies on experimental and natural measles will need to document the contributions of innate amnesia to immunosuppression in the wake of measles.

Acknowledgments

References

1. Avota E, Gassert E, Schneider-Schaulies S. Measles virus-induced immunosuppression: from effectors to mechanisms. Med Microbiol Immunol. 2010; 199(3):227–37. https://doi.org/10.1007/s00430-010-0152-3 PMID: 20376484.

2. Griffin DE. Measles virus-induced suppression of immune responses. Immunol Rev. 2010; 236:176–89. https://doi.org/10.1111/j.1600-065X.2010.00925.x PMID: 20636817.

3. Dörig RE, Marcil A, Chopra A, Richardson CD. The human CD46 molecule is a receptor for measles virus (Edmonston strain). Cell. 1993; 75(2):295–305. https://doi.org/10.1016/0092-8674(93)80071-l PMID: 8402913.

4. Naniche D, Varior-Krishnan G, Cervoni F, Wild TF, Rossi B, Rabourdin-Combe C, et al. Human membrane cofactor protein (CD46) acts as a cellular receptor for measles virus. J Virol. 1993; 67(10):6025–32. https://doi.org/10.1128/JVI.67.10.6025-6032.1993 PMID: 8371352.

5. Noyce RS, Bondre DG, Ha MN, Lin LT, Sisson G, Tsao MS, et al. Tumor cell marker PVRL4 (nectin 4) is an epithelial cell receptor for measles virus. PLoS Pathog. 2011; 7(8):e1002240. https://doi.org/10.1371/journal.ppat.1002240 PMID: 21901103.

6. Mühlebach MD, Mateo M, Sinn PL, Prüfer S, Uhlig KM, Leonard VH, et al. Adherens junction protein nectin-4 is the epithelial receptor for measles virus. Nature. 2011; 480(7378):530–3. https://doi.org/10.1038/nature10639 PMID: 22048310.

7. Tatsuo H, Ono N, Tanaka K, Yanagi Y. SLAM (CDw150) is a cellular receptor for measles virus. Nature. 2000; 406(6798):893–7. https://doi.org/10.1038/35022579 PMID: 10972291.

8. Hsu EC, Iorio C, Sarangi F, Khine AA, Richardson CD. CDw150(SLAM) is a receptor for a lymphotropic strain of measles virus and may account for the immunosuppressive properties of this virus. Virology. 2001; 279(1):9–21. https://doi.org/10.1006/viro.2000.0711 PMID: 11145884.

9. Erlenhoefer C, Wurzer WJ, Löffler S, Schneider-Schaulies S, ter Meulen V, Schneider-Schaulies J. CD150 (SLAM) is a receptor for measles virus but is not involved in viral contact-mediated proliferation inhibition. J Virol. 2001; 75(10):4499–505. https://doi.org/10.1128/JVI.75.10.4499-4505.2001 PMID: 11312320.

10. Pirquet C. Das Verhalten der kutanen Tuberkulinreaktion während der Masern. Dtsch Med Wochenschr. 1908; 34(30):1297–300. https://doi.org/10.1055/s-0028-1135624

11. Ferreira CS, Frenzke M, Leonard VH, Welstead GG, Richardson CD, Cattaneo R. Measles virus infection of alveolar macrophages and dendritic cells precedes spread to lymphatic organs in transgenic mice expressing human signaling lymphocytic activation molecule (SLAM, CD150). J Virol. 2010; 84 (6):3033–42. https://doi.org/10.1128/JVI.01559-09 PMID: 20042501.

12. Mesman AW, de Vries RD, McQuaid S, Duprex WP, de Swart RL, Geijtenbeek TB. A prominent role for DC-SIGN+ dendritic cells in initiation and dissemination of measles virus infection in non-human primates. PLoS ONE. 2012; 7(12):e49573. https://doi.org/10.1371/journal.pone.0049573 PMID: 23227146.

13. Allen IV, McQuaid S, Penalva R, Ludlow M, Duprex WP, Rima BK. Macrophages and Dendritic Cells Are the Predominant Cells Infected in Measles in Humans. mSphere. 2018; 3(3). https://doi.org/10.1128/mSphere.00570-17 PMID: 29743202.

