Mo1354

NEONATAL MESENCHYMAL STEM CELLS FOR THE TREATMENT OF ILEITIS

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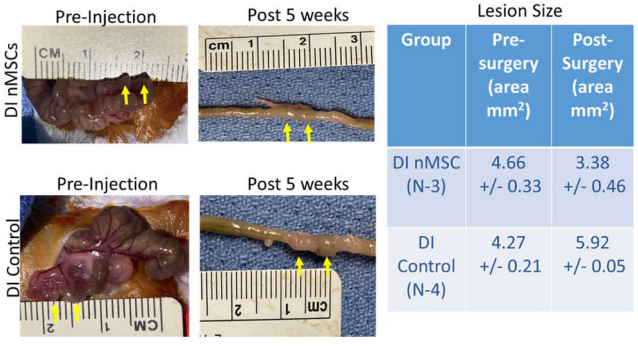
Statement of Purpose: Crohn's disease (CD) is in-part due to a highly pro-inflammatory lesion microenvironment whose progression is accompanied by numerous clinical complications. Current treatment options for CD patients include biologic/pharmacologic anti-inflammatory therapies that are associated with deleterious side effects. Patients who are refractory to therapeutic treatment typically requires surgical intervention. Approximately 70% of patients with CD will require surgery during their lifetime.[1] We propose that neonatal Mesenchymal Stem Cells (nMSCs) with anti-inflammatory and regenerative characteristics can be directly injected into developing small intestine inflammatory lesions in an established mouse model of ileitis capable of mimicking human CD that will positively modulate the inflammatory microenvironment. **Methods:** nMSCs or control media (DMEM) were directly injected into lesions of SAMP1/YitFcsJ mice (n=4 female animals; 10 weeks old). Mice underwent surgery to expose inflammatory lesions on the ileum. Lesions (5 lesions/animal) were independently injected once (1e5 nMSCs/Lesion) with either nMSCS (DI nMSCs) or control media (DI Control). Lesion size pre/post-injections were evaluated (Figure 1). Animals were sacrificed at 15 weeks of age and intestinal tissue was harvested. Subsequent tissue sections were single-stained with immunofluorescent antibodies for inflammatory cells CD68 (macrophages), and cytokines TNFα, IFNγ, and IL-10. Quantitative morphometric analyses were performed on stained tissue sections using ImageJ (n=3 images/lesion- Figure 2). **Results:** Quantified morphometric data represented as percent positive cell or cytokine marker derived from tissue staining experiments with demonstrable decreases in key inflammatory events under DI nMSCs vs DI Control conditions. Specifically: TNFα (42.7±3.6 vs 70.6±3.9); IFNγ(37.4±2.5 vs 70.9±3.7) CD68 (23.0±3.1 vs 66.1±2.8). This was accompanied by an increase in anti-inflammatory IL-10 expression (12.8±0.7 vs 0.1±0.01) and a decrease in lesion size (3.38±0.05 mm2 vs 5.92±0.05 mm2), which is a 27.5% decrease in initial lesion size and a 41.9% decrease in size when compared to control group (P<0.05). **Conclusions:** Chronic intestinal exposure to inflammatory factors exhibited in CD contribute to tissue destruction and impair tissue wound healing. Within the context of our study, we establish that nMSCs can substantially decreases the presence of and down-regulate the expression of pro-inflammatory related cells and cytokines, respectively, in vivo. nMSCs may provide an alternative option for those with CD as treatment also reduces lesion size and promotes wound healing via the upregulation of the pro-regenerative cytokine IL-10. **References:** 1. Surgery for Crohn's Disease & Ulcerative Colitis, Crohn's, and Colitis Foundation, 2021

