6th European Rotavirus Biology Meeting, Dijon, France, 17–20 May 2015

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The European Rotavirus Biology Meeting was established 12 years ago and takes place biannually. Approximately 100 scientists, medical doctors and students of biomedical sciences from 28 countries of five continents participated in this meeting, which was efficiently organized by Pierre Pothier and his staff. Their hospitality and inventive social program were highly appreciated. The aim of the meeting was to review and discuss new developments of rotavirus (RV) research, pathophysiology, immunology, molecular epidemiology and prevention.

In the keynote lecture on ‘Immune responses and protective mechanisms to rotavirus infection’, Harry Greenberg, Stanford University, Palo Alto, CA, USA, explored the well-documented phenomena of host range restriction of RV infection and heterotypic immunity to RV disease. Group A RVs tend to be host specific: their highly reduced ability to grow in heterologous cells and tissues can be deduced from host species-specific interactions of the RV-encoded NSP1 with compounds of different reaction cascades of the innate immune response. Heterotypic protection after natural RV infection or RV vaccination can be explained by the emergence of either cross-reactive neutralizing antibodies or antibodies against internal RV structural proteins, for example, VP6, which counteract RV replication by ‘intracellular neutralization’ [1,2].

RV structure–function & replication studies

Giuditta de Lorenzo of Oscar Burrone’s group, Trieste, Italy, found that particular nucleotide (nt) sequences located in the 5′ untranslated region (5′UTR) of the full length RV (+) ssRNAs regulate their translation after transfection into mammalian cells and were therefore termed translation regulatory motifs (TRMs). The presence of TRMs may in part explain the present lack of success in establishing a helper virus-free reverse genetics system for RVs. Catherine Eichwald, Zuerich, Switzerland, identified the interaction of the cellular transport protein dynein with viroplasmas as necessary for RV replication, which can be blocked by dynein-antagonist drugs. RV-infected cells also are arrested in their S/G2 phase. Using a modification of the helper virus-dependent

KEYWORDS

- immune responses
- molecular epidemiology
- pathogenesis • rotavirus (human and animal)
- vaccine effectiveness
- viral replication

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reverse genetics system for RVs [3], Reimar Johné, Berlin, Germany, succeeded in engineering a RV reassortant containing an avian RV gene on the background of a mammalian RV genome. This finding may be of significance for considering birds as a reservoir for mammalian RV infections.

RV pathogenesis

Marie Hagbom of Lennart Svensson's group, Linköping, Sweden, presented data supporting the hypothesis that the cholinergic anti-inflammatory pathway of cell metabolism [4] can explain the well-documented relative lack of inflammation in RV-infected gut tissue. Sonja Bialowas, also from Lennart Svensson's group, presented data showing that intracellularly expressed RV NSP4 stimulates serotonin release from human enterochromaffin cells *in vitro*. The groups of Didier Poncet, Gif-sur-Yvette, France, and Germain Trugnan, Paris, France, reported details of the molecular mechanisms underlying the stress-related Unfolded Protein Response of RV infected cells. Using glycan microarrays, Jacques Le Pendu, Nantes, France, found that fucosylated glycans act as surface receptors for a wide range of P(8) RVs, mediated by the VP8* subunit of VP4 [5]. Barbara Coulson, Melbourne, Australia, explored the interaction of RVs of P(8), P(4), P(6), P(9) and P(14) genotypes with fucosylated glycans and found significant differences [6]. The significance of differences of binding to fucosylated glycans for the RV epidemiology in different populations is under investigation (Barbara Coulson, Melbourne, Australia [6]; Gael Belliot of Pierre Pothier's group, Dijon, France; Johan Nordgren of Lennart Svensson's group, Linköping, Sweden [7]).

Immune responses & immunopathology

Adrish Sen, Stanford, Palo Alto, CA, USA, reviewed details of the RV-mediated inhibition of the innate immune response of intestinal epithelial cells upon RV infection. Besides the previously described effects on NF- κ B and IRF3, IRF5 and IRF7, downregulation of interferon receptors was recorded, mediated by transient expression of NSP1 alone. The data recorded in cell culture were confirmed by analysis of RV infection of suckling mice [2,8]. Using non-obese diabetic mice as a model, Barbara Coulson found that RV infection induces B- and T-cell activation in mesenteric and pancreatic lymph

nodes and suggested that this may accelerate the onset of Type 1 diabetes [9]. The significance of the data for the molecular pathogenesis remains to be determined. RV VP6 preparations can act as adjuvant for antibody production against norovirus GII-4 and GI-3 virus-like particles in mice (Vesna Blazevic of Timo Vesikari's group, Tampere, Finland). Davide Agnello (Pierre Pothier's group, Dijon, France) pursued his studies on mice vaccinated with RV VP2/VP6 virus-like particles; he found that after intrarectal, but not intranasal immunization RV-specific memory B cells gut-associated lymphoid tissue all carry the α 4, β 7 integrin, permitting a mucosal immune response [10].