14. Grosjean I, Caux C, Bella C, Berger I, Wild F, Banchereau J, et al. Measles virus infects human dendritic cells and blocks their allostimulatory properties for CD4+ T cells. J Exp Med. 1997; 186(6):801–12. https://doi.org/10.1084/jem.186.6.801 PMID: 9294135.

15. Fugier-Vivier I, Servet-Delprat C, Rivailler P, Rissoan MC, Liu YJ, Rabourdin-Combe C. Measles virus suppresses cell-mediated immunity by interfering with the survival and functions of dendritic and T cells. J Exp Med. 1997; 186(6):813–23. https://doi.org/10.1084/jem.186.6.813 PMID: 9294136.

16. Romanets-Korbut O, Kovalevska LM, Seya T, Sidorenko SP, Horvat B. Measles virus hemagglutinin triggers intracellular signaling in CD150-expressing dendritic cells and inhibits immune response. Cell Mol Immunol. 2016; 13(6):828–38. https://doi.org/10.1038/cmi.2015.55 PMID: 26073466.

17. Naniche D, Reed SI, Oldstone MB. Cell cycle arrest during measles virus infection: a G0-like block leads to suppression of retinoblastoma protein expression. J Virol. 1999; 73(3):1894–901. https://doi.org/10.1128/JVI.73.3.1894-1901.1999 PMID: 9971768.

18. Griffin DE, Ward BJ. Differential CD4 T cell activation in measles. J Infect Dis. 1993; 168(2):275–81. https://doi.org/10.1093/infdis/168.2.275 PMID: 8101549.

19. Moss WJ, Ryon JJ, Monze M, Griffin DE. Differential regulation of interleukin (IL)-4, IL-5, and IL-10 during measles in Zambian children. J Infect Dis. 2002; 186(7):879–87. https://doi.org/10.1086/344230 PMID: 12232827.

20. Yu XL, Cheng YM, Shi BS, Qian FX, Wang FB, Liu XN, et al. Measles virus infection in adults induces production of IL-10 and is associated with increased CD4+ CD25+ regulatory T cells. J Immunol. 2008; 181(10):7356–66. https://doi.org/10.4049/jimmunol.181.10.7356 PMID: 18981159.

21. de Vries RD, McQuaid S, van Amerongen G, Yüksel S, Verburgh RJ, Osterhaus AD, et al. Measles immune suppression: lessons from the macaque model. PLoS Pathog. 2012; 8(8):e1002885. https://doi.org/10.1371/journal.ppat.1002885 PMID: 22952446.

22. Condack C, Grivel JC, Devaux P, Margolis L, Cattaneo R. Measles virus vaccine attenuation: suboptimal infection of lymphatic tissue and tropism alteration. J Infect Dis. 2007; 196(4):541–9. https://doi.org/10.1086/519689 PMID: 17624839

23. de Swart RL, Ludlow M, de Witte L, Yanagi Y, van Amerongen G, McQuaid S, et al. Predominant infection of CD150+ lymphocytes and dendritic cells during measles virus infection of macaques. PLoS Pathog. 2007; 3(11):e178. https://doi.org/10.1371/journal.ppat.0030178 PMID: 18020706.

24. Laksono BM, Grosserichter-Wagener C, de Vries RD, Langeveld SAG, Brem MD, van Dongen JJM, et al. In Vitro Measles Virus Infection of Human Lymphocyte Subsets Demonstrates High Susceptibility and Permissiveness of both Naive and Memory B Cells. J Virol. 2018; 92(8). https://doi.org/10.1128/JVI.00131-18 PMID: 29437964

25. Rudak PT, Yao T, Richardson CD, Haeryfar SMM. Measles Virus Infects and Programs MAIT Cells for Apoptosis. J Infect Dis. 2020. https://doi.org/10.1093/infdis/jiaa407 PMID: 32623457.

26. Laksono BM, de Vries RD, Verburgh RJ, Visser EG, de Jong A, Fraaij PLA, et al. Studies into the mechanism of measles-associated immune suppression during a measles outbreak in the Netherlands. Nat Commun. 2018; 9(1):4944. https://doi.org/10.1038/s41467-018-07515-0 PMID: 30470742.

