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Respiratory Syncytial Virus Persistence

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Introduction

Respiratory syncytial virus (RSV) is prevalent and highly infectious, more so than any other respiratory virus. Worldwide, it is a very important pathogen, causing acute upper- and lower-respiratory-tract infections (URT and LRT, respectively), especially in infants and young children [1-6].

Morbidity and Mortality

RSV is considered to be the most frequent cause of pneumonia and bronchiolitis, with bronchiolitis being the single most common cause for the hospitalization of infants [1,5-8]. RSV is also an important cause of morbidity and mortality in the elderly and the immunocompromised. In the elderly it is the second leading cause of viral death, with a reported 5.5% annual incidence; in high-risk adult populations [5,6,9,10] the incidence rises to 10%.

Recent estimates made by the World Health Organization [WHO) indicate that, worldwide, RSV causes 64 million cases of morbidity and 160,000 deaths each year and accounts for more than 60% of acute LRT infection in children and more than 80% in infants [6-8,11].

RSV Infection

Clinical manifestations

Infection by virus starts in the nose and/or the eyes by the introduction of viral particles in an aerosol or by direct contact with fluids containing the virus [1,6,7,12,13]. Once the virus has penetrated the cells of the epithelium, replication of the virus takes place in the nasopharynx; the incubation period is 4–5 days, although in some cases it is longer [7,12,14]. Normally, infection is confined to the superficial cells of the respiratory epithelium and is restricted to the respiratory epithelium [1,4,7,11]. Virus can be spread to the lower respiratory tract (LRT), probably through aspiration of secretions, although the possibility of transmission by cell-to-cell fusion cannot be discarde [4,6,14]. The inflammatory response associated with this infection is extremely complex [15], and involves the release of multiple cytokines and chemokines from epithelium cells and from infiltrating immunocytes, local neuro-immune interactions, and mast-cell degranulation with variable release of leukotrines [16-19].

Epidemiology

LRT infections caused by RSV occur epidemically every year [6-11]. The seasonal appearance of these epidemics seems to vary with latitude, altitude, and climate, with the epidemic pattern tending to occur in clusters. The season in which RSV epidemics occur depends on geographic location and altitude. Although varying from continent to continent, outbreaks usually begin in coastal areas [1,6].

Seasonal RSV outbreaks occur each year throughout the world, with the peak and duration of an outbreak varying from one year to the next. Outbreaks occur during the winter months: in the northern hemisphere, the annual epidemics normally start in November, peak in January and February, and end in May; in the southern hemisphere, the epidemic season runs from May through September. In the tropics, epidemics peak during the rainy season [1,6,11].

Long term sequelae

Young children who have recovered from severe bronchiolitis often develop chronic and recurrent respiratory problems [2,6,19], and appear prone to early allergic sensitization [2,3,6]. The link between RSV infection and the development of sequelae (wheezing, asthma [19-23], and chronic obstructive pulmonary disease (COPD) has been clearly established in several well controlled prospective epidemiological studies [24-26]. RSV bronchiolitis in infancy has been reported to be an important risk factor for subsequent respiratory complication [23,27-31].

RSV Persistence

Because RSV does not produce vigorous immune response that allows reinfection [1,6,7,15], it is likely RSV may alter the immunity response as a strategy to permit persistence in host cells [15,32,33].

In humans

The effects of the sequelae of severe RSV disease may be explained, in part, by viral persistence, with the RSV infection causing an alteration of the airway structure and/or inducing an aberrant immune response [25,29,30]. Continuous stimulation of the immune system by persistent virus infections may cause chronic inflammation or alter the expression of immunoregulatory molecules [35,36], such outcomes may explain the clinical manifestations that persist long after acute viral infection. Infected epithelial cells and macrophages secrete cytokines, chemokines, and other factors that attract lymphocytes and other cells to the site of infection, thus resulting in airway inflammation [37,38]

The seasonality of RSV infection with little activity in summer month suggests that after acute infection the reservoir for RSV is the host and that, under suitable conditions, viral reactivation may result in re-infection and recurrence of the natural cycle [32]. Because, to date, no animal reservoir of RSV has been demonstrated [1,6], viral persistence in humans may be involved in maintaining the virus during inter-epidemic periods.

