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"JÚLIO DE MESQUITA FILHO"

PROGRAMA DE PÓS-GRADUAÇÃO MULTICÊNTRICO EM CIÊNCIAS FISIOLÓGICAS

DISSERTAÇÃO DE MESTRADO

MARIA EDUARDA ALMEIDA TAVARES

O PAPEL DA REV-ERBα COMO POSSIVEL REGULADOR CHAVE EM ALTERAÇÕES MOLECULARES PROSTÁTICAS ASSOCIADAS A SESSÕES AGUDAS DE EXERCICIO FÍSICO EM CAMUNDONGOS IDOSOS

ARAÇATUBA,
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Universidade Estadual Paulista
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Programa de Pós-Graduação Multicêntrico em Ciências Fisiológicas

Dissertação de Mestrado

Maria Eduarda Almeida Tavares

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“Pedras no caminho? Guardo todas, um dia vou construir um castelo...”

- Atribuído a Nemo Nox.

RESUMO

RESUMO

O avanço da idade aumenta a prevalência para o câncer prostático (CaP). A senescência causa declínio hormonal, danificações de DNA, redução da apoptose, aumento de inflamação e estresse oxidativo, culminar no desenvolvimento do CaP. O relógio circadiano coordena o ritmo comportamental e fisiológicos via CLOCK/BMAL1 heterodímero transcricional. O receptor nuclear REV-ERBα forma um loop de feedback que contribui para a função do relógio, modula a biogênese mitocondrial, ciclo celular e controle apoptótico. O exercício físico regula o processo de envelhecimento e pode modificar os genes do relógio na próstata. Contudo, pouco se sabe da expressão da REV-ERBα na próstata e o potencial efeito do exercício físico. Portanto, nosso objetivo foi caracterizar o perfil metabólico e histopatológico prostático em camundongos jovens (6 meses) e camundongos idosos (18 e 24 meses de idade) e verificar a expressão gênica de *Nr1d1* e proteica da REV-ERBα e suas relações metabólicas no microambiente prostático associado ao exercício físico combinado em camundongos idosos. Para avaliar o efeito da idade no desenvolvimento de lesões prostáticas utilizamos camundongos C57BL/6J machos, com idades de 6, 18 e 24 meses. Para avaliar o efeito do ritmo circadiano e do exercício físico no metabolismo prostático durante o envelhecimento utilizamos camundongos de 18 meses sedentários e submetidos ao exercício físico combinado por 3 semanas (3 dias/semana de treinamento físico aeróbio, 40 - 50% do teste de carga incremental; e 2 dias/semana de treinamento físico de força, 40 - 50% de 1 RM). Os animais foram submetidos à eutanásia, a próstata foi coletada e processada para análises bioquímicas, Western Blotting e RT- PCR. Os resultados evidenciaram que durante o envelhecimento os animais de 18 e 24 meses apresentam maior peso prostático, bem como, maiores incidências de neoplasia intraepitelial prostática (NIP) tipo III e IV, infiltrado inflamatório e metaplasia nuclear. Com isso, observamos que animais de 18 meses eram mais suscetíveis a lesões prostáticas e apresentavam maior nível de REV-ERBα e menor expressão de *Bmal1*. Por outro lado, o exercício físico combinado aumentou os níveis de *Bmal1* e reduziu REV-ERBα na próstata., acompanhados pela redução de AMPK/SIRT1/PGC-1α, e aumento de PI3K/AKT e p53/PTEN/caspase 3. Dessa maneira, é possível concluir que camundongos idosos apresentavam lesões NIP IV associadas a metaplasia nuclear e infiltrado inflamatório, podendo evoluir para um adenocarcinoma concomitante a mudanças nos níveis proteico de REV-ERBα prostático. Por outro lado, o exercício físico combinado pode mitigar as alterações moleculares pré-neoplásicas relacionadas à idade, restaurando *Bmal1* e REV-ERBα e com isso regular o metabolismo energético e apoptose celular prostática.

Palavras chaves: senescência, treinamento físico, metabolismo energético, disfunção mitocondrial, histopatologia.