Animal RVs

Increasingly sequences of the genomes of non-species A RVs become available. Tohru Suzuki (Tsukuba, Japan) reported on the classification of human and animal species B RVs and found a large genetic diversity leading to the whole genome differentiation into various genotypes [11]. Exploring urban wild rats as a RV reservoir, Reimar Johné found RVBs related to the IDIR strain, but also a RVA G3P(3)N2 strain which contained eight RNA segments which were classified as novel genotypes and for which the animal reservoir is unknown [12]. RVAs and RVCs of Belgian pigs were characterized by Sebastiaan Theuns (Ghent, Belgium) of the groups of Jelle Matthijnsens and Hans Nauwynck). In contrast to a large diversity of G and P genotypes, the constellation of the other nine genes of RVAs was relatively conserved [13]. Many piglets are infected with RVCs of a large genomic diversity, and regular testing for the presence of RVCs of diseased piglets is advised. Nathan Meade and Ken Mellits (Nottingham, UK) passaged the porcine OSU RV on MA104 cells in which the innate immune response was blocked by constitutional expression of the bovine viral diarrhea virus Npro protein and the parainfluenza virus 5 V protein (collaboration with Rick Randall, St Andrews, Scotland). It is hoped that the OSU RV passaged this way may mutate and become more dependent on growth in these cells. The MA104 cell line dually suppressed in its IFN response and fully susceptible to RV replication arose considerable interest. Sanaa Alaoui Amine (Rabat, Morocco) analyzed RVA isolates obtained from goats and found evidence of interspecies transmission between goats and cattle.

Environment & molecular epidemiology

Takayuki Miura (of Soizick Le Guyader's group, Nantes, France) explored the extent to which RVs and noroviruses (NoVs) are removed from wastewater by passage through membrane bioreactors. To this purpose, the binding of viruses to mixed liquor suspended solids was tested. RVA was less efficiently removed than NoVs. One reason may be differences in the isoelectric points of the two virus species, and experiments to explore this further are underway.

Reports on the molecular epidemiology of RVs in the following countries were presented: Angola (Claudia Istrate, Lisboa, Portugal), Burkina Faso (Isidore Bonkoungou, Ouagadougou, Burkina Faso), Brazil (Adriana Luchs, Sao Paulo, Brazil), France (Alexis de Rougemont, Dijon, France), Germany (Andreas Mas Marques, Berlin, Germany), Greece (Dimitra Koukou, Athens, Greece), Ireland (Helen O'Shea, Cork, Ireland), Italy (Diletta Valentini, Giovanni Ianaro, Roberto Delogu of Franco Ruggeri's group, Rome, Italy; Giovanni M Giammanco and Simona de Gracia, Palermo, Sicily), Mozambique (Nilsa de Deus, Maputo, Mozambique), Slovenia (Andrej Steyer, Ljubljana, Slovenia), Spain (Jesus Rodriguez-Diaz, Javier Buesa, Valencia, Spain), Europe (Daniel Hungerford of Miren Iturriza-Gomara's group, Liverpool, UK) and sub-Saharan Africa (Martin Nyaga of Jeffrey Mphahlele's group, Pretoria, South Africa). There was evidence for zoonotic transmission and emergence of novel RVs in some of the investigations.

RV vaccine effectiveness

Filemon Bucardo and colleagues (Leon, Nicaragua) reported an increase of human RV G12 strains in a population with a high coverage by the RotaTeq vaccine during 2011–2013 [14].

The reasons for this observation are not clear at present. David Allen and colleagues (Public Health England, London, UK) reported a significant decrease of RV-positive specimens in England after the introduction of the Rotarix vaccine in 2013. Carl Kirkwood (Victoria, Australia) described the RV epidemiology in Australia which evolved after introduction of universal RV vaccination in 2007. Due to country-specific public health arrangements, some of the Australian states used Rotarix and some RotaTeq. After RV vaccine introduction, there was an absolute decrease of RV-associated acute gastroenteritis of children in all states. However, more unusual genotypes were observed and an increased number of cases in older children and adults. There was no firm correlation of the isolation of particular RV genotypes in individual states with the type of RV vaccine used [15]. Alena Kajjalainen (Helsinki, Finland) and Timo Vesikari's group (Tampere, Finland) reported that by years five and six after introduction of universal RV vaccination (RotaTeq) in Finland, RV-associated AGE had been reduced by tenfold, and that no unusual RV strains had emerged. It should be noted that special meetings are dedicated to the assessment of RV vaccine effectiveness in Europe and elsewhere (e.g., [16] for a meeting in 2014, with the report of the follow-up meeting of March 2015 being awaited).

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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