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IMPORTÂNCIA DA PROTEASE ADAMTS-1 NA INVASÃO LOCAL E SISTÊMICA DE CÉLULAS DO FIBROSSARCOMA

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RESUMO

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O crescimento e a malignidade de um tumor são ditados pelo microambiente circundante. A matriz extracelular, que faz parte do microambiente tumoral, serve como depósito para fatores biologicamente ativos, como fatores de crescimento e proteases, os quais influenciam no comportamento das células tumorais. A ADAMTS-1 (uma desintegrina e metaloproteinase com motivos trombospondina) é uma protease secretada, conhecida por sua capacidade de modificar a matriz extracelular durante os processos fisiológicos e patológicos. Neste trabalho, avaliamos o papel da ADAMTS-1 na regulação das atividades estimuladas pelos fatores de crescimento (HGF e TGF-β1), sobre a linhagem celular de fibrossarcoma humano (HT1080). Para tanto, foram geradas células HT1080 e HEK293T que superexpressam a protease ADAMTS-1. Ensaios de incorporação de BrdU e expressão de Ki67 demonstraram que a superexpressão de ADAMTS-1 diminuiu a proliferação das células HT1080, na presença do HGF. Ademais, as células HT1080 que superexpressam ADAMTS-1 apresentaram uma velocidade de migração de 6.120 ± 0.416 μm/hora, a qual foi 2 vezes menor que a velocidade de migração das células controle (13.763 ± 1,421 μm/hora), ambas na presença do HGF. Da mesma forma, observamos que a proliferação e a velocidade de migração das células HT1080 (tipo selvagem) diminuiu quando estas foram tratadas com o HGF acrescido ao meio condicionado de outro tipo celular (HEK293T) que superexpressa ADAMTS-1. A seguir, demonstramos que a superexpressão da ADAMTS-1 interrompe a ativação do receptor c-Met, após estimulação com o HGF. Consequentemente, as vias de sinalização *downstream* ERK1/2 e FAK foram perturbadas. Por outro lado, a superexpressão de ADAMTS-1 não afetou a atividade do TGF-β1 associada à proliferação celular e velocidade de migração das celulas HT1080. Embora observamos uma diminuição na fosforilação das smad2/3 nas células que superexpressam ADAMTS-1, esta diminuição não foi suficiente para perturbar as vias de sinalização ERK1/2 e Akt, após o tratamento com o TGF-β1. Adicionalmente, através de cultura 3D em *Hanging drop* mostramos que na presença do HGF, a superexpressão de ADAMTS-1 diminuiu o diâmetro das fibrosarcoesferas (~0,7 mm), quando comparado com o controle (diâmetro das fibrosarcoesferas ~1,3 mm). Nos estudos *in vivo* observamos que na presença do HGF, a superexpressão de ADAMTS-1 perturbou a formação de microtumores. E os poucos microtumores formados, incluindo as células individuais, apresentaram características morfológicas de lesões menos invasivas. Nossos dados sugerem que a ADAMTS-1 está envolvida na regulação das atividades estimuladas pelo HGF, nas células do fibrossarcoma. Esta protease pode então representar um mecanismo endógeno no controle da biodisponibilidade de diferentes fatores de crescimento com influência direta sobre o comportamento das células tumorais.

Palavras-chave: Fibrossarcoma. Matriz extracelular. Metaloproteinases da matriz. ADAMTS1. Fator de crescimento do hepatócito. Fator de crescimento transformante beta.

ABSTRACT

GUERRA, H. N. **Importance of ADAMTS-1 protease in local and systemic invasion of fibrosarcoma.** 2017. 93 p. PhD Thesis (Cell and Tissue Biology) - Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2017.

