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Commentary

IgG3 Snitcher of RSV Infections in the Very Young

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Human respiratory syncytial virus (RSV) is the most frequent cause of lower respiratory tract infections in infants and young children worldwide and also an important pathogen in elderly. Millions of patients get hospitalized and up to 200,000 children die each year due to an RSV infection (Nair et al., 2010). Despite this burden and decades of research there is neither a prophylactic vaccine nor a specific antiviral therapy for RSV. A major obstacle for the development of an RSV vaccine is the lack of a strong correlate of protection. High levels of RSV-neutralizing antibodies have been associated with less severe disease but this association is not strong and sometimes absent (Glezen et al., 1986; Nyiro et al., 2016). Moreover, vaccine trials learned that it is very hard to boost pre-existing RSV-neutralizing antibodies in children and adults.

Maternal derived RSV-specific antibodies can provide some protection in very young infants (Glezen et al., 1986). However, these maternal antibodies wane quickly after birth, which explains why 1-month-old babies are the most likely to develop severe disease upon primary RSV infection (Hall et al., 2009). Remarkably, these primary infections do not elicit immunity against reinfection with RSV (Glezen et al., 1986). This can in part be explained by the poor antibody response in young infants as compared to older children (Murphy et al., 1986). More recently, however, it has become clear that infants younger than 3 months are quite capable of mounting significant RSV-neutralizing antibodies upon RSV infection but that pre-existing maternal antibodies can blunt this (Shinoff et al., 2008). Profound understanding of antibody responses upon primary RSV infection in young infants is crucial for the development and implementation of active and passive anti-RSV vaccination strategies in this age group.

In this issue of *EBioMedicine*, researchers from the pharmaceutical company Daiichi Sankyo teamed up with several clinical departments in Japan to study the age-related humoral responses in patients with RSV who were medically attended (Jounai et al., 2017). Paired acute and convalescent serum samples from 169 children (aged between 0 and 36 months) and 23 adults (aged 24–89 years) were analyzed. Their most remarkable finding is the ability of very young infants (younger than 4 months), to mount a strong IgG3 response upon RSV infection even in the presence of high levels of maternal RSV-neutralizing antibodies. In contrast, a rise in RSV glycoprotein-specific serum IgG1 and IgG2, and RSV-neutralizing antibodies following RSV infection was only observed consistently in infants older than 7 months, *i.e.* when maternal RSV antibodies had become limiting. Why does the IgG3 subclass stand out in the very young as a possible marker for a primary response against RSV? First, RSV-specific IgG3 is virtually absent in infants younger than 4 months. Due to its shorter half-life (7 days compared to 21 days for the other IgG isotypes) IgG3 levels in both the mother and infant decline much faster than IgG1 and IgG2 do (Hornsleth et al., 1985). Secondly, extensive sequence analysis of human IgG transcripts has revealed a clear hierarchy among the IgG subclasses and the extent of affinity maturation: IgG3 < IgG1 < IgG2 < IgG4 (Jackson et al., 2014). This suggests that human B cells tend to follow a programmed sequence of class switches from IgM to IgG3 and subsequently to IgG1, IgG2 and IgG4. Recurrent infections with RSV would thus also gradually favor accumulation of RSV-specific IgG1, IgG2 and IgG4 over IgG3 as an individual grows up.

In the study population of Jounai et al. RSV-specific IgG1 and IgG2 responses upon medical attended RSV infection were undetectable in infants younger than 4 months and could only be observed in about one third of the infants aged between 4 and 7 months (Jounai et al., 2017). In accordance with other reports, the infections did not result in robust RSV-neutralizing antibody responses in these infants (Murphy et al., 1986). In contrast, RSV infections were associated with a more than 4-fold increase in IgG3 levels in 78.3% and 96.4% of 0–4 months old and 4–7 months old infants, respectively. RSV-specific serum IgG3 responses might thus serve as a biomarker for primary RSV infection and associated immune responses. This might be useful to detect subclinical RSV infections in young infants with considerable levels of maternal RSV antibodies, or to monitor early immune responses upon vaccination with live attenuated RSV vaccine candidates. To further explore IgG3 response as a biomarker for RSV infections and associated immune responses, it will be important to define the duration of such an IgG3 response, given its short half-life. In addition, it should be investigated to what extent also subclinical RSV infections result in detectable IgG3 responses. Finally, RSV IgG3 responses should also be investigated in infants less than 1 or 2 months of age. If upon subclinical RSV infections early and strong IgG3 responses occur in very young infants and remain detectable for a prolonged period, this IgG3 mark holds promise as a feasible biomarker.

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Disclosure

The authors declared no conflicts of interest.

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