Although RSV persistence in humans has not been demonstrated, some observations indicate that persistent infections may occur in humans: 1) the presence of RSV antigen in bone biopsies and in cells cultured from patients with Paget disease was detected by using immunohistological assays [39]; 2) shedding of infective RSV was observed in immunocompromised patients [40]; 3) RSV was isolated repeatedly from the nasopharynx of apparently healthy children [41]; 4) RSV nucleic acid was detected in archival postmortem lung tissue from infants, who had died during the summer, without apparent clinical disease having been reported, thus suggesting that the virus

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can persist in lungs after acute infection [42]; and 5) individuals with COPD have been reported to have persistent RSV infection [24,25,43].

Taken together, the findings from these studies suggest the possibility that acute RSV infection in the winter, with subsequent resolution of symptoms, could be followed by chronic persistence of RSV in human lung tissue [14,32]. Furthermore, viral recovery and infectivity might be triggered through suppression of adaptive immunity, thus resulting in re-infection and recurrence of the RSV season the following year [6]. This interpretation of the cycle of RSV infection would be particularly applicable in elderly and COPD patients [5,44].

In animal models

RSV has been reported to persist in experimentally infected guinea pigs and mice. Viral proteins and genomic RNA were found in the lungs of infected guinea pigs at least 60 days after inoculation [45]. which presented persistent airway abnormalities, hyper-reactivity and eosinophila [46-48].

In mice, RSV latency and persistence, has been evidenced by the presence of genomic RNA or messenger RNA, respectively. In RSV infected BALB/c mice, viral genome and messenger RNA, was found in lung homogenates for more than 100 days after acute infection and all signs were resolved [49,50]. By T cells depletion, infective virus at low levels was obtained, suggesting that RSV persists at low-grade replication [49]. Moreover, RSV infection induced airway long-term disease, characterized by chronic inflammation and hyper-reactivity [51].

In vitro

RSV is relatively non-lytic in most human and animal epithelial and immune cell types and easily establishes stable, persistent infections in cell lines by infection with RSV Long strain or temperature-sensitive mutants. These cultures are characterized by low titers of extracellular infective virus and by a high percentage (90-100%), of infected cells presenting viral antigen, with no formation of syncytia and no apparent cellular cytopathology [52-57].

Viral persistence in cell lines experimentally infected with virus provides an excellent system to investigate changes in the expression profiles of virus and host genes by due to the continuous replication of viral genes in a cell by altering non-essential functions ["luxus activities"] viral chronicity can selectively disorder the functions of the infected cell without destroying it [58].

RSV persistent infection in human and mouse cell lines alters gene expression in these cells. The rate of surface viral proteins are severity reduced in persistently RSV infected cells (BCH-4) of BALB/c, compared to that of internal viral proteins and lytically infected human larynx epithelial (HEp-2) cells [59].

DNA microarray analyses of persistently infected cell lines, mouse macrophage-like P388D1 [60], and Hep-2 [61], showed that RSV persistence subverted apoptotic pathways through up- and down-regulation of expression of cellular apoptotic genes. Expression of anti-apoptotic proteins, Bcl-2, Bcl-X, and X-linked inhibitor of apoptosis protein (XIAP), was enhanced [60], and TNF-receptor-associated factor 1 [TRAF1] [61], and baculoviral IAP [60]. Moreover, in both cell lines, the mRNA levels of caspase 3, 8, and 9 were reduced with respect to those of non-infected cells [60,61]. The activity of caspase-3 was reduced and that of caspase-9 could not be detected in infected P388D1 macrophages [60].

RSV persistence in HEp-2 and in P388D1 induced significant changes in the expression of interleukins and chemokines, compared with that in non-infected cells. Increases in the expression of interleukins IL-1b and IL-6 [36], and of chemokines CCL3, MIP-1α, CCL3L1, CCL5 [RANTES], CXCL10 [IP-10], and MIP-2 were reported [61].

The pattern of chemokine expression may determine the nature of the pulmonary cellular infiltrate and, hence, the extent of inflammation [62]. In addition, the up-and/or down-regulation of some cytokines and interleukins has been shown to favor the establishment of virus persistence [63,64].

