MICHELLE PETRONILO SARMENTO

Peptídeo AG73, derivado da laminina, inibindo a proteína podoplanina em linhagem de câncer oral.

Dissertação corrigida apresentada ao Programa de Pós-Graduação em Biologia Celular e Tecidual do Instituto de Ciências Biomédicas da Universidade de São Paulo, para obtenção do Título de Mestre em Ciências.

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RESUMO

SARMENTO, M.P. **Peptídeo AG73, derivado da laminina, inibindo a proteína podoplanina em linhagem de câncer oral.** 2018. 132p. Dissertação (Mestrado em Biologia Celular e Tecidual) – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2018.

A disseminação metastática de células tumorais malignas envolve múltiplas etapas e é uma das principais causas de mortalidade. O microambiente tumoral apresenta um importante papel no processo de tumorigênese. A laminina é um componente do microambiente que pode ser clivado em peptídeos bioativos, como o peptídeo AG73 (domínio globular da cadeia α1) que aumenta a formação/atividade de invadopódios. Invadopódios são protrusões de membrana ricas em actina com atividade proteolítica da matriz pericelular. Além da actina, os invadopódios exibem outras proteínas importantes, como a cortactina e o MT1-MMP. Recentemente, descobriu-se que a podoplanina pode desempenhar um papel importante na atividade dos invadopódios. A podoplanina é uma glicoproteína transmembrana do tipo I, intimamente associada à progressão maligna do câncer. A podoplanina e o peptídeo AG73 influenciam a biologia do câncer. Tal particularidade levou-nos a investigar o papel do peptídeo AG73 na regulação da da podoplanina e invadopódios em linhagem celular derivada de carcinoma de células escamosas oral (Cal 27). As células foram cultivadas em DMEM com SFB e tratadas com o peptídeo AG73. As células tratadas por peptídeo de sequência embaralhada serviram como controles. Imunofluorescência foi realizada para analisar os níveis de proteína de podoplanina, cortactina e MT1-MMP. Os resultados mostraram que o peptídeo AG73 diminuiu os níveis de podoplanina nas células Cal27 em comparação aos controles. Nenhuma alteração foi observada em relação à cortactina e MT1-MMP. Estes resultados foram confirmados por imunofluorescência. As células tratadas com AG73 diminuíram a distribuição da podoplanina em todo o citoplasma em comparação com os controles. Nossos resultados sugerem que o peptídeo derivado da laminina AG73 inibe a podoplanina, uma molécula reguladora do câncer, em células malignas humanas.

Palavras-chave: Carcinoma de células escamosas, matriz extracelular, laminina, podoplanina, invadopódios.

ABSTRACT

SARMENTO, M.P. **The laminin-derived peptide inhibits podoplanin in oral cancer lines.** 2018. 132p. Dissertation (Master Thesis in Cell and Tissue Biology) – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2018.

The metastatic spread of malignant tumor cells involves multiple steps, and is one of the major causes of mortality. The tumor microenvironment has an important role in tumorigenesis process. Laminin is a component of the microenvironment that can be cleaved into bioactive peptides, such as peptide AG73 (globular domain of α1 chain) that increase invadopodia formation/activity. Invadopodia are actin-rich membrane protrusions with proteolytic activity of peri-cellular matrix. In addition to actin invadopodia exhibit other key proteins such as cortactin and MT1-MMP. Recently it has been discovered that podoplanin may play an important role in the invadopodia activity. Podoplanin is a type I transmembrane glycoprotein, closely associated with the malignant progression of cancer. Podoplanin and the peptide AG73 influence cancer biology. This prompted us to investigate the role of peptide AG73 in the regulation of podoplanin and invadopodia formation in a cell line derived from oral squamous cell carcinoma (Cal 27). Cells were cultured in DMEM with FBS and treated with peptide AG73. Cells treated by scrambled peptide served as controls. Immunoblot was carried out to analyze protein levels of podoplanin, cortactin and MT1-MMP. Results showed that the peptide AG73 decreased podoplanin levels in Cal27 cells compared to controls. No alterations were observed with regard to cortactin and MT1-MMP. These results were confirmed by immunofluorescence. Cells treated by AG73 decreased podoplanin distribution throughout the cytoplasm compared to controls. Our results suggest that the laminin-derived peptide AG73 inhibits podoplanin, a cancer regulator molecule, in human malignant cells.

Keywords: Squamous cell carcinoma, extracellular matrix, laminin, podoplanin, invadopodia.