27. Mina MJ, Kula T, Leng Y, Li M, de Vries RD, Knip M, et al. Measles virus infection diminishes preexisting antibodies that offer protection from other pathogens. Science. 2019; 366(6465):599–606. https://doi.org/10.1126/science.aay6485 PMID: 31672891.

28. Petrova VN, Sawatsky B, Han AX, Laksono BM, Walz L, Parker E, et al. Incomplete genetic reconstitution of B cell pools contributes to prolonged immunosuppression after measles. Sci Immunol. 2019; 4 (41). https://doi.org/10.1126/sciimmunol.aay6125 PMID: 31672862.

29. Lau CM, Sun JC. The widening spectrum of immunological memory. Curr Opin Immunol. 2018; 54:42–9. https://doi.org/10.1016/j.coi.2018.05.013 PMID: 29902670.

30. Howson LJ, Salio M, Cerundolo V. MR1-Restricted Mucosal-Associated Invariant T Cells and Their Activation during Infectious Diseases. Front Immunol. 2015; 6:303. https://doi.org/10.3389/fimmu.2015.00303 PMID: 26136743.

31. Napier RJ, Adams EJ, Gold MC, Lewinsohn DM. The Role of Mucosal Associated Invariant T Cells in Antimicrobial Immunity. Front Immunol. 2015; 6:344. https://doi.org/10.3389/fimmu.2015.00344 PMID: 26217338.

32. Haeryfar SM, Mallevaey T. Editorial: CD1- and MR1-Restricted T Cells in Antimicrobial Immunity. Front Immunol. 2015; 6:611. https://doi.org/10.3389/fimmu.2015.00611 PMID: 26697007.

33. Shaler CR, Choi J, Rudak PT, Memarnejadian A, Szabo PA, Tun-Abraham ME, et al. MAIT cells launch a rapid, robust and distinct hyperinflammatory response to bacterial superantigens and quickly acquire an anergic phenotype that impedes their cognate antimicrobial function: Defining a novel mechanism of superantigen-induced immunopathology and immunosuppression. PLoS Biol. 2017; 15(6):e2001930. https://doi.org/10.1371/journal.pbio.2001930 PMID: 28632753.

34. Le Bourhis L, Martin E, Péguillet I, Guihot A, Froux N, Coré M, et al. Antimicrobial activity of mucosal-associated invariant T cells. Nat Immunol. 2010; 11(8):701–8. https://doi.org/10.1038/ni.1890 PMID: 20581831.

35. Kjer-Nielsen L, Patel O, Corbett AJ, Le Nours J, Meehan B, Liu L, et al. MR1 presents microbial vitamin B metabolites to MAIT cells. Nature. 2012; 491(7426):717–23. https://doi.org/10.1038/nature11605 PMID: 23051753.

36. Corbett AJ, Eckle SB, Birkinshaw RW, Liu L, Patel O, Mahony J, et al. T-cell activation by transitory neo-antigens derived from distinct microbial pathways. Nature. 2014; 509(7500):361–5. https://doi.org/10.1038/nature13160 PMID: 24695216.

37. Soudais C, Samassa F, Sarkis M, Le Bourhis L, Bessoles S, Blanot D, et al. In Vitro and In Vivo Analysis of the Gram-Negative Bacteria-Derived Riboflavin Precursor Derivatives Activating Mouse MAIT Cells. J Immunol. 2015; 194(10):4641–9. https://doi.org/10.4049/jimmunol.1403224 PMID: 25870247.

38. Kawano T, Cui J, Koezuka Y, Toura I, Kaneko Y, Motoki K, et al. CD1d-restricted and TCR-mediated activation of valpha14 NKT cells by glycosylceramides. Science. 1997; 278(5343):1626–9. https://doi.org/10.1126/science.278.5343.1626 PMID: 9374463.

