LUANA DOS SANTOS ORTOLAN

CITOADESÃO NA IMUNOPATOGÊNESE DA SÍNDROME DO DESCONFORTO RESPIRATÓRIO AGUDO ASSOCIADO À MALÁRIA

Tese apresentada ao Programa de Pós-Graduação em Imunologia do Instituto de Ciências Biomédicas da Universidade de São Paulo, para obtenção do Título de Doutor em Ciências.

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RESUMO

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A malária é um dos maiores problemas de saúde global, especialmente nas regiões tropicais e subtropicais. Infecções por *Plasmodium* sp. podem levar a complicações pulmonares denominadas síndrome do desconforto respiratório agudo (SDRA), caracterizadas por inflamação aguda, lesão do endotélio alveolar e do parênquima pulmonar e disfunção e aumento da permeabilidade da barreira alvéolo-capilar. O modelo experimental, que utiliza o parasita murino *Plasmodium berghei* ANKA e camundongos da linhagem DBA/2, é empregado no estudo de mediadores imunológicos e fatores que propiciam o estabelecimento das lesões pulmonares associados à SDRA. Camundongos DBA/2 infectados com *Plasmodium berghei* ANKA (PbA) foram classificados de acordo com a causa de morte como SDRA ou HP (hiperparasitemia). Os pulmões foram coletados para análise da capacidade respiratória pulmonar, histopatológica, para ensaios de permeabilidade vascular, para qRT-PCR e imunoistoquímica. Camundongos DBA/2 foram também infectados com PbA luciferase para avaliar a distribuição de parasitas *in vivo*. Para avaliar o efeito anti-inflamatório no desenvolvimento da síndrome, os camundongos foram tratados com Dexametasona. *Ex vivo*, células endoteliais pulmonares de camundongos DBA/2 (CEPP-DBA/2) foram estimuladas com IFN-γ, TNF, VEGF, LPS, extrato do parasita (Ext), eritrócitos parasitados (EP) ou com eritrócitos não parasitados (EnP) em diferentes tempos de exposição. Estas células foram analisadas em ensaios de citoadesão estático e em fluxo, por expressão gênica, em co-culturas com células inflamatórias e em ensaios de inibição de moléculas específicas e de permeabilidade. Nossos resultados demonstraram que há acúmulo de PbA nos pulmões de DBA/2 que desenvolveram SDRA e que TNF e IFN-γ aumentam a citoadesão em CEPP-DBA/2, bem como a expressão de ICAM-1, VCAM-1 e EPCR. Além disso, mostramos que a inibição de TNF diminui a adesão de EP. Também observamos que dexametasona protege os animais da SDRA através da diminuição de fatores inflamatórios, expressão gênica de EPCR e através da inibição da abertura de junções interendoteliais. Em conclusão, identificamos que o aumento da citoaderência de PbA-EP nos pulmões de camundongos DBA/2 está relacionada com a patogênese de SDRA associada à malária e que fatores inflamatórios, especialmente TNF e IFN-γ aumentam a expressão de moléculas de adesão, em especial EPCR. Ainda, concluímos que a intervenção com dexametasona protege os animais do desenvolvimento da SDRA associada à malária (SDRA-AM) devido preservação da permeabilidade da barreira alvéolo-capilar. A intervenção da citoaderênca e da permeabilidade vascular pulmonar com o uso de corticosteróies, pode ser um importante alvo para o tratamento e a prevenção da SDRA-AM.

Palavras-chave: *Plasmodium*. Malária. Adesão. Síndrome do Desconforto Respiratório Agudo. Inflamação.

ABSTRACT

ORTOLAN, L. S. **Cytoadhesion in the immunopathogenesis of malaria-associated acute respiratory distress syndrome.** 2017. 155 p. Ph. D thesis (immunology) - Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2017.

Malaria is one of the most serious global health problems, especially in tropical and subtropical regions. Infections by *Plasmodium sp*. can lead to pulmonary complications named acute respiratory distress syndrome (ARDS), characterized by acute inflammation, damage of the alveolar endothelium and pulmonary parenchyma, dysfunction and increased permeability of the alveolar-capillary barrier. The experimental model, using the murine parasite *Plasmodium berghei* ANKA and DBA/2 mice, is used to study immunological mediators and factors that allow the establishment of lung lesions associated with ARDS. DBA/2 mice infected with *Plasmodium berghei* ANKA (PbA) were classified according to cause of death as ARDS or HP (hyperparasitemia). Lungs were collected for analysis of respiratory capacity, histological analyses by qRT-PCR and immunohistochemistry. DBA/2 mice were also infected with PbA luciferase to evaluate a parasite distribution *in vivo*. To evaluate the anti-inflammatory effect in the ARDS development, DBA/2 mice were treated with dexamethasone. *Ex vivo*, primary culture of pulmonary endothelial cells from DBA/2 mice (PPEC-DBA/2) were stimulated with IFN-γ, TNF, VEGF, LPS, parasite extract (Ext), parasitized erythrocytes (PE) or with non-parasitized erythrocytes at different exposure times. These cells were analyzed through immunofluorescence, static and flow cytoadhesion tests, mRNA expression, cytokines production, co-culture with inflammatory cells and specific molecules inhibition and permeability assays. Our results demonstrate that there was an accumulation of PbA in the lungs of DBA/2 mice which developed ARDS. Also, TNF and IFN-γ increased the cytoadhesion of PE in CEPP-DBA/2, as well as the expression of ICAM-1, VCAM-1 and EPCR. Moreover, the inhibition of TNF decreased the adherence of PE in PPEC-DBA/2. We also observed that dexamethasone protected animals from ARDS by decreasing inflammatory factors, gene expression of EPCR and inhibited the opening of interendothelial junctions. In conclusion, we identified that the increased cytoadherence of PbA-PE in the lungs of DBA/2 mice is related to the pathogenesis of malaria-associated ARDS, and the inflammatory factors (TNF and IFN-γ) increase the expression of adhesion molecules, especially EPCR. In adittion, the treatment with dexamethasone protects the animals from the development of malaria-associated ARDS (MA-ARDS), due to preservention of the alveolar-capillary permeability barrier. The intervention of the cythoadherence and pulmonary vascular permeability using corticosteroids may be an important target for treatment and prevention of MA-ARDS.