ABSTRACT

ABSTRACT

Advancing age increases the prevalence of prostate cancer (PCa). Senescence causes hormonal decline, DNA damage, reduced apoptosis, increased inflammation, and oxidative stress, culminating in the development of PCa. The circadian clock coordinates behavioral and physiological rhythm via CLOCK/BMAL1 transcriptional heterodimer. The REV-ERBα nuclear receptor forms a feedback loop that contributes to clock function, modulates mitochondrial biogenesis, cell cycle and apoptotic control. Physical exercise regulates the aging process and can modify clock genes in the prostate. However, little is known about the expression of REV-ERBα in the prostate and the potential effect of physical exercise. Therefore, our objective was to characterize the prostatic metabolic and histopathological profile in young mice (6 months old) and old mice (18 and 24 months old) and to verify the gene expression of Nr1d1 and REV-ERBα protein and their metabolic relationships in the prostatic microenvironment associated with combined physical exercise in elderly mice. To evaluate the effect of age on the development of prostatic lesions, male C57BL/6J mice aged 6, 18 and 24 months were used. To evaluate the effect of circadian rhythm and physical exercise on prostatic metabolism during aging, we used sedentary 18-month-old mice submitted to combined physical exercise for 3 weeks (3 days/week of aerobic physical training, 40 - 50% load test incremental; and 2 days/week of physical strength training, 40 - 50% of 1 RM). The animals were euthanized, the prostate was collected and processed for biochemical analysis, Western Blotting and RT-PCR. The results showed that during aging, animals aged 18 and 24 months presented greater prostatic weight, as well as higher incidences of prostatic intraepithelial neoplasia (PIN) types III and IV, inflammatory infiltrate and nuclear metaplasia. Thus, we observed that 18-month-old animals were more susceptible to prostatic lesions and had a higher level of REV-ERBα and lower expression of Bmal1. On the other hand, combined physical exercise increased levels of Bmal1 and reduced REV-ERBα in the prostate, accompanied by a reduction in AMPK/SIRT1/PGC-1α, and an increase in PI3K/AKT and p53/PTEN/caspase 3. , it is possible to conclude that elderly mice had PIN IV lesions associated with nuclear metaplasia and inflammatory infiltrate, which could progress to adenocarcinoma concomitantly with changes in prostatic REV-ERBα protein levels. On the other hand, combined physical exercise can mitigate age-related pre-neoplastic molecular alterations, restoring Bmal1 and REV-ERBα and thereby regulating energy metabolism and prostatic cell apoptosis.

Keywords: senescence, physical training, energy metabolism, mitochondrial dysfunction, histopathology.

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LISTA DE ABREVIATURAS

α - Alfa

β – Beta

γ - Gama

% - Porcentagem

AR - Receptor de androgênio

AKT - Proteína quinase B

ACC - Acetil-CoA-carboxilase

AMPK - Proteína quinase ativada por AMP

AMP - Adenosina monofosfato

ATM - Proteína mutada na ataxia telangiectasia

ATR - Proteína relacionadas a ATM e Rad3

ATP - Adenosina trifosfato

BMAL1/ARNTL - do *inglês* Brain and muscle arnt-like

BAD - Agonista da proteína de morte celular associado a BCL2

BCL-2 - Linfoma de células B 2

BAX - Proteína X associada a bcl-2

CRY - do inglês *Cryptochrome*

CLOCK - do inglês - *circadian locomotor output cycles kaput*

CCL - O ligante de quimiocina

CDK - Quinases dependentes de ciclina

CPT1 - Carnitina Palmitoil transferase

CaP - Câncer de próstata

DNA - Ácido desoxirribonucleico

DHT - Di-hidrotestosterona

EGF - Fator de crescimento epidérmico

EROS - Espécies Reativas de Oxigênio

ER - Receptor de estrogênio

FGF - Fator de crescimento de fibroblastos

FATP - Proteína de transporte de ácidos graxos de cadeia longa

FASN - Ácido graxo sintase – do inglês *Fatty Acid Synthase*

FRAP - Capacidade de redução férrica total

GSK-3β - Glicogênio Sintase Quinase 3

GLUT – Transportadora de glicose

HBP: Hiperplasia benigna da próstata

INCA - Instituto Nacional de Câncer

IL-10 - Interleucina 10

IKK - IκB quinase

IFN-γ - interferón-gama

IL - Interleucina

IGF-1 - Fator de crescimento semelhante à insulina tipo 1

JAK - Janus quinase

KO - do inglês *Knockout*

KGF - Fator de crescimento de queratinócitos

LPS - Lipopolissacarídeo

LHRH - Hormônio hipotalâmico liberador de LH

mTOR - Alvo mamífero da rapamicina

MYC - Proto-oncogene myc

MAPK – MAP quinase

MMP - Metaloproteinases da Matriz

MRE11 - Nuclease de reparo de quebra de fio duplo

NBS1 - A síndrome de quebras de Nijmegen

NAD - Dinucleótido de nicotinamida e adenina

NF-kB - factor nuclear kappa B

NCOR - co-repressor 1 do receptor nuclear

OIS – do inglês *Oncogene-induced senescence*

OPA1- Dinamina mitocondrial como GTPase

PPARα - receptores ativados por proliferadores de peroxissoma alfa

PSA -Antígeno prostático específico

p53 - proteína 53

p21 - proteína 21

p16 - proteína 16

p27 - proteína 27

PGC1a ou *Ppargc1a* - O coativador 1-alfa do receptor ativado por proliferador de peroxissoma