39. Mattner J, Debord KL, Ismail N, Goff RD, Cantu C III, Zhou D, et al. Exogenous and endogenous glycolipid antigens activate NKT cells during microbial infections. Nature. 2005; 434(7032):525–9. https://doi.org/10.1038/nature03408 PMID: 15791258.

40. Kinjo Y, Illarionov P, Vela JL, Pei B, Girardi E, Li X, et al. Invariant natural killer T cells recognize glycolipids from pathogenic Gram-positive bacteria. Nat Immunol. 2011; 12(10):966–74. https://doi.org/10.1038/ni.2096 PMID: 21892173.

41. Lee WY, Sanz MJ, Wong CH, Hardy PO, Salman-Dilgimen A, Moriarty TJ, et al. Invariant natural killer T cells act as an extravascular cytotoxic barrier for joint-invading Lyme Borrelia. Proc Natl Acad Sci U S A. 2014; 111(38):13936–41. https://doi.org/10.1073/pnas.1404769111 PMID: 25205813.

42. Rudak PT, Choi J, Haeryfar SMM. MAIT cell-mediated cytotoxicity: Roles in host defense and therapeutic potentials in infectious diseases and cancer. J Leukoc Biol. 2018; 104(3):473–86. https://doi.org/10.1002/JLB.4RI0118-023R PMID: 29668066.

43. Hapil FZ, Wingender G. The interaction between invariant Natural Killer T cells and the mucosal microbiota. Immunology. 2018; 155(2):164–75. https://doi.org/10.1111/imm.12958 PMID: 29893412.

44. Prussin C, Foster B. TCR V alpha 24 and V beta 11 coexpression defines a human NK1 T cell analog containing a unique Th0 subpopulation. J Immunol. 1997; 159(12):5862–70. PMID: 9550382.

45. Sandberg JK, Bhardwaj N, Nixon DF. Dominant effector memory characteristics, capacity for dynamic adaptive expansion, and sex bias in the innate Valpha24 NKT cell compartment. Eur J Immunol. 2003; 33(3):588–96. https://doi.org/10.1002/eji.200323707 PMID: 12616479.

46. Montoya CJ, Pollard D, Martinson J, Kumari K, Wasserfall C, Mulder CB, et al. Characterization of human invariant natural killer T subsets in health and disease using a novel invariant natural killer T cell-clonotypic monoclonal antibody, 6B11. Immunology. 2007; 122(1):1–14. https://doi.org/10.1111/j.1365-2567.2007.02647.x PMID: 17662044.

47. Dusseaux M, Martin E, Serriari N, Péguillet I, Premel V, Louis D, et al. Human MAIT cells are xenobiotic-resistant, tissue-targeted, CD161hi IL-17-secreting T cells. Blood. 2011; 117(4):1250–9. https://doi.org/10.1182/blood-2010-08-303339 PMID: 21084709.

48. Dias J, Sandberg JK, Leeansyah E. Extensive Phenotypic Analysis, Transcription Factor Profiling, and Effector Cytokine Production of Human MAIT Cells by Flow Cytometry. Methods Mol Biol. 2017; 1514:241–56. https://doi.org/10.1007/978-1-4939-6548-9_17 PMID: 27787804.

49. Salou M, Legoux F, Gilet J, Darbois A, du Halgouet A, Alonso R, et al. A common transcriptomic program acquired in the thymus defines tissue residency of MAIT and NKT subsets. J Exp Med. 2019; 216 (1):133–51. https://doi.org/10.1084/jem.20181483 PMID: 30518599.

50. Reantragoon R, Corbett AJ, Sakala IG, Gherardin NA, Furness JB, Chen Z, et al. Antigen-loaded MR1 tetramers define T cell receptor heterogeneity in mucosal-associated invariant T cells. J Exp Med. 2013; 210(11):2305–20. https://doi.org/10.1084/jem.20130958 PMID: 24101382.

51. Benlagha K, Weiss A, Beavis A, Teyton L, Bendelac A. In vivo identification of glycolipid antigen-specific T cells using fluorescent CD1d tetramers. J Exp Med. 2000; 191(11):1895–903. https://doi.org/10.1084/jem.191.11.1895 PMID: 10839805.