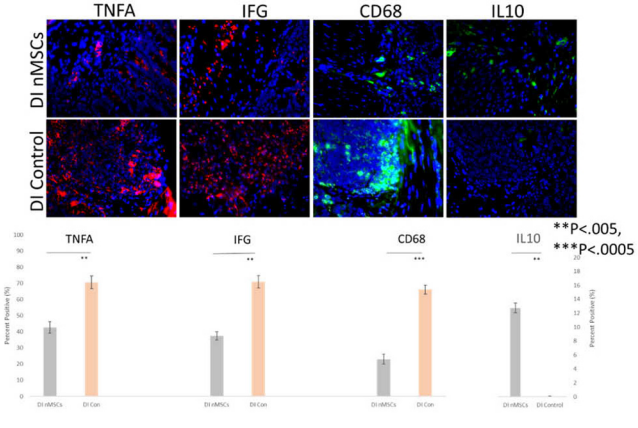
Figure 1



Lesion Size

Group	Pre-surgery (area mm²)	Post-Surgery (area mm²)
DI nMSC (N-3)	4.66 +/- 0.33	3.38 +/- 0.46
DI Control (N-4)	4.27 +/- 0.21	5.92 +/- 0.05

Figure 2



Mo1361

HEPATOCYTE SPECIFIC DELETION OF MICRORNA-34A ALLEVIATES DUCTULAR REACTION AND LIVER FIBROSIS DURING EXPERIMENTAL CHOLESTASIS

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Introduction: Ductular reaction, characterized by the inflammatory growth of reactive bile ducts and liver fibrosis are typical liver changes seen in human primary sclerosing cholangitis (PSC) and cholestasis. While a role for microRNA in inflammation and liver fibrosis has been suggested, it remains unclear how miR-34a participates in this pathogenesis. The current study was performed to clarify the role of hepatocyte specific miR-34a in the cholestasis associated ductular reaction and liver fibrosis. **Methods**: The healthy control and PSC patient liver samples were used for RNA extraction, frozen section histopathology, protein extraction and in situ hybridization analysis. A hepatocyte specific miR-34a knockout mouse was established by crossing floxed miR-34a mice with the albumin cre mice. Hematoxylin and eosin staining, immunohistochemistry, immunofluorescnece, SuperArray quantitative PCR assay, qPCR analysis, and genotyping PCR were performed to characterize the cholestasis progression in both wild-type and hepatocyte specific miR-34a knockout mice subjected to either sham or bile duct ligation surgery. Ductular reaction and liver fibrosis were characterized by CK-19, α-SMA and Collagen A1 expressions as well as Sirius red staining. **Results**: In liver samples from human PSC patients, we demonstrated an enhanced expression of miR-34a by in situ hybridization and real-time PCR analysis. An enhanced ductular reaction as determined by CK19 staining, and increased liver fibrosis (Sirius red staining) and mRNA expression of ACTA2 (α-SMA) and collagen A1. Aberrant protein expression of senescence markers p16, p21 and mRNA expressions of p16, p21 and p53 were also observed in human PSC liver compared with normal control liver samples. Hepatocyte specific miR-34a deletion successfully down regulated miR-34a in mouse hepatocytes without affecting miR-34a expression in heart. Bile duct ligation induced liver injury which was characterized by necrosis, fibrosis, and immune cell infiltration. In contrast in the miR-34a knockout a significant decrease in liver damage was seen. This may be the result of a decrease in the biliary ductular pathology after ligation associated with cholangiocyte senescence and fibrotic responses. The miR-34a-mediated ductular reactions may be functioning through Sirt-1-mediated senescence and fibrosis. Therefore the hepatocyte-derived miR-34a appears to regulate LPS-induced cholangiocyte senescence and the fibrotic response through paracrine effects. **Conclusion:** The current study demonstrated that hepatocyte specific miR-34a plays an important role in biliary senescence and fibrotic responses in a bile duct ligation mouse model. These findings provide new insight into the function of hepatocyte specific microRNA-regulated liver fibrosis with potential therapeutic benefits in human cholestatic liver diseases.

