

Liver Transplant Recipients Older Than 60 Years Have Lower Survival and Higher Incidence of Malignancy

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Older age is not considered a contraindication for liver transplantation, but age-related morbidity may be a cause of mortality. Survival and the incidence of the main post-transplant complications were assessed in 111 adult liver transplant recipients. They were divided in two groups according to their age (patients younger than 60 years, n = 54; patients older than 60 years, n = 51) and both groups were compared. Older patients were more frequently transplanted for hepatitis C (p = 0.03) and hepatocellular carcinoma (p = 0.05) and their liver disease was less advanced (Child-Pugh and MELD scores were significantly lower; p = 0.004 and p = 0.05, respectively). After transplantation, older patients had a significantly lower survival (p = 0.02). Higher age was independently associated with mortality (hazard ratio for each 10-year increase: 2.1; 95% confidence interval: 1.1-4.0; p = 0.02). The incidence of de novo neoplasia and nonskin neoplasia were higher in older patients (p = 0.02 and p = 0.007, respectively). Malignancy was the cause of death in one patient younger than 60 years and in 12 patients older than 60 years (p = 0.002). In multivariate analysis, a higher age and smoking were independently associated with a higher risk of dying of de novo neoplasia. In conclusion, older liver transplant recipients have a significantly lower survival than younger patients. Malignancy is responsible for this decreased survival.

Key words: Age. Liver transplantation. Neoplasia. Survival.

Pancreatic cancer escape variants that evade immunogene therapy through loss of sensitivity to IFN γ -induced apoptosis

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Combined injections into experimental tumor nodules of adenovirus encoding IL-12 and certain chemokines are capable

to induce immune-mediated complete regressions. In this study, we found that the combination of two adenoviruses, one encoding IL-12 and other MIP3 α (AdCMVIL-12+AdCMVMIP3 α) was very successful in treating CT-26-derived colon carcinomas. However, in experimental tumors generated from the pancreatic carcinoma cell line Panc02 such combined treatment induces 50% of macroscopic complete regressions, although local relapses within 1 week are almost constant. We derived cell lines from such relapsing tumors and found that experimental malignancies derived from their inoculum were not amenable to treatment in any case with AdCMVIL-12+AdCMVMIP-3 α . Importantly, relapsing cell lines were insensitive to in vitro induction of apoptosis by IFN γ , in clear contrast with the original Panc02 cells. Comparative analyses by cDNA arrays of relapsing cell lines versus wild-type Panc02 were performed revealing an important number of genes (383) whose expression levels were modified more than two-fold. These changes grouped in certain gene ontology categories should harbor the mechanistic explanations of the acquired selective resistance to IFN γ .

Anti-ICAM-2 monoclonal antibody synergizes with intratumor gene transfer of interleukin-12 inhibiting activation-induced T-cell death

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Purpose: Systemic treatment with an anti-ICAM-2 monoclonal antibody (mAb; EOL4G8) eradicates certain established mouse tumors through a mechanism dependent on the potentiation of a CTL-mediated response. However, well-established tumors derived from the MC38 colon carcinoma cell line were largely refractory to this treatment as well as to intratumor injection of a recombinant adenovirus encoding interleukin-12 (IL-12; AdCMVIL-12). We sought to design combined therapy strategies with AdCMVIL-12 plus anti-ICAM-2 mAbs and to identify their mechanism of action. **Experimental design:** Analysis of antitumor and toxic effects were performed with C57BL/6 mice bearing established MC38 tumors. Anti-ovalbumin T-cell receptor transgenic mice and tumors transfected with this antigen were used for in vitro and in vivo studies on activation-induced cell death (AICD) of CD8(+) T cells. **Results:** Combined treatment with various systemic doses of EOL4G8 mAb plus intratumor injection of AdCMVIL-12 induced complete regression of MC38 tumors treated 7 days after implantation. Unfortunately, most of such mice succumbed to a systemic inflammatory syndrome that could be prevented if IFN- γ activity were neutralized once tumors had been resected.

Importantly, dose reduction of EOL4G8 mAb opened a therapeutic window (complete cure of 9 of 18 cases without toxicity). We also show that ICAM-2 ligation by EOL4G8 mAb on activated CTLs prevents AICD, thus extending IFN-gamma production. **Conclusions:** Combination of intratumor gene transfer of IL-12 and systemic anti-ICAM-2 mAb display synergistic therapeutic and toxic effects. CTL life extension resulting from AICD inhibition by anti-ICAM-2 mAbs is the plausible mechanism of action.

