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Avaliação da terapia celular utilizando células-tronco mesenquimais para o tratamento de cirrose hepática em ratos *Wistar*

Tese apresentada ao Programa de Pós-Graduação em Anatomia dos Animais Domésticos e Silvestres da Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo para obtenção do título de Mestre em Ciências

Departamento:

Cirurgia

Área de Concentração:

Anatomia dos Animais Domésticos e Silvestres

Orientador:

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São Paulo
2014

RESUMO

RUI, L. A. **Avaliação da terapia celular utilizando células-tronco mesenquimais para o tratamento de cirrose hepática em ratos *Wistar***. [Evaluation of cell therapy using mesenchymal stem cells for treatment of liver cirrhosis in *Wistar* rats.]. 2014. 137 f. Tese (Mestrado em Ciências) - Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo, São Paulo, 2014.

A cirrose hepática é uma doença crônica e irreversível com modificações histológicas caracterizadas por nódulos de regeneração e desarranjo de hepatócitos, com aumento difuso de tecido conjuntivo e perda de função. As células-tronco têm sido amplamente estudadas para o tratamento de injúrias hepáticas. Fibrose e cirrose foram induzidas em ratos *Wistar*, através da aplicação de tioacetamida (TAA) intraperitoneal a 200 mg/kg por 8 ou 14 semanas, seguido de terapia celular com aplicação intravenosa única de $1x10^6$ células-tronco de membrana amniótica de ratas. Amostras de sangue foram coletadas para análises bioquímicas, e tecido hepático para histologia e imunohistoquímica. A histopatologia para colorações de hematoxilina-eosina para graduação e estadiamento da lesão hepática foi realizada, com observação de alterações celulares; picrosírius para quantificação do colágeno parenquimal; ácido periódico-Schiff para mucopolissacarídeos neutros e glicogênio; e alcian blue para mucopolissacarídeos ácidos. Imunohistoquímica foi realizada para marcação de PCNA, colágenos tipo 1 e 3, e α-SMA. O cultivo celular apresentou ótimo crescimento, sendo transduzido com GFP e negativo para micoplasma. Os animais induzidos experimentalmente mostraram baixo ganho de peso durante o experimento, com notável recuperação nas duas primeiras semanas após término da indução. A mortalidade experimental foi de 10 %. A indução da fibrose e cirrose hepática obtiveram sucesso no período de 8 e 14 semanas, respectivamente Análises macroscópicas mostraram melhor aspecto de fígados cirróticos após terapia celular. Não houve diferenças estatísticas após a terapia celular para as análises bioquímicas, graduação, estadiamento, alterações celulares, proliferação de ductos, mucopolissacarídeos ácidos e neutros e imunohistoquímicas para colágeno 1 e 3, PCNA e α-SMA. Houve, porém, uma tendência a melhora na graduação e estadiamento da fibrose e cirrose com redução da atividade necroinflamatória; redução na proliferação de ductos; menor deposição de mucopolissacarídeos ácidos e neutros; diminuição das alterações celulares com indicativos de menor grau de lesão tecidual e maior grau de regeneração; diminuição da expressão de α-SMA e colágenos 1 e 3; e aumento do PCNA. O colágeno intralobular teve diminuição após terapia celular em fígados fibróticos. Em animais induzidos a

cirrose, houve diminuição de ambos colágenos interlobular e intralobular. Conclui-se que houve uma tendência de melhora dos animais após tratamento com células-tronco da membrana amniótica de ratas, o que nos encoraja a aplicação de protocolos de terapia celular. Apesar dos resultados promissores, um maior número de animais precisa ser testado para que se tenham mais dados, que possam dar subsídios para o uso destas células na prática clínica para o tratamento da cirrose hepática.

Palavras-chave: Fibrose hepatica. Cirrose hepatica. Tioacetamida. Células-tronco. Membrana Amniótica.

