LUÍS BRUNO DA CRUZ E ALVES DE MORAES

**Análise dos efeitos do transplante de células
mononucleares da medula óssea em camundongos
submetidos à lesão eletrolítica do hipocampo dorsal**

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RESUMO

Alves-de-Moraes LBC. Análise dos efeitos do transplante de células mononucleares da medula óssea em camundongos submetidos à lesão eletrolítica do hipocampo dorsal [dissertação (Mestrado em Biotecnologia)]. São Paulo: Instituto de Ciências Biomédicas da Universidade de São Paulo; 2010.

Duas propriedades básicas caracterizam as células-tronco: o estado de indiferenciação e a capacidade de se autorrenovar e dar origem a células diferenciadas. Entre as células-tronco adultas, as células da medula óssea representam o tipo mais bem conhecido, tendo já demonstrado grande versatilidade para utilização em procedimentos de transplante e terapia celular experimental. Assim sendo, com o objetivo de caracterizar o potencial dessa categoria de células-tronco como um instrumento terapêutico para a correção de lesões do tecido nervoso, foram analisados os efeitos do transplante de células mononucleares da medula óssea marcadas com a proteína fluorescente verde (EGFP, “enhanced green fluorescent protein”) sobre camundongos C57BL/6 que tiveram a região do hipocampo dorsal danificada por lesão eletrolítica. Diversos relatos têm mostrado que o hipocampo e estruturas adjacentes desempenham papel importante em diferentes aspectos do controle das emoções, entre eles a regulação da ansiedade. Existem evidências mostrando que lesões nessa região provocam desinibição comportamental, com diminuição de reações que expressam medo e ansiedade. Portanto, a partir desses pressupostos, o presente estudo investigou se a terapia celular seria capaz de modificar os efeitos comportamentais da lesão eletrolítica do hipocampo dorsal. Para isso, os camundongos receberam, sete dias após a indução de lesão eletrolítica bilateral no hipocampo dorsal, meio de cultura ou células mononucleares da medula óssea. Uma semana após o transplante, os animais foram submetidos à avaliação comportamental no labirinto em cruz elevado (LCE), um modelo de estudo amplamente utilizado em pesquisas sobre a ansiedade animal. Ao todo, foram conduzidas três sessões de avaliação no LCE, com intervalo de sete dias entre cada avaliação. Trinta e cinco dias após a indução da lesão hipocampal, os camundongos foram sacrificados e os encéfalos retirados para a realização de análise imuno-histoquímica do tecido cerebral. Os resultados da

avaliação comportamental mostraram que a lesão hipocampal produziu um efeito desinibitório, quadro que se mostrou atenuado, a partir do segundo período de observação, nos animais transplantados com as células mononucleares. Essa análise indicou também que as reexposições ao LCE tiveram um efeito ansiogênico nos animais testados, fenômeno que se mostrou menos intenso naqueles que sofreram a lesão no hipocampo e que, aparentemente, não recebeu influência do tratamento com células medulares. Pela análise imuno-histoquímica, foi observada presença reduzida de células EGFP⁺ no cérebro dos animais lesionados. Quando presentes, essas células encontravam-se predominantemente associadas a vasos sanguíneos, e sem indícios de diferenciação. Diante da não recuperação da citoarquitetura tissular nos animais lesionados que receberam o transplante, acredita-se que os benefícios observados sobre o comportamento tenham resultado de um efeito parácrino das células mononucleares, possivelmente pela liberação de fatores bioativos que auxiliaram na ação de mecanismos endógenos para restituição parcial das funções do hipocampo. Em conclusão, os resultados deste estudo mostram que o transplante de células da medula óssea tem potencial para reduzir prejuízos funcionais decorrentes de lesões cerebrais, e novas investigações necessitam ser conduzidas para uma identificação mais precisa dos mecanismos responsáveis por esse efeito.

Palavras-chave: Hipocampo. Lesão eletrolítica. Ansiedade. Labirinto em cruz elevado. Células-tronco. Medula óssea.

ABSTRACT

Alves-de-Moraes LBC. Analysis of the effects of bone marrow mononuclear cells transplantation in mice submitted to electrolytic lesion of the dorsal hippocampus [dissertation]. São Paulo: Instituto de Ciências Biomédicas da Universidade de São Paulo; 2010.