Mo1362

BUTYRYLCHOLINESTERASE(BUCHE) MEDIATED HEPATIC STELLATE CELL ACTIVATION BY SARM1/NF-KB SIGNALING

Cheng Liu

Background: Butyrylcholinesterase (BuChE) was up-regulated in stress-induced injury such non-alcoholic steatohepatitis (NASH), anxiety, and depression. However, the pathological role and underlying signaling pathway of BuChE in stress-induced liver injury have not been well established. **Methods** the serum of BuChE content were detected from 80 patients with NASH and 67 anxiety patients. The stress models were induced by NASH, electronic foot shock (ES) and restraint stress (RS) in mice. Isolation liver cells to analysis the BuChE origin. **Results**: BuChE increased in stress-induced injury patients and mice. Meanwhile, The liver fibrogenesis factors such as *Acta2, TGFb1,* and *Col1a1* increased significantly in stress-induced models such as NASH, ES and RS mice as compared with non-treated (NT), which indicating hepatic stellate cell activation. BuChE mainly derived from liver hepatocytes. The inflammation factors such as *Tnfa, Mcp1, Cxcl1* and NF-κB p-p65 increased significantly in response to BuChE in LX2 and mHSC cells indicating NF-κB participated in BuChE induced HSC activation. As compared with WT mice, the fibrogenesis factors such as *Acta2* and *Col1a1* increased significantly *Sarm1*$^{-/-}$ mice, the mHSC from *Sarm1*$^{-/-}$ mice produced significantly higher *Tnfa* and *Mcp1* as compared with WT in response to BuChE stimulation. **Conclusions**: Stress-induced HSC activation and liver injury mainly derived from BuChE up-regualtion. BuChE mediated HSC activation by SARM1/NF-κB signaling.

Mo1363

ADIPOSE TISSUE DERIVED STEM CELLS ATTENUATE CARBON TETRACHLORIDE INDUCED LIVER CIRRHOSIS IN RATS

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Background and Aims: Recently, mesenchymal stem cells have been found to exert hepatoprotective effects against acute liver injury, steatohepatitis, and fibrogenesis. Here, we evaluated whether human adipose tissue derived stem cells (hADSCs) could attenuate CCl_4 induced liver cirrhosis in rats. ***Methods:*** Liver cirrhosis was induced by intraperitoneal injections of CCl_4 (0.1 ml/100 g body weight) twice a week for 8 weeks. hADSCs was isolated and cultured on polyethylene discs coated with hydroxyapatite and 2 cm diameter disc was surgically implanted on the right lateral lobe of the liver. Discs implanted without hADSCs served as control. The animals were injected again with CCl_4 once a week for another 8 weeks. All the animals were sacrificed at the end of 16th week. ***Results:*** Serial administrations of CCl_4 resulted in well developed fibrosis and early cirrhosis at 8th weeks which maintained until the 16th week. Animals treated with hADSC discs depicted over 50% decrease of cirrhosis including type I and type III collagens. There was significant increase in serum total proteins and albumin levels. Staining for α-smooth muscle actin and TGF-β1 demonstrated marked decrease compared to the animals without hADSC treatment.

At 16th week, human Lamin B1 and CD73 were stained conspicuously on the liver surface treated with hADSC discs. ***Conclusions:*** The data clearly demonstrated that treatment with hADSC disc markedly reduced hepatic fibrosis and early cirrhosis and improved liver functions. The pleiotropic and paracrine factors secreted from the multipotent hADSCs may serve as reparative functions in the attenuation of liver cirrhosis. *Email: georgej@kanazawa-med.ac.jp