Conclusion

Mounting evidence, obtained in prospective studies in humans, suggests that RSV may persist latently or at a low level of replication in immunologically privileged sites in the lung and that RSV persistence may be associated with the link between RSV LRT infection and sequelae of airway hyper-reactivity. Moreover, RSV persistence has been suggested as an aggravating agent in patients with stable COPD and in those suffering exacerbations. Because no animal reservoir has been described for this virus, RSV persistence in humans has been proposed to explain not only these sequelae, but also virus survival between seasonal epidemics.

Results of studies in animals experimentally infected with RSV not only have documented instances of RSV persistence, but also have led to the hypothesis that RSV persists at low replication levels in the lung.

Persistence of RSV in immune and non-immune cell lines of both humans and animals has been reported and significant changes in the gene expression of pro-inflammatory interleukins and chemokines of the host have been observed. Persistent RSV infection of the lung may lead to prolonged inflammation and chronic respiratory disease. A continuous and/or unbalanced production of some cytokines may contribute to such a scenario.

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References

1. Collins PL, Melero JA (2011) Progress in understanding and controlling respiratory syncytial virus: Still crazy after all these years. Virus Res 162: 80-99.
2. Hall CB (1983) Respiratory syncytial virus. Isr J Med Sci 19: 889-891.
3. Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Hall CB (2009) The burden of respiratory syncytial virus infection in young children. N Engl J Med 360: 588-598.
4. Hall CB, Douglas RG, Geiman JM (1976) Respiratory syncytial virus infections in infants: quantitation and duration of shedding. J Pediatr 89: 11-15.
5. Dowell SF, Anderson LJ, Gary HE, Erdman DD, Plouffe JF, et al. (1996) Respiratory syncytial virus is an important cause of community-acquired lower respiratory infection among hospitalized adults. J Infect Dis 174: 456-462.
6. Collins PL, Crowe JEJ (2007) Respiratory Syncytial Virus and Metapneumovirus. Philadelphia P A Lippincott Williams & Wilkins p 1601-1646.
7. Tregoning JS, Schwarze J (2010) Respiratory viral infections in infants: causes clinical symptoms virology and immunology. Clin Microbiol Rev 23: 174-198.
8. Shay DK, Holman RC, Roosevelt GE, Clarke MJ, Anderson LJ (2001) Bronchiolitis-associated mortality and estimates of respiratory syncytial virus-associated deaths among US children 1979-1997. J Infect Dis 183: 16-22.
9. Falsey AR, Walsh EE (2000) Respiratory syncytial virus infection in adults. Clin Microbiol Rev 13: 371-384.

10. Falsey AR (2005) Respiratory syncytial virus infection in elderly and high-risk adults. Exp Lung Res 31 Suppl 1: 77.

11. Welliver RC (2003) Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. J Pediatr 143: S112-117.

12. Hall CB, Douglas RG, Schnabel KC, Geiman JM (1981) Infectivity of respiratory syncytial virus by various routes of inoculation. Infect Immun 33: 779-783.

13. Greenough A (2002) Respiratory syncytial virus infection: clinical features, management, and prophylaxis. Curr Opin Pulm Med 8: 214-217.

14. McNamara PS, Smyth RL (2002) The pathogenesis of respiratory syncytial virus disease in childhood. Br Med Bull 61: 13-28.

15. Openshaw PJ, Tregoning JS (2005) Immune responses and disease enhancement during respiratory syncytial virus infection. Clin Microbiol Rev 18: 541-555.

16. van Schaik SM, Tristram DA, Nagpal IS, Hintz KM, Welliver RC, et al. (1999) Increased production of IFN-gamma and cysteinyl leukotrienes in virus-induced wheezing. J Allergy Clin Immunol 103: 630-636.

17. Piedimonte G, Renzetti G, Auais A, Di Marco A, Tripodi S, et al. (2005) Leukotriene synthesis during respiratory syncytial virus bronchiolitis: influence of age and atopy. Pediatr Pulmonol 40: 285-291.

18. Volovitz B, Welliver RC, De Castro G, Krystofik DA, Ogra PL (1988) The release of leukotrienes in the respiratory tract during infection with respiratory syncytial virus: role in obstructive airway disease. Pediatr Res 24: 504-507.

19. Zeng R, Li C, Li N, Wei L, Cui Y (2011) The role of cytokines and chemokines in severe respiratory syncytial virus infection and subsequent asthma. Cytokine 53: 1-7.

