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New Respiratory Viral Infections

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In the last 10 years, there are many new or newly identified respiratory viral pathogens described in human, including (1) SARS-coronavirus, (2) avian influenza viruses (H5N1, H9N2, H7N7, H 7N3 and H10N7), (3) human metapneumovirus, (4) coronaviruses NL 63 and HKU 1, (5) bocavirus and (6) human rhinovirus C. I shall focus on those viruses that Hong Kong has contributed in either discovery or characterisation.

1. Severe acute respiratory syndrome (SARS) is caused by a previously unrecognized coronavirus (CoV) which jumped species and became adapted to be transmissible between humans in 2002[1]. Enormous scientific knowledge about this SARS-CoV has been accumulated and aspects of its pathogenesis defined[2]. However it is still unclear why some members of the same family or housing estate with SARS outbreak were more susceptible to SARS than others. Similarly, why children have a lower incidence of SARS with milder clinical course as compared to adults remains unknown.

   We have therefore studied the polymorphisms of 15 innate immune response genes in a case-control gene association study of over 1,000 SARS patients and controls, and identified several susceptibility genes, which may explain partly the genetic susceptibility to SARS. They are genes encoding for interferon-gamma[3], p 21, RANTES[4] and mannose binding lectin (MBL)[5]. Of these, we also demonstrated MBL has direct biological activity against SARS-CoV[5]. This knowledge may also shed lights on therapeutics and prophylactics. We also compared the interferon and chemokine responses to SARS-CoV in adult and cord blood dendritic cells, and identified different developmental responses between neonates and adults as well as high induction of chemokines but low induction of interferons by SARS-CoV[6]. The dysregulation of chemokine and interferon responses in SARS may be mediated through the SARS-CoV non-structural protein 1 (nsp 1)[7,8]. Moreover, we did a risk-stratified seroprevalence study of SARS-CoV among children living in housing estates with SARS outbreak and in areas with no SARS[9]. We concluded subclinical SARS in children are rare. Hence the lower incidence of SARS in children is not due to subclinical infection, and children will not be ready sources of SARS infection.

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2. Avian influenza A virus H5N1 was first transmitted from chicken to human in Hong Kong in 1997[10]. Over 330 human H5N1 cases, associated with multiple recurrent H5N1 outbreaks in poultry, were reported since December 2003 in Asia, Europe and Africa, with mortality of 60%. The pathogenesis of H5N1 infection resulting in such high mortality is still far from clear. We therefore studied the roles of death receptor ligands in H5N1 infection using human monocyte-derived macrophages (MDMs) as model. We found H5N1-infected MDMs could induce T cell apoptosis, mediated through TNF-related apoptosis-inducing ligand (TRAIL)[11]. This may partially explain the severe lymphopenia in human H5N1 infection. Moreover we compared the chemokines and chemokines receptors expression between adult and cord blood MDMs infected with avian influenza viruses as chemokines are implicated in ARDS, and found avian influenza viruses induced higher chemokines and their receptors expression than human influenza viruses. Adult macrophages also had higher expression in CCL 3, CCR 1 and CCR 5 than cord blood macrophages when infected by H5N1 virus[12]. We have preliminary data to suggest such cytokines and chemokines response may be virus strain specific[13].

3. Human metapneumovirus (hMPV) was first described in 2001 in Netherlands[14] now documented to circulate and infect all children by 5-10 years old in Europe, America, Asia, Australia and S Africa[15,16], including Hong Kong[17]. hMPV is responsible for URI and LRTI in infants, young children and the elderly. Co-infection of hMPV with other viruses such as SARS-CoV has been documented in Hong Kong and are not associated with more severe clinical course[18]. Interestingly, hMPV-associated LRTI can be reduced by conjugate pneumococcal vaccine, suggesting pneumococcal coinfection with hMPV is of clinical relevance[19].

4. Human coronavirus (HCoV) NL 63 was first described in a 7-month old child with bronchiolitis and conjunctivitis in 2004 in Netherlands[20] and HKU 1 in an elderly patient with pneumonia in 2005 in Hong Kong[21]. HCoV-NL 63 has the same cellular receptor as SARS-CoV, i. e. ACE 2 and is associated with URI, croup, asthma exacerbation in children[22-24]. HCoV-HKU 1 is associated with RTI in individuals of all ages and has been reported in Australia, Europe and America[25,26]. Acute enteric disease with HCoV-HKU 1 detected in stool has been reported in France[27] but the overall significance of HCoV-HKU 1 in gastroenteritis is still not clear.

5. Human bocavirus (HBoV) was first described in 2005 in Sweden in children with RTI[28], now reported to circulate widely in the world. HBoV is related to parvovirus B 19, and co-infection with other respiratory viruses is a frequent feature (>80%), raising issues on the significance of HBoV infection on its own. HBoV can be detected in serum of patients and such viremia suggests HBoV may cause diseases beyond the respiratory tract[29-30]. We have demonstrated HBoV can be detected in fecal specimens in children with acute gastroenteritis[31]. A single lineage of HBoV is associated with both respiratory tract and enteric infection[31].

6. A previously unidentified human rhinovirus (HRV) species, HRV-C, has been reported in Hong Kong, Australia and United States[32]. HRV-C is circulating worldwide and an important cause of febrile wheeze and asthmatic exacerbations in children.

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