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Commentary

Localization of Viral Antigens Improves Understanding of Congenital Rubella Syndrome Pathophysiology☆

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Rubella virus (RV) is responsible for benign postnatal and deadly antenatal infections. Its involvement in developmental defects in children following congenital transmission was first made by Sir Norman McAlister Gregg in 1941. Indeed, the maternal primary infection results in an RV viremia and placental transfer. If it occurs before 12 weeks of gestation, during organogenesis, it can result in severe fetal damage causing miscarriage or malformations primarily affecting the cardiovascular system, eyes, ears and the central nervous system; it is fatal in nearly one third of cases during the first year of life (Töndury and Smith, 1966). This severe RV infection acquired in utero early in pregnancy is named as Congenital Rubella Syndrome or CRS. In 2014, 141 CRS cases were reported from 114 countries mostly from South-East Asia (n = 86/141), although reporting is probably inconsistent according to the authors themselves (Grant et al., 2015). This number had been estimated as closer to 100,000 cases each year in developing countries alone (Cutts and Vynnycky, 1999). To better understand the pathogenesis of CRS in the absence of an animal model, the first histopathological explorations were conducted in some of the 20,000 fetuses infected during the 1964–1965 epidemics in the US when about 12.5 M Rubella cases were reported (National Communicable Disease Center, 1969). Although these studies identified histological lesions in the heart, blood vessels, crystalline lens, ears, brain, teeth and liver consistent with clinical features and sequelae of CRS, they did not solved the mechanisms of virus teratogenicity (Töndury and Smith, 1966; Esterly and Oppenheimer, 1969). In particular, until recently, the exact nature of the cell types infected with RV remained unknown.

The objective of the study by Lazar and colleagues was therefore to identify, through immunohistochemical staining of viral antigens, infected cells in tissues from CRS cases to better understand the molecular details of the CRS pathogenesis (Lazar et al., 2016). The authors relied on the exploration of three fatal cases of CRS in term and close to term babies diagnosed during the outbreak in Romania in 2011–2012. This report provided at least two principle findings, which contribute significantly to our understanding of the CRS pathophysiology. The first was the detection of RV antigens in fibroblasts in the myocardium of 2 patients without detection of histological signs of myocarditis or viral antigens in cardiac myocytes. Infection restricted to cardiac fibroblasts, associated with the detection of viral antigens in adventitial fibroblasts of large blood vessels, raises the question of the mechanism by which congenital cardiovascular malformations (patent ductus arteriosus and branch pulmonary artery stenosis) arise in CRS patients. This suggests that RV positive myocardial cells assessed in two previous studies could be transiently infected cells during the acute phase of the disease and not persistently infected cells linked with congenital malformations observed in the CRS (Woods et al., 1966; Nguyen et al., 2014). This also excludes a priori cytolytic injury of cardiac myocytes and more likely suggests a disturbance of the normal development of the cardiovascular system through cardiac fibroblasts infection, which form structural scaffolding for the attachment of cardiac cell types during development, express growth factors and cytokines and regulate proliferation of embryonic cardiomyocytes (Deb and Ubil, 2014). The second main finding identified viral antigens in the progenitor cell of granular layer in the brain. If lesions of the granular layer had already been reported, the description of RV progenitor cells infection is a novelty that could connect mental retardation and microcephaly observed in the CRS to the involvement of multipotent neural stem cells that give rise to precursors of many neuronal or glial lineages involved in the normal CNS development. These results shed new light on the possible pathophysiology of neurological impairment observed in the CRS since the only mechanism described so far was the in vitro infection of astrocytes that can lead

☆ Commentary article to accompany the manuscript by Lazar and colleagues titled: « Immunolocalization and distribution of rubella antigen in fatal congenital rubella syndrome ».

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in vivo to an alteration of the normal brain functioning resulting in neurological deficit (Chantler et al., 1995).

These conclusions complement the work by Nguyen and colleagues recently published in EBioMedicine, in which the authors described pathological examination conducted on 3 aborted fetuses with CRS acquired during the 2011–2012 rubella epidemic in Vietnam (Nguyen et al., 2014). In this second observation, ocular lesions with congenital cataract and hepatic involvement associating necrotizing and inflammatory changes were predominant. RV antigens were detected in multiple cell types in multiple organs, particularly via infiltrating CD34 positive hematopoietic mononuclear cells, as well as in epithelial cells in ciliary body representing a possible cause of cataracts. The only common feature between these two studies was the neural cell infection in both cases. Contrasting results in RV antigen positive cells could be related to the difference between gestational age of the CRS cases studied including either aborted fetuses at 13, 22 and 23 weeks, respectively, in Nguyen's work or term babies, or close to the term, in Lazar's report. This could reflect the wide range of cell types infected at the initial, acute and disseminated phase of the disease, distinct from the narrower spectrum of persistently infected cells in the organs where the virus is capable of causing chronic typical CRS lesions.

The work of Lazar and colleagues opens many lines for future research. In this study, tissue samples from the eyes and ears were not available for study by immunohistochemistry while these two organs are among the main targets of CRS. Future studies should also establish a causal link between the cells hosting the virus and the CRS malformation syndrome assessing the impact of persistent viral infection on the functions and abilities of proliferation, regeneration and differentiation of cardiac fibroblasts and neural progenitors. Finally, it would be also necessary to distinguish between direct virus induced cytopathic effect and indirect inflammatory injuries of the targeted organs particularly to explain the lung histological lesions.

In conclusion, this work is one of the rare opportunities to advance understanding of the mechanism by which congenital rubella infection can cause a malformative syndrome in fetus during pregnancy. The investigations conducted in preterm and term babies, by highlighting the viral antigens distribution in multiple tissues, provided additional and complementary data to morphological studies performed to date, identifying infected cell types consistent with CRS features that can explain its pathogenesis. It now remains to complete this necessary descriptive work by adding the mechanistic data still missing.

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