52. Matsuda JL, Naidenko OV, Gapin L, Nakayama T, Taniguchi M, Wang CR, et al. Tracking the response of natural killer T cells to a glycolipid antigen using CD1d tetramers. J Exp Med. 2000; 192(5):741–54. https://doi.org/10.1084/jem.192.5.741 PMID: 10974039.

53. Chen Z, Zhu S, Wang L, Xie D, Zhang H, Li X, et al. Memory Follicular Helper Invariant NKT Cells Recognize Lipid Antigens on Memory B Cells and Elicit Antibody Recall Responses. J Immunol. 2018; 200 (9):3117–27. https://doi.org/10.4049/jimmunol.1701026 PMID: 29581354.

54. Wang H, D'Souza C, Lim XY, Kostenko L, Pediongco TJ, Eckle SBG, et al. MAIT cells protect against pulmonary Legionella longbeachae infection. Nat Commun. 2018; 9(1):3350. https://doi.org/10.1038/s41467-018-05202-8 PMID: 30135490.

55. Wong EB, Gold MC, Meermeier EW, Xulu BZ, Khuzwayo S, Sullivan ZA, et al. TRAV1-2(+) CD8(+) T-cells including oligoconal expansions of MAIT cells are enriched in the airways in human tuberculosis. Commun Biol. 2019; 2:203. https://doi.org/10.1038/s42003-019-0442-2 PMID: 31231693.

56. Mpina M, Maurice NJ, Yajima M, Slichter CK, Miller HW, Dutta M, et al. Controlled Human Malaria Infection Leads to Long-Lasting Changes in Innate and Innate-like Lymphocyte Populations. J Immunol. 2017; 199(1):107–18. https://doi.org/10.4049/jimmunol.1601989 PMID: 28576979.

57. Howson LJ, Napolitani G, Shepherd D, Ghadbane H, Kurupati P, Preciado-Llanes L, et al. MAIT cell clonal expansion and TCR repertoire shaping in human volunteers challenged with Salmonella Paratyphi A. Nat Commun. 2018; 9(1):253. https://doi.org/10.1038/s41467-017-02540-x PMID: 29343684.

58. Suliman S, Murphy M, Musvosvi M, Gela A, Meermeier EW, Geldenhuys H, et al. MR1-Independent Activation of Human Mucosal-Associated Invariant T Cells by Mycobacteria. J Immunol. 2019; 203 (11):2917–27. https://doi.org/10.4049/jimmunol.1900674 PMID: 31611259.

59. Rahman MA, Ko EJ, Bhuyan F, Enyindah-Asonye G, Hunegnaw R, Helmold Hait S, et al. Mucosal-associated invariant T (MAIT) cells provide B-cell help in vaccinated and subsequently SIV-infected Rhesus Macaques. Sci Rep. 2020; 10(1):10060. https://doi.org/10.1038/s41598-020-66964-0 PMID: 32572140.

60. Galli G, Pittoni P, Tonti E, Malzone C, Uematsu Y, Tortoli M, et al. Invariant NKT cells sustain specific B cell responses and memory. Proc Natl Acad Sci U S A. 2007; 104(10):3984–9. https://doi.org/10.1073/pnas.0700191104 PMID: 17360464.

61. Guillonneau C, Mintern JD, Hubert FX, Hurt AC, Besra GS, Porcelli S, et al. Combined NKT cell activation and influenza virus vaccination boosts memory CTL generation and protective immunity. Proc Natl Acad Sci U S A. 2009; 106(9):3330–5. https://doi.org/10.1073/pnas.0813309106 PMID: 19211791.

62. Reilly EC, Thompson EA, Aspeslagh S, Wands JR, Elewaut D, Brossay L. Activated iNKT cells promote memory CD8+ T cell differentiation during viral infection. PLoS ONE. 2012; 7(5):e37991. https://doi.org/10.1371/journal.pone.0037991 PMID: 22649570.

63. Shimizu K, Asakura M, Shinga J, Sato Y, Kitahara S, Hoshino K, et al. Invariant NKT cells induce plasmacytoid dendritic cell (DC) cross-talk with conventional DCs for efficient memory CD8+ T cell induction. J Immunol. 2013; 190(11):5609–19. https://doi.org/10.4049/jimmunol.1300033 PMID: 23630347.