Articular Cartilage Degeneration After Frozen Meniscus and Achilles Tendon Allograft Transplantation: Experimental Study in Sheep

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Purpose: The purpose of this study was to analyze cartilage degeneration in knees after total medial meniscectomy, transplantation of fresh-frozen meniscus allograft, and Achilles tendon allograft. Type of Study: Experimental study. Methods: We have studied the articular cartilage in the medial compartment of the left knees in 32 sheep aged 5 to 6 months, with 8 animals in each group. The study was performed after meniscectomy (group I), transplantation of fresh-frozen meniscus allograft (group II), use of fresh-frozen Achilles tendon allograft (group III), and in a control group (group IV). For the histologic study, all samples were stained with Masson's trichrome and Safranin-O. Mankin's score was applied to grade the histologic damage to the articular cartilage. **Results:** The group with the greatest number of degenerative changes was group III, followed by groups I and II. The percentage of thickness of cartilage detected by Safranin-O stain was found to be significantly different in both tibia and femur between the control group and the other 3 groups, but not among groups I, II, and III. The immunoreactivity of the articular surfaces in tibia and femur showed notable differences in all the groups. Collagen X was present in the degenerative hypertrophic chondrocytes in the damaged articular surfaces. **Conclusions:** Meniscal replacement with meniscal and Achilles tendon allografts provides partial protection against articular damage after a meniscectomy.

Key words: Meniscus. Achilles tendon. Allograft. Knee. Cartilage. Transplantation.

Limb salvage in bone sarcomas in patients younger than age 10: a 20-year experience

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The authors present their experience over the last 20 years in limb salvage procedures of a consecutive series of 40 children under 10 years of age (range 2-10 years) with bone sarcomas. Nineteen were osteogenic sarcomas and 21 were Ewing sarcomas. Only one case, located in the distal phalanx of the toe, was treated by straightforward amputation. Intercalary allografts and Canadell's technique were used to preserve joints whenever possible, and prosthesis or osteoarticular allografts were used when the joint surface was involved. Survival rate in this series was 75%. There were four local recurrences. At the last follow-up (mean 11.2 years, range 5-19 years postop), 90% of the patients preserved their limbs. Eighty percent of the authors' results were excellent or good according to the Musculoskeletal Tumor Society Scale. Limb salvage is a real possibility even in young children with bone sarcomas. The age of the patient itself is not a contraindication for limb salvage.

Different expression of MMPs/TIMP-1 in human atherosclerotic lesions. Relation to plaque features and vascular bed

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Background: Proteolytic imbalance might determine arterial remodeling and plaque destabilization in atherosclerotic vessels. The aim of this study was to examine differences in the patterns of metalloproteinases (MMPs) and MMP inhibitor (TIMP-1) expression in advanced human atheromas, both in relation to the plaque features and the vascular bed involved. **Methods and results:** Immunohistochemistry for MMP-1, -3, -9 and TIMP-1 as well as the collagen content were measured in vascular sections from patients undergoing peripheral revascularization (carotid n=11, femoral n=23) and aorto-coronary bypass surgery (mammary arteries n=20, as controls). Increased expression of all MMPs was detected in atherosclerotic as compared with control sections (P<0.01). Aneurysmal plaques showed a significant increase of MMP-1 and -3 and a reduction in total collagen (P<0.05) in relation to occlusive lesions. Calcification areas in atherosclerotic plaques were consistently associated with increased TIMP-1 expression (P<0.01). Finally, MMP-9 expression was higher in occlusive lesions from carotid than femoral arteries (P<0.01). **Conclusions:** Aneurysm lesions expressed higher MMP-1 and -3 expression than occlusive plaques, and MMP-9 was mainly detected in carotid as compared

with femoral arteries. TIMP-1 was associated with arterial calcification. These differences in the MMPs/TIMP-1 expression might determine the evolution of advanced atherosclerotic plaques and contribute to its vulnerability.

Antioxidant vitamins increase the collagen content and reduce MMP-1 in a porcine model of atherosclerosis: implications for plaque stabilization

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Abstract of: Atherosclerosis 2003;167:45-53

Degradation of extracellular matrix, particularly interstitial collagen, promotes plaque instability and contributes to restenosis after vascular injury. We have explored the effects of vitamins C and E on the collagen content and metalloproteinase-1 (MMP-

1) expression after angioplasty in hypercholesterolemic pigs. Iliac angioplasty was performed on 18 minipigs divided into three diet groups: a normal-cholesterol (NC), a high-cholesterol (HC) and a high-cholesterol plus vitamins C + E (HCV). Four weeks later, after sacrifice, the vascular collagen content and MMP-1 protein expression, along with the plasma caseinolytic activity and lipid peroxidation, were measured. MMP-1 was also determined in arterial rings stimulated with native low-density lipoproteins (LDL) isolated from experimental groups. Cholesterol-rich diet augmented plasma lipid peroxidation ($P < 0.05$), reduced the collagen content and increased vascular MMP-1 expression after injury ($P < 0.05$). Enhanced caseinolytic activity (identified as MMP-1) was also observed in HC plasma samples and in supernatants from arterial rings incubated with HC-LDL. Vitamins C and E markedly increased neointimal collagen content ($P < 0.01$), reduced the hypercholesterolemia-induced changes in vascular MMP-1 ($P < 0.05$) and diminished plasma and ex vivo caseinolytic activity. Vitamins C and E may help stabilize atherosclerotic plaque after angioplasty and favor vascular remodeling by increasing collagen content and reducing vascular MMP-1 expression in porcine hypercholesterolemia.

Key words: Antioxidant vitamins. Hypercholesterolemia. Atherosclerosis. Collagen. Metalloproteinase-1.