1. INTRODUÇÂO

Dados na Organização Mundial de Saúde indicam que 8,8 milhões de pessoas morrem de câncer a cada ano e as estatísticas preveem que em 2030 ocorrerão 27 milhões de novos casos. (WHO, 2017). Dentre os subtipos tumorais, o carcinoma epidermóide oral representa 95% de todas as formas de câncer de cabeça e pescoço, e na última década sua incidência aumentou em 50% (RIVIERA, 2014), apresentando alta taxa recidiva sendo o gênero masculino o mais acometido por essa neoplasia (WANG, 2013). No Brasil, o Instituto Nacional do Câncer (INCA) estimou que no ano de 2016, 596 mil novos casos câncer, sendo 11,140 de cavidade oral que ocupa a quinta colocação na população masculina (INCA, 2016).

A tumorigênese é um processo de vários passos, cuja progressão depende do acumulo sequencial de mutações nas células (ASHKENAZI, 2008), conferindo à estas um maior potencial proliferativo, evasão à apoptose, angiogênese sustentada e capacidade de invadir e formar metástases. Além das alterações adquiridas pelas células neoplásicas, o microambiente onde elas se encontram também desempenha importante papel no processo de tumorigênese (HANAHAN; WEINBERG 2011).

Entre os elementos do microambiente tumoral destacamos a matriz extracelular (MEC). Essa matriz é uma complexa rede tridimensional de macromoléculas formada por colágenos, proteoglicanos e glicoproteínas, influenciando diversos aspectos da tumorigênese e progressão tumoral (WERB, 2012; AUMAILLEY 2013). Nos epitélios, as células formam uma camada fina e flexível de matriz altamente especializada, a lâmina basal, estrutura laminar constituída principalmente por lamininas, colágeno tipo IV, nidogênio e perlecan (YURCHENCO, 2011). A laminina é um dos principais componentes da lamina basal. Trata-se de uma gliproteína heterodímera de formato cruciforme, composta por 3 cadeias polipeptídicas intituladas α, β e γ (KIKKAWA *et al.,* 2013). Existem pelo menos 16 isoformas da laminina, com massa molecular variando entre 400 a 900 kDa (AUMAILLEY, 2013).

Durante o processo de invasão tumoral, 2 etapas são observadas: Na matriz extracelular ocorre o remodelamento tecidual pela degradação proteolítica (JOHNSEN et al., 1998), seguido pela migração celular (HEGERFELDT *et al.,* 2002). A proteólise da matriz, por sua vez, abre caminho para a invasão tumoral,

ativa moléculas latentes e gera novas moléculas bioativas (SCHENK e QUARANTA, 2003).

A laminina, assim como outras moléculas da matriz, é clivada por proteases como as MMPs. Tal processo pode gerar fragmentos e peptídeos com diferentes efeitos biológicos (SCHENK e QUARANTA 2003; FREITAS et al., 2004). Sabemos que esses peptídeos bioativos são responsáveis por importantes etapas da biologia tumoral, como migração, invasão, secreção de proteases, e formação de invadopódios (FREITAS and JAEGER, 2002; NASCIMENTO et al., 2011).

Nosso laboratório vem estudando a regulação da formação e atividade de invadopódios por peptídeos derivados da laminina (NASCIMENTO et al., 2010; NASCIMENTO et al. 2011). Invadopódios são protrusões de membrana ricas em actina e proteinas ligantes de actina, como a cortactina (LINDER et al., 2007). Adicionalmente, invadopódios possuem a capacidade de realizar digestão da matriz peri-celular, em especial através da protease MT1-MMP (TAKKUNEN et al., 2010, COURTNEIDGE, 2012).

A podoplanina está presente em invadopódios, podendo ser considerada um biomarcador do câncer, em especial do carcinoma epidermóide (DANG et al. 2014; MARTIN-VILLAR et al., 2014; LI et al., 2015; OCHOA-ALVAREZ et al. 2015). Adicionalmente, nosso Laboratório possui fortes evidências que peptídeos da laminina, como C16 e AG73, induzem formação e atividade de invadopódios. Dessa forma, nos interessamos em estudar se o peptídeo AG73, derivado da laminina, regularia podoplanina em invadopódios de linhagem celular derivada de carcinoma epidermóide oral.

7. CONCLUSÕES

7.1 O peptídeo AG73, derivado da laminina, inibe a proteína podoplanina em linhagem de câncer oral.

7.2 O peptídeo AG73 não altera os níveis de proteínas relacionadas a invadopódios, como cortactina e MT1-MMP.

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