20. Hall CB, Walsh EE, Long CE, Schnabel KC (1991) Immunity to and frequency of reinfection with respiratory syncytial virus. J Infect Dis 163: 693-698.

21. Glezen WP, Taber LH, Frank AL, Kasel JA (1986) Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 140: 543-546.

22. Pullan CR, Hey EN (1982) Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. Br Med J 284: 1665-1669.

23. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, et al. (2005) Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. Am J Respir Crit Care Med 171: 137-141.

24. Wilkinson TM, Donaldson GC, Johnston SL, Openshaw PJ, Wedzicha JA (2006) Respiratory syncytial virus airway inflammation and FEV1 decline in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 173: 871-876.

25. Sikkel MB, Quint JK, Mallia P, Wedzicha JA, Johnston SL (2008) Respiratory syncytial virus persistence in chronic obstructive pulmonary disease. Pediatr Infect Dis J 27: S63-70.

26. Simoes EA, Carbonell-Estrany X (2003) Impact of severe disease caused by respiratory syncytial virus in children living in developed countries. Pediatr Infect Dis J 22: S13-18.

27. Sigurs N, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, et al. (2010) Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. Thorax 65: 1045-1052.

28. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, et al. (2003) Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 289: 179-186.

29. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, et al. (1999) Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 354: 541-545.

30. Korppi M, Hyvarinen M, Piippo-Savolainen E (2008) Asthma after early RSV infection--how to control? Pediatr Infect Dis J 27: 191-192.

31. Bruhn FW, Mokrohisky ST, McIntosh K (1977) Apnea associated with respiratory syncytial virus infection in young infants. J Pediatr 90: 382-386.

32. Tripp RA (2004) The brume surrounding respiratory syncytial virus persistence. Am J Respir Crit Care Med 169: 778-779.

33. Kim EY, Battaile JT, Patel AC, You Y, Agapov E, et al. (2008) Persistent activation of an innate immune response translates respiratory viral infection into chronic lung disease. Nat Med 14: 633-640.

34. Di Rosa F, Barnaba V (1998) Persisting viruses and chronic inflammation: understanding their relation to autoimmunity. Immunol Rev 164: 17-27.

35. Wald O, Weiss ID, Galun E, Peled A (2007) Chemokines in hepatitis C virus infection: pathogenesis prognosis and therapeutics. Cytokine 39: 50-62.

36. Guerrero-Plata A, Ortega E, Gomez B (2001) Persistence of respiratory syncytial virus in macrophages alters phagocytosis and pro-inflammatory cytokine production. Viral Immunol 14: 19-30.

37. Culley FJ, Pennycook AM, Tregoning JS, Hussell T, Openshaw PJ (2006) Differential chemokine expression following respiratory virus infection reflects Th1- or Th2-biased immunopathology. J Virol 80: 4521-4527.

38. Krishnan S, Halonen M, Welliver RC (2004) Innate immune responses in respiratory syncytial virus infections. Viral Immunol 17: 220-233.

39. Mills BG, Singer FR, Weiner LP, Holst PA (1981) Immunohistological demonstration of respiratory syncytial virus antigens in Paget disease of bone. Proc Natl Acad Sci USA 78: 1209-1213.

40. Couch RB, Keitel WA, Cate TR (1997) Improvement of inactivated influenza virus vaccines. J Infect Dis 176: S38-44.

41. Isaia G, Teodosiu O, Popescu G, Athanasiu P, Sternberg I, et al. (1985) Persistence of viruses in the nasopharynx of apparently healthy children aged 0-5 years. Virologie 36: 175-179.

42. Cubie HA, Duncan LA, Marshall LA, Smith NM (1997) Detection of respiratory syncytial virus nucleic acid in archival postmortem tissue from infants. Pediatr Pathol Lab Med 17: 927-938.

43. Donaldson GC, Wedzicha JA (2006) COPD exacerbations 1 Epidemiology. Thorax 61: 164-168.

44. Falsey AR, Formica MA, Hennessey PA, Criddle MM, Sullender WM, etal. (2006) Detection of respiratory syncytial virus in adults with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 173: 639-643.