Keywords: *Plasmodium*. Malaria. Adhesion. Acute Respiratory Distress Syndrome. Inflammation.

1 INTRODUÇÃO

Malária é uma doença infecciosa parasitária de grande impacto para a saúde pública e para o desenvolvimento econômico mundial, pois ainda hoje representa risco para as mais diversas populações, especialmente para aquelas localizadas em áreas tropicais e subtropicais. Esta enfermidade está fortemente associada à pobreza, sendo que as taxas de mortalidade mais altas encontram-se em países com menor PIB per capita (WORLD HEALTH ORGANIZATION, 2012).

De acordo com a organização mundial da saúde (OMS), em 2015, 3,2 bilhões de pessoas estiveram expostas ao risco de ser infectadas e desenvolver a doença e nesse mesmo ano, a estimativa foi de 214 milhões de novos casos. Em 2015 a malária foi responsável pela morte de aproximadamente 438.000 pessoas (WORLD HEALTH ORGANIZATION, 2015).

Das cinco espécies de *Plasmodium* que infectam humanos, *Plasmodium falciparum* é responsável pelo maior número de casos graves e fatais nos trópicos (OLUPOT-OLUPOT; MAITLAND, 2013). Embora considerada por muito tempo como malária benigna, nos últimos anos as infecções por *P. vivax* também têm sido descritas como causadoras de malária grave, inclusive com casos fatais (NAING et al., 2014).

Acidose e hipolglicemia são os distúrbios metabólicos mais comuns da malária e as principais complicações incluem malária cerebral, comprometimento pulmonar, falências renal e hepática, anemia grave, quadros hemorrágicos, além da malária placentária, as quais podem progredir rapidamente para a morte em horas ou dias. Em muitos pacientes, estas manifestações podem aparecer concomitantemente (MILLER et al., 2013; TRAMPUZ et al., 2003).

Um importante aspecto da patogênese da malária grave resulta na habilidade de eritrócitos parasitados (EP) serem sequestrados na microvasculatura. Este envolvimento pode ser um resultado direto do bloqueio dos vasos sanguíneos ou efeitos causados pela interação entre os EP e o endotélio, incluindo a resposta inflamatória local (HUGHES; BIAGINI; CRAIG, 2010). Além disso, a adesão promove o desaparecimento das formas assexuadas do parasita da circulação periférica, evitando assim, que os mesmos sejam destruídos no baço (GREENWOOD et al., 2008; MILLER et al., 2002; POUVELLE et al., 2000).

Entre as alterações pulmonares causadas pela malária grave, a Síndrome do Desconforto Respiratório Agudo (SDRA) tem sido associada a diferentes enfermidades e não somente em decorrência da malária (LANGE et al., 2012; MOHAN; SHARMA; BOLLINENI, 2008; REISS; UHLIG; UHLIG, 2012; RISCILI et al., 2011).

A SDRA associada à malária (SDRA-AM) pode ocorrer a qualquer momento durante a infecção, incluindo antes, durante ou mesmo após o tratamento com antimaláricos, quando parasitemia já decaiu (MOHAN; SHARMA; BOLLINENI, 2008).

Muitos estudos têm sido realizados desde então para tentar esclarecer os mecanismos de patogênese desta doença. Todavia, apesar das inovações na medicina de tratamento intensivo, em 2005 a incidência estimada de SDRA em adultos foi de aproximadamente 200 mil casos e a mortalidade ainda permanece maior que 40 % (BHARGAVA; WENDT, 2012; GROMMES; SOEHNLEIN, 2011; MATTHAY; ZEMANS, 2011).