64. Bennett MS, Trivedi S, Iyer AS, Hale JS, Leung DT. Human mucosal-associated invariant T (MAIT) cells possess capacity for B cell help. J Leukoc Biol. 2017; 102(5):1261–9. https://doi.org/10.1189/jlb.4A0317-116R PMID: 28807929.

65. Perry RT, Halsey NA. The clinical significance of measles: a review. J Infect Dis. 2004; 189(Suppl 1): S4–16. https://doi.org/10.1086/377712 PMID: 15106083.

66. Trottein F, Paget C. Natural Killer T Cells and Mucosal-Associated Invariant T Cells in Lung Infections. Front Immunol. 2018; 9:1750. https://doi.org/10.3389/fimmu.2018.01750 PMID: 30116242.

67. Moss WJ, Griffin DE. Measles. Lancet. 2012; 379(9811):153–64. https://doi.org/10.1016/S0140-6736(10)62352-5 PMID: 21855993.

68. Beckford AP, Kaschula RO, Stephen C. Factors associated with fatal cases of measles. A retrospective autopsy study. S Afr Med J. 1985; 68(12):858–63. PMID: 3877996.

69. Shanks GD, Hu Z, Waller M, Lee SE, Terfa D, Howard A, et al. Measles epidemics of variable lethality in the early 20th century. Am J Epidemiol. 2014; 179(4):413–22. https://doi.org/10.1093/aje/kwt282 PMID: 24284015.

70. Akramuzzaman SM, Cutts FT, Wheeler JG, Hossain MJ. Increased childhood morbidity after measles is short-term in urban Bangladesh. Am J Epidemiol. 2000; 151(7):723–35. https://doi.org/10.1093/oxfordjournals.aje.a010267 PMID: 10752800.

71. Le Bourhis L, Dusseaux M, Bohineust A, Bessoles S, Martin E, Premel V, et al. MAIT cells detect and efficiently lyse bacterially-infected epithelial cells. PLoS Pathog. 2013; 9(10):e1003681. https://doi.org/10.1371/journal.ppat.1003681 PMID: 24130485.

72. Kurioka A, Ussher JE, Cosgrove C, Clough C, Fergusson JR, Smith K, et al. MAIT cells are licensed through granzyme exchange to kill bacterially sensitized targets. Mucosal Immunol. 2015; 8(2):429–40. https://doi.org/10.1038/mi.2014.81 PMID: 25269706.

73. Booth JS, Salerno-Goncalves R, Blanchard TG, Patil SA, Kader HA, Safta AM, et al. Mucosal-Associated Invariant T Cells in the Human Gastric Mucosa and Blood: Role in Helicobacter pylori Infection. Front Immunol. 2015; 6:466. https://doi.org/10.3389/fimmu.2015.00466 PMID: 26441971.

74. Jeffery HC, van Wilgenburg B, Kurioka A, Parekh K, Stirling K, Roberts S, et al. Biliary epithelium and liver B cells exposed to bacteria activate intrahepatic MAIT cells through MR1. J Hepatol. 2016; 64 (5):1118–27. https://doi.org/10.1016/j.jhep.2015.12.017 PMID: 26743076.

75. Miyazaki Y, Miyake S, Chiba A, Lantz O, Yamamura T. Mucosal-associated invariant T cells regulate Th1 response in multiple sclerosis. Int Immunol. 2011; 23(9):529–35. https://doi.org/10.1093/intimm/dxr047 PMID: 21712423.

76. Salio M, Gasser O, Gonzalez-Lopez C, Martens A, Veerapen N, Gileadi U, et al. Activation of Human Mucosal-Associated Invariant T Cells Induces CD40L-Dependent Maturation of Monocyte-Derived and Primary Dendritic Cells. J Immunol. 2017; 199(8):2631–8. https://doi.org/10.4049/jimmunol.1700615 PMID: 28877992.