Mo1364

THE BURDEN OF VACCINE-PREVENTABLE INFECTIONS IN LIVER TRANSPLANT RECIPIENTS

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Background Requiring immunosuppression to prevent graft rejection, recipients of solid organ transplant, such as liver transplant (LTx), are at increased susceptibility of developing serious infection with significant risk of hospitalization and death. This risk can be decreased and often eliminated for vaccine-preventable infections (VPI) with adherence to vaccine guidelines. Despite widely available and highly effective vaccines, VPI still occur. It is imperative to evaluate immunization status and administer needed vaccines. The aim of this study is to examine admissions rates for VPI, clinical outcomes, and associated health care cost in LTx recipients. **Methods** This is a retrospective cohort study using the National Inpatient Sample database from 2015-2017. Inclusion criteria were patients with principal diagnoses of VPI (herpes zoster, varicella zoster, influenza and pneumococcal pneumonia) as identified by respective ICD-10 codes. Exclusion criteria were age < 18 years and elective admission. The primary outcomes were occurrence of VPI in recipients of LTx and odds of admission for VPI compared to those without LTx. Secondary outcomes were inpatient mortality rates, hospital length of stay (LOS), total hospitalization costs and charges compared to patients with VPI and no LTx history. Chi-square or Fischer's exact test was used for categorical variables and the student's t test was used for continuous variables. Multivariate analyses were used to adjust for age, gender, Charlson Comorbidity Index, income in patient zip code, hospital region, location, size and teaching status. **Results** A total of 70,130 patients with LTx were identified. Of these, 1280 were admitted with VPI (1.83%). The mean age was 60 years and 50.0% were females. The most common VPI was influenza (55.98%), followed by herpes zoster (32.43%), pneumococcal pneumonia (8.49%), varicella (0%). Recipients of LTx had significantly greater odds of admission for VPI compared to patients without LT (aOR 2.05). There was no significant difference in mortality rates for patients with LTX and non-VPI (5.6%), compared to patients with LTx and VPI (2.3%). The LOS for VPI in LTx recipients was 5.69 days, incurring $63,321 of total hospitalization charges. All outcomes are shown in Table 1. **Conclusions** In the United States, admissions for VPI occur in those with and without LTx with significant associated mortality, LOS, and associated health care cost. History of LTx was independently associated with increased odds of admission for VPI compared to those without LTx. Adherence to vaccination guidelines has the potential to prevent a significant amount of those admission, reduce mortality associated with VPIs, and decrease healthcare cost associated with those admissions. Further prospective studies are needed to better characterize these outcomes in vaccinated liver transplant recipients.

Table 2: Univariate and multivariable analysis of VIP in patients with Liver Transplant

Variable	Unadjusted Odds ratio (95% confidence interval)	p-value	Adjusted Odds ratio (95% confidence interval)	p-value
Liver Transplant	1.681 (1.485-1.902)	<0.001	2.055 (1.795-2.353)	<0.001
Age	1.019 (1.019-1.020)	<0.001	1.018 (1.017-1.018)	<0.001
Female	0.987 (0.985-0.999)	0.038	0.979 (0.966-0.993)	0.003
Charlson comorbidity score	1.073 (1.072-1.075)	<0.001	1.017 (1.014-1.020)	<0.001
Race				
White	Reference		References	
Black	0.813 (0.798-0.827)	<0.001	1.017 (0.991-1.044)	0.197
Hispanic	0.863 (0.845-0.881)	<0.001	1.141 (1.103-1.181)	<0.001
Asian or Pacific Islander	1.098 (1.059-1.138)	<0.001	1.122 (1.166-1.276)	<0.001
Native American	1.073 (0.994-1.157)	0.070	1.306 (1.196-1.427)	<0.001
Other	0.876 (0.843-0.910)	<0.001	1.089 (1.027-1.154)	<0.001
Primary expected payer				
Medicare	Reference		Reference	
Medicaid	0.540 (0.530-0.550)	<0.001	0.963 (0.938-0.989)	0.005
Private Insurance	0.621 (0.611-0.632)	<0.001	1.047 (1.024-1.070)	<0.001
Self-pay	0.570 (0.550-0.590)	<0.001	1.097 (1.053-1.142)	<0.001
No-charge	0.594 (0.533-0.662)	<0.001	1.134 (1.006-1.280)	0.039
Other	0.560 (0.535-0.586)	<0.001	0.850 (0.803-0.900)	<0.000
Median income in patient zip code				
Quartile 1	Reference		Reference	
Quartile 2	1.050 (1.033-1.068)	<0.001	1.014 (0.992-1.036)	0.216
Quartile 3	1.096 (1.078-1.114)	<0.001	1.055 (1.030-1.081)	<0.001
Quartile 4	1.120 (1.101-1.140)	<0.001	1.076 (1.045-1.109)	<0.001
Hospital Urban and Teaching Status				
Rural	Reference			
Urban nonteaching	0.872 (0.852-0.892)	<0.001	0.891 (0.852-0.932)	<0.001
Urban teaching	0.863 (0.845-0.881)	<0.001	0.949 (0.912-0.988)	<0.001
Hospital bedsize				
Small	Reference		Reference	
Medium	0.878 (0.862-0.893)	<0.001	0.914 (0.883-0.946)	<0.001
Large	0.899 (0.885-0.914)	<0.001	0.947 (0.916-0.979)	0.001
Hospital region				
Northeast	Reference		Reference	
Midwest	1.145 (1.124-1.167)	<0.001	1.156 (1.107-1.206)	<0.001
South	0.936 (0.920-0.952)	<0.001	0.991 (0.952-1.033)	0.673
West	1.145 (1.123-1.168)	<0.001	1.217 (1.162-1.273)	<0.001