A mortalidade por SDRA em hospitais tem sido alta desde que a síndrome foi descrita, atualmente varia entre 40 a 50 % na maioria dos casos e os principais fatores que influenciam na sobrevida incluem idade, tipo de condição médica, gravidade do dano pulmonar, presença de disfunção orgânica extrapulmonar e sepse em curso. A sobrevivência à alta hospitalar é mais baixa em pacientes com sepse grave e pneumonia e maior em pacientes com trauma. Aproximadamente 80 % de todas as mortes ocorrem dentro de 2 a 3 semanas após o aparecimento da síndrome e apenas uma pequena porção de pacientes morrem de hipoxemia (VILLAR; BLANCO; KACMAREK, 2016), sem o suporte ventilatório, a mortalidade é ainda maior, em torno de 80 % (VILLAR; BLANCO; KACMAREK, 2016).

A SDRA é caracterizada por lesão alveolar difusa, inflamação aguda dos alvéolos e do parênquima pulmonar. Observa-se também a perda da função e o aumento da permeabilidade da barreira epitelial do alvéolo e do capilar pulmonar, resultando em edema pulmonar de origem não-cardiogênica, diminuição da capacidade de trocas gasosas, aumento da atividade leucocitária e de mediadores inflamatórios nos pulmões, culminando em insuficiência respiratória em pacientes críticos (ANSTEY et al., 2002; GOODMAN et al., 2003; GROMMES; SOEHNLEIN, 2011).

A SDRA-AM pode ocorrer em infecções por *P. falciparum* como uma única complicação ou pode ser acompanhada por outros distúrbios levando a uma disfunção

de múltiplos órgãos (MOHAN; SHARMA; BOLLINENI, 2008; TAYLOR et al., 2012). A SDRA-AM também já foi descrita em associação às infecções por *P. vivax, P. ovale* e *P. malariae* e também em infecções por *P. knowlesi*, sendo a mais frequente de suas complicações (DESCHEEMAEKER et al., 2009; LEE; MAGUIRE, 1999; MOHAN; SHARMA; BOLLINENI, 2008; PRICE et al., 2007; TAN et al., 2008).

A patogenia da SDRA-AM é multifatorial e, tanto fatores do hospedeiro quanto do parasita, possuem papéis cruciais no desenvolvimento da doença. Embora tenha sido descrita há muito tempo, a mortalidade de pacientes permanece alta nas unidades de terapia intensiva e ainda não se conhece os mecanismos de desenvolvimento da doença. Também são desconhecidas formas de diagnóstico precoce, que permitam um tratamento efetivo antes do estabelecimento da forma grave da síndrome e, que consequentemente, evite a morte do paciente (GOOD et al., 2005; MOHAN; SHARMA; BOLLINENI, 2008). A mesma pode estar associada a danos do endotélio da microvasculatura pulmonar, ativação de mecanismos pró-inflamatórios, sequestro de parasitas nos pulmões, acidose metabólica, falência cardíaca. (GOOD et al., 2005).

Mecanismos ligados à imunidade inata têm se mostrado importantes para o controle precoce da infecção pelo plasmódio por meio do aumento de citocinas e da ativação da resposta imune celular (ARTAVANIS-TSAKONAS; RILEY, 2002; MITCHELL et al., 2005). Entretanto, uma resposta inflamatória excessiva e/ou prolongada contribui para a patogênese e para o aparecimento dos sinais e dos sintomas associados à malária grave, incluindo anemia severa, malária cerebral, pulmonar e placentária (SCHOFIELD, 2007).

7 CONCLUSÕES

- Camundongos DBA/2 infectados com *P. berghei* ANKA que desenvolvem SDRA vão à óbito entre o 7º e 12º dpi e apresentam aumento da pausa respiratória e diminuição da frequência respiratória;
- Camundongos DBA/2 infectados com *P. berghei* ANKA que desenvolvem SDRA apresentam maior acúmulo de eritrócitos parasitados nos pulmões em em relação aos animais que desenvolvem HP, sugerindo fortemente que este acumulo está envolvido na patogênese desta síndrome;
- Animais que desenvolvem SDRA apresentam maior marcação de ICAM-1 nos pulmões em relação a animais HP no 7º dpi;
- Apesar da dexametasona não diminuir a mortalidade dos camundongos DBA/2 infectados com *P. berghei* ANKA, este fármaco diminui a inflamação e protege do desenvolvimento da SDRA;
- Dexametasona também é capaz de diminuir o aumento da permeabilidade vascular pulmonar em animais tratados, bem como em células endoteliais pulmonares primárias de camundongos DBA/ (CEPP-DBA/2) estimuladas;
- Eritrócitos parasitados com *Plasmodium berghei* ANKA (EP-PbA) são capazes de aderir nas CEPP–DBA/2 *ex vivo* e a adesão é maior na presença de citocinas pró-inflamatórios como IFN-γ e TNF;
- TNF é capaz de aumentar a expressão gênica de ICAM-1, VCAM e EPCR, atuando como um importante indutor inflamatório na patogênese da SDRA;
- EP-PbA não aumentam diretamente a expressão de moléculas de adesão, mas estimulam a produção de TNF;
- IFN-γ é capaz de aumentar a expressão gênica de ICAM-1 contribuindo para a citoadesão de EP-PbA;
- Dexametasona protege as células endoteliais do aumento da permeabilidade através da diminuição da abertura de junções interentdoteliais.

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