77. Haeryfar SMM, Shaler CR, Rudak PT. Mucosa-associated invariant T cells in malignancies: a faithful friend or formidable foe? Cancer Immunol Immunother. 2018; 67(12):1885–96. https://doi.org/10.1007/s00262-018-2132-1 PMID: 29470597.

78. Lamichhane R, Schneider M, de la Harpe SM, Harrop TWR, Hannaway RF, Dearden PK, et al. TCR- or Cytokine-Activated CD8(+) Mucosal-Associated Invariant T Cells Are Rapid Polyfunctional Effectors That Can Coordinate Immune Responses. Cell Rep. 2019; 28(12):3061–3076.e3065. https://doi.org/10.1016/j.celrep.2019.08.054 PMID: 31533031.

79. Leng T, Akther HD, Hackstein CP, Powell K, King T, Friedrich M, et al. TCR and Inflammatory Signals Tune Human MAIT Cells to Exert Specific Tissue Repair and Effector Functions. Cell Rep. 2019; 28 (12):3077–3091.e3075. https://doi.org/10.1016/j.celrep.2019.08.050 PMID: 31533032.

80. Hinks TSC, Marchi E, Jabeen M, Olshansky M, Kurioka A, Pediongco TJ, et al. Activation and In Vivo Evolution of the MAIT Cell Transcriptome in Mice and Humans Reveals Tissue Repair Functionality. Cell Rep. 2019; 28(12):3249–3262.e3245. https://doi.org/10.1016/j.celrep.2019.07.039 PMID: 31533045.

81. Constantinides MG, Link VM, Tamoutounour S, Wong AC, Perez-Chaparro PJ, Han SJ, et al. MAIT cells are imprinted by the microbiota in early life and promote tissue repair. Science. 2019; 366(6464). https://doi.org/10.1126/science.aax6624 PMID: 31649166.

82. Treiner E, Duban L, Bahram S, Radosavljevic M, Wanner V, Tilloy F, et al. Selection of evolutionarily conserved mucosal-associated invariant T cells by MR1. Nature. 2003; 422(6928):164–9. https://doi.org/10.1038/nature01433 PMID: 12634786.

83. Martin E, Treiner E, Duban L, Guerri L, Laude H, Toly C, et al. Stepwise development of MAIT cells in mouse and human. PLoS Biol. 2009; 7(3):e54. https://doi.org/10.1371/journal.pbio.1000054 PMID: 19278296.

84. Lynch L, O'Shea D, Winter DC, Geoghegan J, Doherty DG, O'Farrelly C. Invariant NKT cells and CD1d (+) cells amass in human omentum and are depleted in patients with cancer and obesity. Eur J Immunol. 2009; 39(7):1893–901. https://doi.org/10.1002/eji.200939349 PMID: 19585513.

85. Morison R. Remarks On Some Functions of the Omentum. Br Med J. 1906; 1(2350):76–8. https://doi.org/10.1136/bmj.1.2350.76 PMID: 20762478.

86. Meza-Perez S, Randall TD. Immunological Functions of the Omentum. Trends Immunol. 2017; 38 (7):526–36. https://doi.org/10.1016/j.it.2017.03.002 PMID: 28579319.

87. van Wilgenburg B, Scherwitzl I, Hutchinson EC, Leng T, Kurioka A, Kulicke C, et al. MAIT cells are activated during human viral infections. Nat Commun. 2016; 7:11653. https://doi.org/10.1038/ncomms11653 PMID: 27337592.

88. Loh L, Wang Z, Sant S, Koutsakos M, Jegaskanda S, Corbett AJ, et al. Human mucosal-associated invariant T cells contribute to antiviral influenza immunity via IL-18-dependent activation. Proc Natl Acad Sci U S A. 2016; 113(36):10133–8. https://doi.org/10.1073/pnas.1610750113 PMID: 27543331.

89. Paquin-Proulx D, Avelino-Silva VI, Santos BAN, Silveira Barsotti N, Siroma F, Fernandes Ramos J, et al. MAIT cells are activated in acute Dengue virus infection and after in vitro Zika virus infection. PLoS Negl Trop Dis. 2018; 12(1):e0006154. https://doi.org/10.1371/journal.pntd.0006154 PMID: 29357366.