The growth and malignancy of a tumor are dictated by the surrounding microenvironment. The extracellular matrix forms part of the tumor microenvironment, and serves as a reservoir for biologically active factors, such as growth factors and proteases that influence the tumor cell behavior. ADAMTS-1 (a disintegrin and metalloproteinase with thrombospondin motifs) is a secreted protease that has the ability to modify the extracellular matrix during physiological and pathological processes. Here, we addressed the role played by ADAMTS-1 regulating HGF and TGF-β1 activities in the high-grade fibrosarcoma cell line (HT1080). For this, we generated HT1080 and HEK293T cells that overexpress ADAMTS-1. BrdU incorporation and Ki67 expression assays demonstrated that ADAMTS-1 overexpression induced a significant decrease of HT1080 cell proliferation, in the presence of HGF. In addition, the HT1080 cells overexpressing ADAMTS-1 presented a migration velocity of 6.120 ± 0.416 μm/hour, which was at least 2 times lower than the control cell migration velocity (13.763 ± 1.421 μm/hour), both in presence of HGF. Likewise, when HT1080 cells were treated with HGF added into the conditioned medium of other cell type (HEK293T) that overexpressed ADAMTS-1, we observed a decrease of cell proliferation and migration velocity. Next, we demonstrate that ADAMTS-1 overexpression interrupts c-Met activation upon HGF stimulation. Consequently, the downstream ERK1/2 and FAK signaling pathways are disturbed. On the other hand, ADAMTS-1 overexpression failed to affect TGF-β1 activity associated with HT1080 cell proliferation and migration velocity. Although we observed a decrease of smad2/3 phosphorylation in HT1080 cells overexpressing ADAMTS-1, this partial reduction was not sufficient to alter ERK1/2 and Akt activation, after treatment with TGF-β1. Additionally, through 3D culture in Hanging drop we showed that in presence of HGF, ADAMTS-1 overexpression decreased the fibrosarcospheres diameter (~0.7 mm), as compared to the control (fibrosarcospheres diameter of ~1.3 mm). *In vivo* studies showed that in presence of HGF, ADAMTS-1 overexpression disrupted the formation of microtumors. These microtumors, including individual cells, presented characteristics of low invasive tumor cells (rounded morphology). Our results suggest that ADAMTS-1 is involved in regulating HGF-related functions on fibrosarcoma cells. This protease may then represent an endogenous mechanism in controlling the bioavailability of different growth factors that have a direct influence on tumor cell behavior.

Keywords: Fibrosarcoma. Extracellular matrix. Matrix metalloproteinases. ADAMTS1. Hepatocyte growth factor. Transforming growth factor beta.

INTRODUÇÃO

O fibrossarcoma é um câncer de origem mesenquimal, de alta malignidade e agressividade. Deriva-se do tecido conjuntivo denso e se caracteriza pela presença de fibroblastos malignos (imaturos); os quais apresentam uma divisão celular rápida e desorganizada, formando assim tumores sólidos (JAYAMATHI et al., 2010; NIKITOVIC et al., 2013). Na clínica, o fibrossarcoma apresenta elevado índice de recorrência local e baixa incidência de metástase hematogênica e/ou metástase em linfonodos regionais (KOTRASHETTI et al., 2012; NIKITOVIC et al., 2013).

A progressão do câncer não depende apenas de novas habilidades adquiridas pelas células tumorais, mas também da interação com seu microambiente. Como é sabido, a matriz extracelular (MEC) faz parte do microambiente tumoral; e esta matriz é constituída por uma rede complexa de macromoléculas, tais como glicoproteínas, colágenos, glicosaminoglicanos e proteoglicanos (BRESNICK; WEBER; ZIMMER, 2015; DECLERCK et al., 2004; KIM; TURNBULL; GUIMOND, 2011).

No microambiente tumoral, o papel da MEC não está limitado a atuar somente como uma barreira física contra a invasão tumoral. Também serve como depósito para fatores biologicamente ativos, como fatores de crescimento, proteases, hormônios, entre outros, os quais influenciam no comportamento das células tumorais (DECLERCK et al., 2004).

Encontra-se bem estabelecido na literatura que um evento chave na invasão e metástase dos tumores é a clivagem ou degradação dos componentes da MEC por ação de proteases (FOLKMAN; SHING, 1992). Entre estas proteases temos à ADAMTS-1, o primeiro membro identificado da família ADAMTS (uma desintegrina e metaloproteinase com motivos trombospondina). Esta protease se caracteriza por apresentar um peptídeo sinalizador, um pró-domínio, um domínio metaloproteinase dependente de zinco, um domínio semelhante a desintegrina, três motivos trombospondina tipo I (TSP-1), um domínio rico em cisteína e uma região espaçadora. É importante mencionar que todos os membros da família ADAMTS não apresentam o domínio transmembrânico e são, portanto, secretadas na matriz (KUNO et al., 2004).