Table 2: Independent predictors of admission for VPI

Table 1: Demographic characteristics of VPI in patients with and without liver transplant

Baseline Characteristic		Patients with VPI without LT N=522,610	Patients with VPI with LT N=1,280	Total N=523,890	P-Value
Age (years)	Mean (Std. Error)	67 (+/- 0.538)	60 (+/- 0.857)		<0.001
Gender	Female	288,975 (55.3%)	640 (50.0%)	289,615 (55.3%)	0.087
Race	White	364,890 (69.8%)	845 (66.0%)	365,735 (69.8%)	<0.001
	Black	72,245 (13.8%)	65 (5.1%)	72,310 (13.8%)	
	Hispanic	52,270 (10.0%)	240 (18.8%)	52,510 (10.0%)	
	Asian/Pacific Islander	15,860 (3.0%)	45 (3.5%)	15,905 (3.0%)	
	Native American	3,405 (0.6%)	20 (1.6%	3,425 (0.7%)	
	Other	13,940 (2.6%)	65 (5.1%)	14,005 (2.7%)	
Median Income in Zip Code	$1-$38,999	159,400 (30.5%)	325 (25.4%)	159,725 (30.5%)	0.031
	$39,000-$47,999	134,140 (25.7%)	330 (25.8%)	134,470 (26.7%)	
	$48,000-62,999	124,810 (23.9%)	280 (21.9%)	125,090 (23.9%)	
	$63,000 or more	104,260 (19.9%)	345 (27.0%)	104,605 (19.9%)	
Insurance Carrier	Medicare	333,300 (63.8%)	830 (64.8%)	334,130 (63.8%)	0.040
	Medicaid	67,295 (12.9%)	135 (10.5%)	67,430 (12.9%)	
	Private Insurance	93,705 (17.9%)	290 (22.7%)	93,995 (17.9%)	
	Self-pay	17,000 (3.3%)	5 (0.4%)	17,005 (3.2%)	
	No-charge	1,650 (0.3%)	0 (0.0%)	1,650 (0.3%)	
	Other	9,660 (1.8%)	20 (1.6%)	9,680 (1.8%)	
Hospital Urban and Teaching Status	Metropolitan teaching	51,710 (9.8%)	75 (5.9%)	51,785 (9.8%)	<0.001
	Metropolitan non-teaching	143,660 (27.4%)	175 (13.7%)	143,835 (27.5%)	
	Rural	336,240 (64.3%)	1030 (80.5%)	337,270 (64.4%)	
Hospital Bed size	Small	106,785 (20.4%)	140 (10.9%)	106,925 (20.4%)	<0.001
	Medium	150,665 (28.9%)	280 (21.9%)	150,945 (28.8%)	
Hospital	Large	265,160 (50.7%)	860 (67.2%)	266,020 (50.8%)	
Hospital region	Northeast	102,675 (19.6%)	205 (16.0%)	102,880 (19.6%)	0.076
	Midwest	119,995 (22.9%)	240 (18.8%)	120,235(22.9%)	
	South	193,780 (37.1%)	520 (40.6%)	194,300 (37.1%)	
	West	106,160 (20.3%)	315 (24.6%)	106,475 (20.3%)	
Death during hospitalization		18,975 (5.6%)	30 (2.3%)	19,005 (3.6%)	0.271
Length of Stay	Mean (Std. Error)	6.071 (+/- 0.023)	5.688 (+/- 0.404)		0.344
Total charges	Mean (Std. Error)	$60,940.71 (+/- 371.646)	$63,321.38 (+/- 6123.614)		0.698
Charlson Index (avg)	Mean (Std. Error)	5.168 (+/- 0.011)	5.33 (+/- 0.189)		0.388
		Without LT = 47,769,180	With LT = 70,130	Total 47,839,310	
Vaccine Preventable Infections	Herpes Zoster	111,040 (20.97%)	420 (32.43%)	111,460 (0.23%)	<0.001
	Varicella	5,705 (1.08%)	40 (0%)	5,745 (0.012%)	<0.001
	Influenza	337,215 (63.67%)	725 (55.98%)	337,940 (0.706%)	<0.001
	Pneumococcus	74,630 (14.09%)	110 (8.49%)	74,740 (0.156%)	0.985

