1179-81 **Computerized Community Cholesterol Control (4C)**

Harel Gilutz, Julian Zelingher, Yaakov Henkin, Dan Y. Bonneh, Zvi Liss, Roni Peleg, Max Mayslus, Reuben Ilia, Avi Porath, *Soroka Medical Center, Beer Sheva, Israel, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel.*

Introduction: The majority of patients with coronary artery disease (CAD) are eligible for lipid-lowering drugs, yet most of them are sub-optimally managed. A Community Health Information Network integrated with Computer-based Clinical Decision Support Systems is an effective communication modality to facilitated guideline implementation.
Objectives: To study the impact of "smart CHIN - CDSS communicator" in CAD for secondary prevention.
Methods: Patients were from 113 demographically-matched clinics, 56 clinics in the intervention group, and 57 clinics following routine practice (control). We developed a computerized engine that incorporates computerized databases and creates a comprehensive prospective registry including demographics, diagnosis, laboratory results and medication. This system detected patients requiring screening and who were eligible for lipid lowering drugs, then mailed automatic remainders to the primary medical teams in the intervention group clinics recommending screening or medium dose of statins. Periodic reinforcement of reminding is performed every 4 months.
Results: Out of 2528 patients with CAD who were enrolled, by August 2001, 1558 had been followed for 4 months. Those in an intervention group clinic demonstrated an improved lipid profile screening (65% vs 50%) (p<0.01), and a higher percent of patients achieved target levels (21% vs 13%) (p<0.0001).
Conclusions: A computerized automatic reminder generator was shown to have a significantly positive short- term effect on use and results of secondary prevention measures. This intervention is expected to have a major impact on the clinical course of CAD disease. Clinical evaluation of cardiac event reduction will take place in January 2002, after one year of follow-up.

ORAL CONTRIBUTIONS

860 Macrophages, Lymphocytes, and Cytokines: Role in Atherosclerosis

Tuesday, March 19, 2002, 2:00 p.m.-3:30 p.m.
Georgia World Congress Center, Room 264W

2:00 p.m.

860-1 **Activated Monocytes Induce Smooth Muscle Cell Apoptosis: Role of the FasLigand/Fas Death Receptor Pathway**

Sanjay S. Vasudevan, Puvi N. Seshiah, Neuza Lopes, Tao Wang, Chunming Dong, Pascal J. Goldschmidt-Clermont, *Duke University Medical Center, Durham, North Carolina.*

Background: Plaque instability and rupture are central features of atherothrombotic syndromes. Vulnerable plaques have a decreased number of vascular smooth muscle cells (VSMC), a rudimentary extracellular matrix protein content and an increased number of monocytes/macrophages (MM), in their fibrous caps. We have shown that VSMC death is due to interaction of these cells with MM activated by M-CSF. Furthermore, such VSMC killing by MM requires the tight binding of MM to VSMC mediated by CD11b-CD18. We hypothesized that, once tightly bound to VSMC, MM kill VSMC by activating their Fas death pathway, thus leading to apoptosis of VSMC.
Methods: FasL and Fas expression were studied on VSMC and MM co-cultured for 72hours, in the presence of M-CSF (100ng/ml). Monocytes were identified by CD14-FITC staining. Similar experiments were conducted using a Fas-Fc fusion protein that inhibits FasL/Fas mediated apoptosis.
Results: As shown previously, apoptosis of VSMC was induced by MM, but only in the presence of M-CSF (57.8± 0.8%). We used a pan-caspase inhibitor (ZVAD fmk) to show that death of VSMC induced by M-CSF-activated MM was indeed by apoptosis. When VSMC were pre-incubated with ZVAD fmk (10μM/ml), apoptosis induced by M-CSF activated MM was completely abrogated (15.4±0.4%), and similar to control VSMC with monocytes deprived of M-CSF (12.2±1.6%). Next, we tested the role of Fas/Fas-ligand in the apoptotic death of VSMC induced by M-CSF-activated MM. Fas expression was detected only on VSMC and not the surface of MM. Fas-L was detected on MM. VSMC apoptosis triggered by M-CSF-activated MM was nearly completely prevented when co-cultures were treated with huReFas-Fc fusion protein (2μg/ml) (27.0± 1.0%, p≤0.005 vs. identical conditions, except for the omission of huReFas-Fc). This apoptotic index was not different from that seen in control VSMC with unactivated MM (15.7± 3.5%, p≤0.06) (with or without huReFas-Fc, 2μg/ml).
Conclusions: This data suggests a mechanism for plaque destabilization and rupture where VSMC death induced by M-CSF-activated MM is by apoptosis and the FasL/Fas death receptor pathway could play a major role in this process.

2:15 p.m.