O mecanismo de ação da ADAMTS-1 na progressão tumoral ainda não está claramente definido. Embora a molécula inteira de ADAMTS-1 promova a metástase,

os fragmentos da molécula que não possuem atividade catalítica e apresentam um motivo TSP1 na sua estrutura, mostraram um efeito antimetastático. Portanto, dependendo do local de auto-clivagem proteolítica, a ADAMTS-1 pode estar relacionada à atividade antitumoral (PORTER et al., 2005) ou atividade pró-tumoral e estimuladora de metástase (LIU; XU; YU, 2006; LU et al., 2009).

Além disso, ADAMTS-1 possui um efeito anti-angiogênico, devido à ligação direta desta protease com o fator de crescimento do endotélio vascular (VEGF). Esta interação impede então ao VEGF de se ligar e ativar seu respectivo receptor (KUNO et al., 2000; RUSSELL et al., 2003; SANDY et al., 2001). Por outro lado, ADAMTS-1 promove a angiogênese e invasão tumoral, através da sua atividade *sheddase* sobre os precursores transmembrânicos do fator de crescimento epidermal ligado a heparina (HB-EGF), e a subsequente ativação do seu respectivo receptor (LIU; XU; YU, 2006). Dessa forma, ADAMTS-1 representa um mecanismo endógeno no controle da biodisponibilidade dos diferentes fatores de crescimento (LIU; XU; YU, 2006; MARGOSIO et al., 2003).

Neste trabalho, buscamos elucidar o papel da protease ADAMTS-1 e sua íntima ligação com o microambiente tumoral do fibrossarcoma. Nosso enfoque foi estudar o efeito da protease ADAMTS-1 na regulação das atividades estimuladas pelos fatores de crescimento (HGF e TGF-β1), sobre a linhagem celular derivada de fibrossarcoma.

Os ensaios foram então realizados a partir de células de fibrossarcoma humano (HT1080) transduzidas para superexpressar ADAMTS-1, e as quais foram tratadas apenas com os fatores de crescimento de interesse. Por outro lado, células de fibrossarcoma não transduzidas (selvagens) foram tratadas com os fatores de crescimento de interesse adicionados ao meio condicionado coletado de outro tipo celular, o qual também foi transduzido para superexpressar ADAMTS-1. Desta forma, o meio condicionado enriquecido com ADAMTS-1, mimetiza a protease secretada por outros tipos celulares presentes no microambiente tumoral.

A proliferação celular foi analisada através dos ensaios de incorporação de Bromodesoxiuridina (BrdU) e expressão de Ki67. A velocidade de migração foi determinada utilizando-se ensaios de *time-lapse* e o plugin *MTrackJ* do *software Fiji/ImageJ.* Investigamos também os mecanismos através dos quais ADAMTS-1 interfere com as atividades estimuladas por HGF ou TGF-β1. Além disso, estudamos por meio de ensaios de cultura 3D em *Hanging Drop*, a capacidade de formação de

fibrosarcoesferas em diferentes condições. Por outro lado, a capacidade de formação de microtumores *in vivo* foi analisada utilizando-se o ensaio de microinjeção de células tumorais em embriões de *zebrafish* transgênicos Tg (fli1:EGFP).

CONCLUSÃO

Baseados nos resultados dos experimentos realizados, concluímos que a superexpressão de ADAMTS-1:

i.) afeta os processos celulares de proliferação e migração das células de fibrossarcoma (HT1080), estimulados pelo fator de crescimento de hepatócitos (HGF);

ii.) não afeta as respostas celulares de proliferação e migração em células HT1080, estimuladas pelo fator de crescimento transformante beta (TGF-β1);

iii.) interrompe a ativação do receptor c-Met, além das suas vias de sinalização *downstream* ERK1/2 e FAK, nas células HT1080 após 15 minutos de estimulação com o HGF;

iv.) prejudica a formação de fibrosarcoesferas a partir das células HT1080 estimuladas com HGF;

v.) perturba a formação de microtumores de HT1080 *in vivo*, após estimulação com o HGF. Os microtumores e as células que não tiveram a capacidade de formar microtumores apresentaram características morfológicas de lesões menos invasivas.

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