ABSTRACT

RUI, L. A. **Evaluation of cell therapy using mesenchymal stem cells for treatment of liver cirrhosis in *Wistar* rats.** [Avaliação da terapia celular utilizando células-tronco mesenquimais para o tratamento de cirrose hepática em ratos *Wistar*]. 2014. 137 f. Tese (Mestrado em Ciências) - Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo, São Paulo, 2014.

Liver cirrhosis is a chronic and irreversible disease with histological changes characterized by regenerative nodules and disarray of hepatocytes with diffuse increase in connective tissue and loss of function. Stem cells have been extensively studied for the treatment of liver injury. Fibrosis and cirrhosis was induced in *Wistar* rats by application of thioacetamide (TAA) intraperitoneally at 200 mg/kg for 8 or 14 weeks, followed by cell therapy with a single intravenous administration of $1x10^6$ stem cells from amniotic membrane of rats. Blood samples were collected for biochemical analyzes, and liver tissue for histology and immunohistochemistry. Histopathology by hematoxylin-eosin for grading and staging of hepatic injury with observation of cellular changes was performed; picrosirius for quantification of parenchymal collagen; periodic acid-Schiff for neutral mucopolysaccharides and glycogen; and alcian blue for acid mucopolysaccharides. Immunohistochemistry was performed for PCNA, type 1 and 3 collagens, and α-SMA. Cell culture showed optimal growth, being transduced with GFP and negative for mycoplasma. Animals induced to liver disease showed low weight gain during the experiment, with remarkable recovery in the first two weeks after completion of induction. Experimental mortality was 10%. Induction of fibrosis and cirrhosis was successful after the period of 8 and 14 weeks, respectively. Macroscopic analysis showed improvement in the aspect of cirrhotic livers after cell therapy. There were no statistical differences after cell therapy for biochemical analyzes, grading, staging, cellular changes, proliferation of ducts, acidic and neutral mucopolysaccharides and immunohistochemistry for collagen 1 and 3, PCNA and α-SMA. There was, however, a tendency on improvement in grading and staging of fibrosis and cirrhosis with reduced necroinflammatory activity; reduction in the proliferation of ducts; lower deposition of acidic and neutral mucopolysaccharides; decrease in cellular changes indicating a lower degree of tissue damage and a greater degree of regeneration; decreasing on the expression of α-SMA and type 1 and 3 collagens; and increased PCNA. Intralobular collagen decreased after cell therapy in fibrotic livers. In cirrhotic animals, there was a decrease of both interlobular and intralobular collagen. We conclude that was a trend to improvement of animals after treatment with stem cells derived from amniotic

membrane of rats, which encourages the application of cell therapy protocols. Despite the promising results, a larger number of animals must be tested, so we can have more data to make allowances for the use of these cells in clinical practice for the treatment of liver cirrhosis.

Keywords: Liver fibrosis. Liver cirrhosis. Thioacetamide. Stem cells. Amniotic Membrane.

INTRODUÇÃO

Uma das enfermidades que mais acomete o fígado em seres humanos é a cirrose (ROBBINS; COTRAN; KUMAN, 1996), que se caracteriza por apresentar modificações nos lóbulos hepáticos, principalmente por formação de nódulos de regeneração (ANTHONY et al., 1978) e desarranjo na disposição cordonal dos hepatócitos, formando ilhas irregulares de células hepáticas, circundada por grande quantidade de tecido conjuntivo (MACLACHLAN; CULLEN, 1998).

A hepatite crônica também vem sendo comumente identificada nas diversas raças de cães, (STROMBECK; GRIBBLE, 1978; ANDERSSON; SEVELIUS, 1991; DILL-MACKY, 1995; SEVELIUS, 1995; FUENTEALBA et al., 1997), sendo uma manifestação clínica de várias etiologias (ROTHUIZEN, 2004). Para os médicos veterinários, ela é considerada uma doença frustrante, devido aos poucos dados publicados referentes a medicamentos ou estratégias terapêuticas para seu tratamento, progredindo inevitavelmente para a cirrose, e ainda com mau prognóstico (WATSON, 2004). Quatro pontos devem auxiliar a melhor compreensão e tratamento da cirrose hepática em cães: compreensão dos mecanismos que associam perda de capacidade regenerativa com fibrose tecidual; conhecimento amplo das etiologias de processos hepáticos agudos e crônicos; predisposição racial e estudo mais abrangente de diversos tratamentos e associações de drogas que poderiam reverter o processo. (WATSON, 2004).