860-2 **IL-12 Mediated Activation of Cytotoxic CD4 T Cells in Acute Coronary Syndromes**

Takako Nakajima, Amr E. Abbas, Stephanie Schultz, Kenneth J. Warrington, Stephen L. Kopecky, Robert L. Frye, Jorg J. Goronzy, Cornelia M. Weyand, *Mayo Clinic, Rochester, Minnesota.*

Background: The inflammatory infiltrate in unstable plaque is unusual in that it contains a specialized subset of clonally expanded CD4+ T cells that lack the CD28 molecule. The functional profile and the signals required to activate CD4+CD28- T cells in the plaque are not known.
Methods: CD4+CD28-T cell clones (n=60) were isolated from 3 patients with plaque instability and subjected to gene profiling. Selective expression of genes was confirmed by PCR and FACS analysis and gene products of interest were further analysed on freshly harvested peripheral blood lymphocytes. Functional activities of T cell clones were examined in cytotoxicity assays on endothelial target cells.
Results: CD4+CD28- T cell clones were distinct from classical CD4+CD28+ T cells in that they possessed a cytolytic machinery and killed endothelial cells. They also overexpressed CD161, a C type lectin typically found on NK cells where it amplifies cytotoxic function. Frequencies of CD4+CD161+ T cells were twofold increased in the blood of patients with unstable angina (17.6 %) as compared to stable angina (9.8 %, p<0.003) and matched controls (7.9 %, p=<0.001). We hypothesized that the appearance of CD161 on CD4 T cells was a consequence of recent activation and explored the ability of pro-inflammatory cytokines (IL-2, IL-12, IL-15, and IL-18) to upregulate CD161. Culture of CD4+CD28- but not CD4+CD28+ T cell clones in IL-12 promptly induced CD161 on the surface, even in the absence of T cell receptor crosslinking.
Conclusions: Patients with ACS have T cells that can be activated in response to IL-12 without the need for antigen recognition. The accumulation of CD4+CD161+ cells in the circulation of these patients indicates that a marked proportion of their T cells are constitutively activated, likely by the exposure to the pro-inflammatory cytokine IL-12. Expression of the lectin CD161 prepares these T cells for rapid transmigration through endothelial cells, preferred recruitment into tissue lesions and accelerated cytotoxicity.

2:30 p.m.

860-3 **Monocyte Chemotactic Protein 1 Amplifies Serotonin-Induced Vascular Smooth Muscle Cell Proliferation**

Takuya Watanabe, Takashi Katagiri, Rajbabu Pakala, Claude R. Benedict, *Third Department of Internal Medicine, Showa University School of Medicine, Tokyo, Japan, Division of Cardiology, University of Texas-Houston Health Science Center, Houston, Texas.*

Background: Monocyte chemotactic protein 1 (MCP-1), which is synthesized by vascular cells, is a chemoattractant for monocytes and has been implicated in a wide range of acute and chronic inflammatory processes characterized by monocyte infiltration, including atherosclerosis. However, it is unclear whether MCP-1 is able to modulate vascular smooth muscle cell (VSMC) proliferation. We assessed the effect of MCP-1 on VSMC proliferation and its interaction with serotonin (5-HT), a mitogen for VSMCs.
Methods: Growth-arrested VSMCs were stimulated with different concentrations of MCP-1 (25-200 ng/ml) and 5-HT (5 and 50 microM) in serum-free medium. DNA synthesis in VSMCs was measured by [3H]thymidine incorporation.
Results: 5-HT at a concentration of 5 or 50 microM significantly stimulated DNA synthesis by 1.8- or 2.1-fold over the control value, respectively (p < 0.0001). However, MCP-1 at concentrations tested did not have any significant effect on DNA synthesis. Even though MCP-1 (50 ng/ml) by itself is not mitogenic, when added to 5-HT, it significantly amplified the mitogenic effect of 5-HT compared with that of 5-HT alone (p < 0.0001). The 5-HT2A receptor antagonist sarpogrelate (10 microM) and its major metabolite M-1 (0.1 microM), pertussis toxin (10 ng/ml), Src family protein tyrosine kinase (PTK) inhibitor PP2 (1 microM), protein kinase C (PKC) inhibitor Ro31-8220 (0.1 microM), and MAPK kinase inhibitor PD098059 (10 microM) significantly inhibited the mitogenic effect of 5-HT and its interaction with MCP-1. Anti-MCP-1 antibody (2 microg/ml) and the JAK2 inhibitor AG490 (10 microM) significantly inhibited the interaction of MCP-1 with 5-HT. Further, the amplified mitogenic effect of 5-HT with MCP-1 was completely reversed by the combined use of sarpogrelate with anti-MCP-1 antibody.
Conclusions: Our results suggest that MCP-1 amplifies the mitogenic effect of 5-HT on VSMCs. The mitogenic effect of 5-HT may be mediated by the G protein-Src family PTK-PKC-MAPK pathway. The activation of JAK2/STAT3 pathway by MCP-1 in addition to the MAPK pathway by 5-HT may explain the potentiating effect of MCP-1 on 5-HT-induced mitogenesis.

2:45 p.m.

860-4 **MCP-1 Induces Activation of MAP-Kinases ERK, JNK, and p38 MAPK in Human Endothelial Cells**

Martina Werle, Katherina Hanna, Joerg Kreuzer, *Department of Cardiology, University of Heidelberg, Heidelberg, Germany.*

Background: Activation of vascular endothelial cells (EC) plays an important pathogenic role in the development of atherosclerosis. Monocyte chemoattractant protein-1 (MCP-1) is a potent chemoattractant of monocytes. Besides induction of monocyte recruitment, it has been suggested that MCP-1 can also affect cellular responses of EC.
Methods: We now investigated whether MCP-1 activated the three major mitogen activated protein (MAP)-kinases extracellular signal-regulated kinase (ERK), c-Jun amino terminal kinase (JNK) and p38 MAPK.
Results: Stimulation of EC with MCP-1 induced a time-dependent activation of all three