Two basic properties characterize stem cells: the state of undifferentiation and the ability to self-renew and give rise to differentiated cells. Among adult stem cells, bone marrow cells represent the best-known type, having ever demonstrated great versatility for use in transplant procedures and experimental cell therapy. Therefore, in order to characterize the potential of this class of stem cells as a therapeutic tool for the correction of nervous tissue injury, the effects of the transplantation of bone marrow mononuclear cells (BMMC) labeled with the enhanced green fluorescent protein (EGFP) on C57BL/6 mice that had the dorsal portion of the hippocampus damaged by electrolytic lesion were analyzed. Several reports have shown that the hippocampus and adjacent structures play an important role in different aspects of the control of emotions, including the regulation of anxiety. There is evidence that lesions in this region cause behavioral disinhibition, with reduction of reactions expressing fear and anxiety. Therefore, from these assumptions, this study investigated whether cell therapy would be able to modify the behavioral effects of electrolytic lesion in the dorsal hippocampus. For this purpose, mice were given, seven days after induction of bilateral electrolytic lesion into the dorsal hippocampus, culture medium or BMMC. One week after transplantation, animals had their behavior assessed in the elevated plus-maze (EPM), a study model widely used in research on animal anxiety. On the whole, three assessment sessions in the EPM were carried out, with seven days separating each trial. Thirty-five days after the induction of hippocampal lesion, mice were sacrificed and their brains removed to immunohistochemical analysis of the nervous tissue. The results of the behavioral assessment showed that the hippocampal lesion produced disinhibition, an effect which was lessened, from the second observation period, in animals transplanted with BMMC. This analysis also pointed out that the re-exposures to the maze led to an anxiogenic effect in the tested animals, a phenomenon that was less intense in

those ones who underwent the injury in the hippocampus and, apparently, did not receive the influence of the treatment with bone marrow cells. From the immunohistochemical analysis, it was observed a reduced presence of EGFP⁺ cells into the brains of injured animals. When present, these cells were predominantly associated with blood vessels, without evidence of differentiation. Given the non-recovery of the tissue cytoarchitecture in injured mice which received the transplant, it is believed that the observed benefits on the behavior resulted from a paracrine effect of the mononuclear cells, possibly by the release of bioactive factors that helped in the action of endogenous mechanisms for partial restitution of the hippocampal functions. In conclusion, present results confirm which the transplantation of bone marrow cells holds potential to reduce functional impairment caused by brain damage, and further investigations need to be conducted to identify more precisely the mechanisms responsible for this effect.

Keywords: Hippocampus. Electrolytic lesion. Anxiety. Elevated plus-maze. Stem cells. Bone marrow.

INTRODUÇÃO

Por sua estreita relação neuroanatômica com diferentes núcleos cerebrais e por ser uma região neural com participação fundamental em muitos dos aspectos que se referem à cognição, às emoções e ao comportamento, o hipocampo tem sido objeto de intensa investigação. Busca-se, com grande interesse, a compreensão de seu intrincado funcionamento e de suas complexas interações, enfocando com frequência as anormalidades estruturais e neurofisiológicas que se apresentam durante o curso de diferentes enfermidades cerebrais.

De fato, dada a importância das funções desempenhadas pelo hipocampo, danos a essa estrutura tendem a resultar em sério prejuízo para o funcionamento psíquico normal. Essa constatação tem sido possibilitada pelo fato de o hipocampo ser particularmente vulnerável a diversos processos patológicos, como isquemia (Gong et al., 2000; Hodges et al., 1997; Squire e Zola, 1996), epilepsia (Ang et al., 2006; Reid e Stewart, 1997; Zhou et al., 2007) e doença de Alzheimer (Panegyres, 2004; Rowan et al., 2005; Simonian e Hyman, 1995). No caso específico da doença de Alzheimer, o hipocampo é uma das primeiras estruturas danificadas e, embora afete diferentes regiões, a doença é particularmente intensa na região CA1 (Bahr et al., 1998; Giannakopoulos et al., 1997; Hof et al., 2003; Jolas et al., 2002; Katayama et al., 1990; Stepanichev et al., 2004). Anormalidades têm também sido localizadas no hipocampo em pacientes com esquizofrenia. Alterações na transmissão glutamatérgica, no hipocampo e em suas eferências, têm sido implicadas na fisiopatologia da doença (Collinge e Curtis, 1991; Csernansky e Bardgett, 1998; Floresco et al., 2001; Gao et al., 2000; Harrison et al., 1991; Ohnuma et al., 2000; Tsai et al., 1995).

Portanto, é de amplo reconhecimento que a manifestação desse espectro de psicopatologias e condições neurodegenerativas pode impedir o correto funcionamento do hipocampo e prejudicar significativamente a qualidade de vida dos indivíduos afetados. A depender do tipo e da extensão dos danos, que não raro cursam na forma de uma grave e progressiva perda de células nervosas, os indivíduos acometidos podem vir a manifestar severa debilidade cognitiva e sérios distúrbios comportamentais, como pode ser observado, por exemplo, com os pacientes portadores da doença de Alzheimer. Desta maneira, os diferentes

processos de neurodegeneração do hipocampo dão ensejo a estudos que busquem aproveitar o potencial, ainda pouco explorado, das células-tronco como um instrumento para a reposição das células destruídas nessa região.

De fato, o emprego das células-tronco na ciência médica consolida-se cada vez mais em termos de potencialidade terapêutica para a correção de processos traumáticos e degenerativos, e se justifica não só cientificamente, mas também por razões sociais, econômicas e pelos efeitos que poderá provocar em diversas áreas do conhecimento. A partir desses aspectos, destaca-se a importância da pesquisa básica em colaborar para que num futuro próximo siga-se uma fase em que a terapia celular deixe de ser apenas uma esperança e ocupe seus reais espaços de aplicação, por meio da transferência de conhecimento do laboratório para a prática médica.