O crescimento progressivo e difuso do tecido conectivo fibroso conduz o fígado a apresentar um aspecto nodular, levando à interrupção da arquitetura geral normal deste órgão, e progredindo para cirrose. Com o avanço da cirrose hepática, ocorrências secundárias podem ocorrer, tais como o aumento da pressão portal, hemorragia visceral, encefalopatia hepática, síndrome hepatorrenal, e peritonite bacteriana (HEIDELBAUGH; BRUDERLY, 2006).

Há algumas maneiras de se tratar este processo patológico, dentre as quais a hepatectomia parcial (HASHIMOTO et al., 1998; BARATTA et al., 1996; FAUSTO; LAIRD; WEBBER, 1995), podendo estar associada à inibição da enzima conversora de angiotensina pelo lisinopril (RAMALHO et al., 2001); oxigenação hiperbárica (OZDOGAN et al., 2005); transplantação hepática; emprego de células-tronco hepática (TARLÁ et al., 2006); utilização de substâncias com efeito hepatotrófico, tal como vitaminas, aminoácidos, sais minerais, insulina, glucagon, triiodotironina e glicose

(PARRA, 1982; PARRA et al., 1992; PARRA et al., 1994; PARRA et al., 1995a; PARRA et al., 1995b); vários fatores com ação regulatória como as citocinas (IL-6, IL-1a, e TNF-α) (MICHALOPOULOS; DEFRANCES, 1997); a terapia gênica ativadora do plasminogênio tipo uroquinase (SALGADO et al., 2006); e a proteína ALR, amplificadora da regeneração hepática (DAYOUB et al., 2006).

Seguindo as considerações éticas, os procedimentos experimentais em humanos são muito limitados, e devido a isto, há uma grande necessidade e importância de se optar pelos modelos animais, uma vez que mimetizem a patologia a ser observada (LALEMAN et al., 2006).

Há vários protocolos preconizados de como se obter modelos experimentais que caracterizem a cirrose hepática através da indução desta injúria por drogas hepatotóxicas, dentre as quais, a utilização de tetracloreto de carbono (CCL_4). Contudo, há um inconveniente: a variação de óbito de 30% durante a indução (LEE; GROSZMANN, 1999). Díaz-Gil et al. (1999) utilizaram esta mesma droga intraperitonealmente e obtiveram cirrose com 11 semanas de indução. A dimetilnitrosamina (DMN) é outra hepatoxina utilizada para indução. Entretando, é uma droga hepatotóxica, carcinogênica e mutagênica, onde uma extensa fibrose foi alcançada com 3 semanas de aplicação, com uma taxa de óbito em torno de 42% (GEORGE et al., 2001). A dieta de L-aminoácido por deficiência de colina, causa fibrose com 16 semanas, não sendo relatado óbito (SAKAIDA et al., 1998). Ainda temos a tioacetamida (TAA) administrada via oral, que foi utilizada por Laleman et al. (2006), progredindo para quadro cirrótico com 18 semanas, e apresentando óbito de 16%. Já pela injeção dessa droga via intraperitoneal, foi possível obter cirrose com apenas 14 semanas e os autores relataram que a taxa de mortalidade foi bem menor em torno de 4 % (GUERRA et al., 2009).

Estudos demonstram que injúrias hepáticas agudas e crônicas podem potencialmente ser tratadas com transplante de células-tronco (FLOHR et al., 2009). Recentemente, HWANG et al. (2011) demonstraram sucesso com a implantação de células-tronco mesenquimais derivadas de medula óssea no tratamento de falência hepática, em um modelo de cirrose hepática induzido por tioacetamida em ratos, após 8 semanas de indução. Neste trabalho os pesquisadores obtiveram ação dessas células em células ovais progenitoras e hepatócitos, e resultando em efeitos terapêuticos variados,

tais como: reparo de hepatócitos danificados, restauração do glicogênio intracelular e resolução da fibrose.