Table 1: Baseline characteristics

Mo1365

THE RISK OF GASTROINTESTINAL BLEED WITH ANTIPLATELET THERAPY IN CIRRHOTICS UNDERGOING LIVER TRANSPLANT EVALUATION

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Introduction Non-alcoholic steatohepatitis(NASH) is predicted to be the number one cause of need for liver transplant (LT).Patients with NASH cirrhosis are at high risk of mortality due to cardiovascular events.Left heart catheterization(LHC) is utilized for evaluation of cirrhotics with risk factors including hyperlipidemia, hypertension, diabetes mellitus, tobacco use, and age >60 years.Consequently, cirrhotics may need to be on dual anti-platelet therapy(-DAPT) following angioplasty.Data regarding the use of DAPT and the risk of GI bleed(GIB) in cirrhotics is scant. Objective To review the occurrence of GIB in cirrhotics on DAPT compared to those not on DAPT who are undergoing LT evaluation. Methods We conducted a retrospective review of adult cirrhotics who received a LHC as part of LT evaluation between 2014 and 2021.A logistic regression was used to compare outcomes with Welch's t-test for continuous variables and Pearson Chi-Square test for categorical variables. Results A total of 291 patient were included, 33 patients received LHC with angioplasty and subsequently placed on DAPT(DAPT group), and 258 patients received LHC without intervention and did not require DAPT(control group).Baseline characteristics showed no statically significant differences between groups; DAPT group compared to the control group had male patients(69.70%vs65.12%,p=0.6019), age(60vs59,p=0.4999), NASH as the most common cause of cirrhosis (45.45%vs46.12%,p=0.9421), MELD score (17.42vs18.05 p=0.6059), GFR (63.51vs70.99,p=0.2381), platelets (102.21vs100.49,p=0.8604), previous variceal bleed(VB)(27.27%vs22.09%,p=0.5035), measures for prevention of VB (42.42%vs51.55%,p=0.3235), and occurrence of LT (30.30%vs44.19%,p=0.1289).In the DAPT group compared to the control group, GIB occurred in 9.09%vs14.73% (p=0.3808) showing there were no statistically significant differences on univariate and multivariate analysis with an odds ratio of 0.5789 (95%CI (0.1682-1.9922) p=0.3860).When DAPT group was compared to control group, 33.33%vs31.58% (p=0.7016) of patients with GIB were found to have VB, and death occurred within 12 months in 3.03%vs5.81% (p=0.9033).DAPT group is compared to the control group 33.33%vs23.68% (p=0.7079) of patients with GIB received LT after the bleed. Conclusion Despite the presumed increased risk of GIB with DAPT use in cirrhotics, the occurrence of GIB was not more frequent in the DAPT group.One patient died in the DAPT group from VB, it is difficult to speculate based on the results if GIB is not more frequent but could be more deadly.The use of DAPT did not increase the occurrence of GIB in cirrhotics with CAD undergoing LT evaluation.To our knowledge, this is the first study to review the occurrence of GIB on DAPT in this