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Binding Of Apoptotic Fetal Cardiocytes By Anti-Ro Antibodies Stimulates uPA/uPAR- Dependent Macrophage Infiltration and M2 Type Phenotype

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Abstract: #1764

Presenter: Briasouli, Paraskevi PhD

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Date: Monday, October 28, 2013

Time: 5:00 PM

Location: Hilton - Sapphire A

Session Title: Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis II: Mechanisms that contribute to autoimmune inflammation (/apps/MyAnnualMeeting/Session/5306)

Abstract Category: Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis

Type: Oral

Description:

Background/Purpose:

Organ injury induced by antibodies characteristic of Sjogren's Syndrome and Systemic Lupus Erythematosus, while varied in the adult and fetus, may share in common a link between apoptosis and ultimate fibrosis. In congenital heart block (CHB), surface binding of maternal anti-Ro antibodies to apoptotic cardiocytes decreases their removal by healthy cardiocytes, increases uPAR-(urokinase plasminogen activator receptor) dependent uPA activation, plasmin activity and stimulation of TGFbeta signaling. Immunological staining of CHB hearts reveals extensive TGFbeta in the septal region and macrophage infiltration with intense uPA expression. Since TGFbeta mediates chemotaxis of macrophages and stimulates urokinase expression, this study evaluated the hypothesis that anti-Ro binding to apoptotic cardiocytes exploits the plasmin-mediated activation of TGFbeta to trigger macrophage infiltration and polarization to a fibrosis- associated M2 phenotype.

Methods:

Chemotaxis, immunoblot and immunofluorescence assays were used.

Results:

A thin membrane chemotaxis assay showed directed migration of calcein-labeled THP-1 macrophages towards supernatants from co-cultures of healthy cardiocytes and apoptotic cardiocytes incubated with IgG fractions from mothers whose sera contain anti-Ro antibodies and who had a child with CHB (opsonized apo-CHB-IgG) compared to co-cultures of healthy cardiocytes and apoptotic cardiocytes incubated with control IgG (apo-nl-IgG) (80% migration CHB-IgG vs 39% migration nl-IgG; p=0.05; n=3). The effect was similar to that induced by TGFbeta and dependent on both TGFbeta and plasmin activity since supernatants of cocultures of healthy cardiocytes with apo-CHB-IgG in the presence of either aprotinin (10 µg/mL) or TGFbeta inhibitor SD543423 1µM did not induce macrophage migration. Similar results were obtained with supernatants of healthy cardiocytes cultured with apoptotic cardiocytes incubated with affinity purified anti-Ro60 (67% migration AP60-IgG vs 30% migration nl-IgG). Immunofluorescence revealed increased surface uPA expression only on macrophages incubated with supernatants of co-cultures of healthy cardiocytes with apo-CHB-IgG. Furthermore real time PCR confirmed that the increased uPA was due to de novo mRNA expression To evaluate whether the

macrophages were polarized towards a pro-fibrotic M2 phenotype, surface CD206 was assessed and increased expression of CD206 was only observed following exposure to supernatants from co-cultures of healthy cardiocytes and apo-CHB-IgG. Immunoblot analysis of THP-1 macrophages showed that IRF4 but not IRF5 knockdown, mediator of M2 and M1 macrophage associated transcriptional program respectively, led to reduced uPA expression when incubated with supernatants from cocultures of healthy cardiocytes and apo-CHB-IgG.

Conclusion:

These data suggest that binding of anti-Ro antibodies to apoptotic cardiocytes by virtue of increased uPAR-dependent uPA activity triggers TGFbeta mediated macrophage infiltration and polarization towards a profibrotic M2 phenotype amplifying a cascade of events that promote myofibroblast transdifferentiation and scar.

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