Outros trabalhos recentes apontam as células-tronco mesenquimais derivadas de membrana amniótica como uma linhagem promissora no tratamento da cirrose hepática, sendo capazes de se implantar no fígado *in vitro* e se diferenciar na linhagem hepatogênica (TAMAGAWA et al., 2007). Ainda, em estudos envolvendo a cirrose hepática induzida por tetracloreto de carbono em roedores, células derivadas do epitélio de membrana amniótica promoveram redução de citocinas pró-inflamatórias, assim como do colágeno parenquimal e da concentração de células estreladas ativadas, tal como a expressão de marcadores para hepatócitos (MANUELPILLAI et al., 2010; ZHANG et al., 2011).

Um dos principais objetivos no tratamento da cirrose hepática é a resolução da fibrose; apesar da função hepática ser vital para a sobrevivência, a morbidade da doença hepática crônica é mais frequentemente associada a complicações da hipertensão portal, tal como hemorragia visceral, ascite, e comprometimento renal; e a hipertensão portal está intimamente relacionada com a fibrose hepática (GILCHRIST; PLEVRIS, 2010).

Com base nos dados da literatura, em relação a taxa de mortalidade, neste trabalho utilizamos a tioacetamida, e acredita-se que o período de indução de 8 semanas com TAA é insuficiente para gerar um quadro avançado de cirrose, mas suficiente para uma fibrose (HATAKEYAMA et al., 2002; DEKEL et al., 2003; IIMURO et al., 2003; GNAINSKY et al., 2004) e, portanto, neste estudo, optou-se pela comparação do tratamento de animais em 2 diferentes estágios de indução, de 8 e 14 semanas de aplicação da TAA, tendo como base também o fato de que as células-tronco mesenquimais migram mais facilmente ao local da injúria em lesões agudas (DALAKAS et al., 2004) .

Com isso, neste trabalho, foram utilizadas células-tronco derivadas de membrana amniótica de ratos da mesma espécie, buscando avaliar uma melhora no quadro clínica da doença e, também uma possível regeneração hepática e restauração da arquitetura vascular e nodular do órgão em diferentes estágios de comprometimento do órgão.

CONCLUSÕES

Diante dos resultados observados após a terapia celular utilizando células-tronco de membrana amniótica de rato para tratamento de fibrose e cirrose hepática em ratos *Wistar* pelo modelo da tioacetamida, foi possível concluir:

1) O modelo da tioacetamida foi eficaz para indução da fibrose e cirrose hepáticas durante 8 e 14 semanas de administração, respectivamente;
2) No geral, houve pouca melhora em relação aos animais não tratados, sendo as únicas diferenças significativas a redução da deposição de colágeno intralobular e interlobular na cirrose; e do intralobular na fibrose; entretanto vários parâmetros se mostram com tendências de melhora nos animais tratados como:

   - As enzimas hepáticas apresentaram melhora tanto nos animais tratados quanto naqueles não tratados;

   - A graduação e o estadiamento tiveram discreta melhora através da terapia celular;

   - As alterações celulares tiveram discreta melhora na lesão e aumento da regeneração tecidual;

   - A deposição de mucopolissacarídeos ácidos e neutros teve uma discreta redução;

   - A proliferação de ductos diminuiu com a terapia celular;

   - Houve tendência a um aumento do PCNA após terapia celular, e redução da expressão do colágeno 1 e 3 e de α-SMA.
3) As alterações acima não apresentaram diferenças estatísticas significativas. Porém, houve tendências a melhora, o que nos encoraja acreditar que este protocolo possa no futuro ser utilizado em animais/humanos entretanto, novos experimentos com um número maior de animais possam ser realizados.

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