Considerando a necessidade de criação e seleção de terapias candidatas para o tratamento de quadros agudos e neurodegenerativos no sistema nervoso e a ampla gama de possibilidades que emerge da aplicação das células-tronco, o uso dessas células se qualifica como uma proposta científica e tecnicamente viável para evitar o aparecimento ou, uma vez deflagrado processo, reverter os processos fisiopatológicos que conduzem à morte neuronal. Apesar das importantes contribuições que este campo de estudo vem recebendo nos últimos anos, a aplicação de terapia celular experimental para a recuperação do hipocampo danificado ainda não possui grande número de trabalhos, necessitando, portanto, de novos resultados e da reafirmação dos já disponíveis.

Sendo assim, acredita-se que as informações apresentadas no presente estudo podem justificar e mostrar a relevância de projetos e programas de pesquisa voltados ao desenvolvimento de novos procedimentos para o estudo e aplicação da terapia celular experimental em lesões do hipocampo, proporcionando, com isto, o entendimento do potencial de alcance e da janela de oportunidade para este trabalho. Espera-se, deste modo, que os resultados obtidos possam fornecer informações importantes para a caracterização específica do potencial das células-tronco como ferramenta terapêutica e contribuir com fundamentos metodológicos para futura aplicação de terapia celular em modelos experimentais para corrigir ou reduzir a perda de células decorrente de processos neurodegenerativos, traumas e outros tipos de injúria do hipocampo e do sistema nervoso em geral.

Feitas essas considerações, e com base nas informações apresentadas, o presente estudo foi desenhado com o intuito de avaliar a capacidade das células mononucleares da medula óssea como elemento de recuperação em animais submetidos à lesão eletrolítica do hipocampo dorsal. Como hipótese central do trabalho, havia a expectativa de que tais células, uma vez transplantadas, migrassem e se integrassem à região lesionada para promover tanto a regeneração tissular como a recuperação funcional. Essa possibilidade foi analisada utilizando-se como método de referência a comparação dos resultados de uma análise imunohistoquímica do tecido hipocampal com os de uma análise comportamental dos animais experimentais.

CONCLUSÃO

Os resultados da avaliação comportamental mostraram que a lesão eletrolítica no hipocampo dorsal desencadeou um quadro de desinibição comportamental, expresso pelo aumento da exploração dos braços abertos do labirinto em cruz elevado, nos camundongos analisados. As lesões também aumentaram o comportamento de exploração do centro do aparelho, mas tiveram efeito inespecífico sobre a atividade locomotora e não afetaram a frequência de defecação. Adicionalmente, os resultados mostraram que o transplante de células mononucleares da medula óssea nos animais com dano hipocampal ocasionou modificações no padrão exploratório, contribuindo, ao menos em parte, para reverter a tendência ansiolítica do comportamento manifestado no labirinto, mais especificamente a partir do segundo período de avaliação.

Os níveis de ansiedade também sofreram alteração ao longo do período de avaliação. As reexposições ao LCE tiveram um efeito antagônico ao da lesão hipocampal, ocasionando uma queda nas medidas que denotavam redução da ansiedade nos animais testados, possivelmente em decorrência da formação de uma memória aversiva induzida na primeira exposição. Esse fenômeno ansiogênico mostrou-se menos intenso nos camundongos que foram submetidos à lesão do hipocampo e, aparentemente, não sofreu influência do tratamento com as células medulares.

Quanto à atividade migratória das células transplantadas, a análise imuno-histoquímica conduzida na segunda etapa da investigação identificou sinais da presença de células EGFP⁺ no cérebro dos animais lesionados, porém em uma frequência pouco expressiva. As células marcadas foram encontradas predominantemente associadas a vasos sanguíneos, e apresentavam aspecto indiferenciado. Quando localizadas no parênquima cerebral, as células EGFP⁺ exibiam, na maioria das ocorrências, características morfológicas semelhantes às de células microgliais de diferentes estágios de desenvolvimento.

A partir da não constatação de regeneração da citoarquitetura do tecido hipocampal nos animais lesionados que receberam o transplante, pode-se postular que os benefícios observados sobre o comportamento tenham resultado de um efeito parácrino das células mononucleares, possivelmente pela liberação de fatores

tróficos e imunomodulatórios que poderiam atuar cooperativamente na ação de mecanismos endógenos para a restituição da homeostase e compensação parcial das funções prejudicadas pela injúria na região do hipocampo.

Considerados em conjunto, os resultados obtidos neste estudo indicam que a terapia com células mononucleares da medula óssea pode ser um instrumento útil para a redução de prejuízos funcionais decorrentes de lesões cerebrais, contudo, novas investigações, com outras abordagens metodológicas, necessitam ser conduzidas para uma identificação mais precisa dos mecanismos responsáveis por esse efeito.

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