45. Hegele RG, Hayashi S, Bramley AM, Hogg JC. (1994) Persistence of respiratory syncytial virus genome and protein after acute bronchiolitis in guinea pigs. Chest 105: 1848-1854.

46. Bramley AM, Vitalis TZ, Wiggs BR, Hegele RG (1999) Effects of respiratory syncytial virus persistence on airway responsiveness and inflammation in guinea-pigs. Eur Respir J 14: 1061-1067.

47. Riedel F, Oberdieck B, Streckert HJ, Philippou S, Krusat T, et al. (1997). Persistence of airway hyperresponsiveness and viral antigen following respiratory syncytial virus bronchiolitis in young guinea-pigs. Eur Respir J 10: 639-645.

48. Streckert HJ, Philippou S, Riedel F (1996) Detection of respiratory syncytial virus (RSV) antigen in the lungs of guinea pigs 6 weeks after experimental infection and despite of the production of neutralizing antibodies. Arch Virol 141: 401-410.

49. Schwarze J, O'Donnell DR, Rohwedder A, Openshaw PJ (2004) Latency and persistence of respiratory syncytial virus despite T cell immunity. Am J Respir Crit Care Med 169: 801-805.

50. Mejias A, Chavez-Bueno S, Gomez AM, Somers C, Estripeaut D, et al. (2008) Respiratory syncytial virus persistence: evidence in the mouse model. Pediatr Infect Dis J 27: S60-62.

51. Estripeaut D, Torres JP, Somers CS, Tagliabue C, Khokhar S, et al. (2008) Respiratory syncytial virus persistence in the lungs correlates with airway hyperreactivity in the mouse model. J Infect Dis 198: 1435-1443.

52. Baldridge P, Senterfit LB (1976) Persistent infection of cells in culture by respiratory syncytial virus. Proc Soc Exp Biol Med 151: 684-688.

53. Peeples M, Levine S (1981) Characteristics of a persistent respiratory syncytial virus infection in HeLa cells. Virology 113: 141-149.

54. Panuska JR, Midulla F, Cirino NM, Villani A, Gilbert IA, et al. (1990) Virus-induced alterations in macrophage production of tumor necrosis factor and prostaglandin E2. Am J Physiol 259: L396-402.

55. Sarmiento RE, Tirado R, Gomez B (2002) Characteristics of a respiratory syncytial virus persistently infected macrophage-like culture. Virus Res 84: 45-58.

56. Tirado R, Ortega A, Sarmiento RE, Gomez B (2005) Interleukin-8 mRNA synthesis and protein secretion are continuously up-regulated by respiratory syncytial virus persistently infected cells. Cell Immunol 233: 61-71.

57. Valdovinos MR, Gomez B (2003) Establishment of respiratory syncytial virus persistence in cell lines: association with defective interfering particles. Intervirology 46: 190-198.

58. Oldstone MB (2009) Anatomy of viral persistence. PLoS Pathog 5: e1000523.

59. Martinez I, Bustos J, Melero JA (2001) Reduced expression of surface glycoproteins in mouse fibroblasts persistently infected with human respiratory syncytial virus (HRSV). Arch Virol 146: 669-683.

60. Nakamura-Lopez Y, Villegas-Sepulveda N, Sarmiento-Silva RE, Gomez B (2011) Intrinsic apoptotic pathway is subverted in mouse macrophages persistently infected by RSV. Virus Res 158: 98-107.

61. Martinez I, Lombardia L, Herranz C, Garcia-Barreno B, Dominguez O, et al. (2009) Cultures of HEp-2 cells persistently infected by human respiratory syncytial virus differ in chemokine expression and resistance to apoptosis as compared to lytic infections of the same cell type. Virology 388: 31-41.

62. Culley FJ, Pennycook AM, Tregoning JS, Dodd JS, Walzl G, et al. (2006) Role of CCL5 (RANTES) in viral lung disease. J Virol 80: 8151-8157.

63. Ejrnaes M, Filippi CM, Martinic MM, Ling EM, Togher LM, et al. (2006) Resolution of a chronic viral infection after interleukin-10 receptor blockade. J Exp Med 203: 2461-2472.

64. Brooks DG, Trifilo MJ, Edelmann KH, Teyton L, McGavern DB, et al. (2006) Interleukin-10 determines viral clearance or persistence in vivo. Nat Med 12: 1301-1309.