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POSTER PRESENTATION Open Access

Respiratory syncytial virus replication induces Indoleamine 2,3-dioxygenase (IDO) activation in human dendritic cells

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Objective/purpose

Induction of IDO in dendritic cells (DCs) depletes the essential amino acid, tryptophan, and generates a family of catabolites known as kynurenines (KYN). IDO activity is reported to have immunomodulatory effects, including the selective induction of apoptosis in T-helper 1 (Th1) lymphocytes, an effect not seen with Th2 cells that are dominant in allergic asthma. Infants hospitalized for RSV-related bronchiolitis have increased risk of developing asthma (48% vs. 8% in control). Induction of IDO activity by RSV may explain the link between RSV bronchiolitis and asthma pathogenesis. IDO is induced by various cytokines and a number of non-airway viruses; however, RSV has not yet been studied. We hypothesize that RSV induce IDO activation in human dendritic cells (DCs).

Methods

Primary human dendritic cells (DCs) were infected with sucrose gradient purified RSV with a multiplicity of infection (MOI) rate of 1.0. Flow cytometry and confocal microscopy were used to confirm infection. We measured KYN in culture media by a spectrophotometric method using Ehrlich reagent. We blocked RSV infection with the RSV-mAb, Palivizumab, and UV-inactivation to determine a role for infection. The potent competitive inhibitor of viral RNA polymerase, Ribavirin, was used to block RSV replication and protein synthesis. To evaluate dependency of RSV-induced IDO induction on different cell signaling pathways, we used a variety of specific inhibitors including MEK inhibitor I (120 nM), MEK inhibitor II (4 μM), SB202190 (p38-MAPK, 3 μM), JNK inhibitor II (1 μM), IKK inhibitor II (Wedelolactone, 30 μM), IKK inhibitor III (BMS-345541, 3 μM) and relevant negative controls.

Findings

DCs incubated with RSV showed a 35% shift in flow cytometry compared to uninfected control DCs (n = 12) thus confirming infection of DCs. KYN, as a marker of IDO induction, was increased 13.2 fold in supernatants of infected DCs compared with control DCs (43.6 vs. 3.3 μM, n = 6). Inactivation of virus by Palivizumab or UV resulted in 99% decrease in levels of KYN compared to controls (n = 3). Infecting DCs with higher MOI of UV-inactivated RSV (up to 20, n = 3) did not induce IDO. Addition of Ribavirin to culture media reduced KYN release in a dose-dependent manner with 50% reduction at 220 μM (n = 3), without having any blocking effect on positive controls (IFN-γ induced KYN release) at similar concentrations. Except for SB202190, none of the specific inhibitors of signaling pathway including NF-κB, JNK-MAPK and MEK/ERK-MAPK showed any significant inhibitory effect on IDO induction by RSV (n = 3). SB202190, the specific inhibitor of P38-MAPK, blocked 51% (IC_{50}= 300 nM) and 92% (3 μM) of KYN release (n = 3); negative controls showed no inhibitory effect.

Deliverables

Our data showing IDO to be induced in DCs following infection with RSV is novel. Further, the observation that induction was dependent on viral replication was unexpected. Although NF-κB is reported to have a role in IDO induction, our data suggest that RSV-induced kynurenine release may occur through an NF-κB-independent pathway.

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Relevance

These data support our hypothesis that RSV plays a role in the development of an immune response towards a Th2 pattern. Prevention of RSV infection could decrease the incidence of asthma. We expect to be publishing these novel findings in 2010.

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