AIP - atrofia inflamatória proliferativa -PIA

NIP - neoplasia intraepitelial prostática - PIN

PI3K - fosfatidil-inositol 3-quinase

PER - do inglês *Period*

PVN – Núcleo paraventricular

PTEN - fosfatase homóloga à tensina

REV-ERBα - receptores nucleares 1 membro do grupo D 1 (*Nr1d1*)

RAD51 - RAD51 Recombinase

ROR - receptor órfão

RXR - Receptor retinóide X

RAS – do inglês *Rat Sarcoma vírus*

RAF - RAF proto-oncogene

ROS - do *inglês* reactive oxygen species

SASP: O fenótipo secretor associado a senescência

SAMP8 - do *inglês* - Senescence-accelerated mouse-prone 8

SIRT1 - sirtuina 1

SHBG - globulina ligadora de hormônios sexuais

STAT - Transdutoras de sinal e ativadoras de transcrição

SCN – Núcleo supraquiasmático

SOD - superóxido dismutase

T - Testosterona

TBARs - espécies reativas ao ácido tiobarbitúrico

TLR – Toll like receptor

TNF-α - fator de necrose tumoral alfa

SUMÁRIO

INTRODUÇÃO GERAL

O câncer de próstata (CaP) é um dos cânceres com maior incidência e taxa de mortalidade no mundo [1], é previsto para o ano de 2023 cerca de 288.300 novos casos de CaP e aproximadamente 34.700 mortes apenas nos EUA [2]. No Brasil para o triênio de 2023 -2025 cerca de 71.730 novos casos de câncer de próstata foram previstos [3], sendo o tipo de câncer maligno com maior incidência e taxa de mortalidade entre os homens no Brasil [4]. De acordo com Miller et al., [5], a maior taxa de incidência de CaP está entre 50-65 anos de idade. Ainda, a hereditariedade, o uso excessivo de álcool, tabagismo, hábitos alimentares como uso de dieta hiperlipídica e a prática insuficiente de atividade física [6,7], podem potencializar o risco do CaP [8–10]. Portanto, o desenvolvimento de terapias que retardem o desenvolvimento e a progressão do câncer de próstata é de extrema importância para a população idosa.

Durante o processo de envelhecimento, ocorrem modulações significativas no metabolismo energético, no sistema hormonal e na resposta imunológica na próstata. Essas alterações desencadeiam uma hiperestimulação das vias intracelulares, como é o caso da via PI3K/AKT, assim como um aumento na sinalização androgênica. Paralelamente, observa-se uma redução nos níveis de supressores tumorais, como PTEN e p53, que desempenham papéis cruciais na regulação do crescimento celular, juntamente com uma diminuição da atividade da caspase 3, uma enzima envolvida na apoptose [11]. A influência dessas modulações nas vias celulares promove um cenário propício para o aumento da proliferação celular, concomitantemente à redução dos marcadores p53, p21 e p27, os quais normalmente induzem a parada do ciclo celular e a apoptose programada [12]. Esse contexto cria um microambiente favorável ao desenvolvimento de lesões pré-neoplásicas e, em última instância, ao surgimento de carcinoma prostático [13].

O envelhecimento afeta todos os aspectos da nossa fisiologia e comportamento, incluindo o relógio circadiano. A sincronização adequada dos ritmos circadianos é crucial para a saúde e o bem-estar. O núcleo supraquiasmático (SCN) é o marca-passo central do ritmo circadiano. O SCN recebe informações sobre os ciclos de luz e escuridão por meio de fotorreceptores na retina, que são transmitidas ao SCN por meio de projeções neuronais. Essa intrincada comunicação possibilita a formação da criticidade no relógio central, e como resultado direto, promove a coordenação da produção de hormônios, regula a temperatura corporal, controla o ciclo de sono-vigília e influencia uma variedade de processos biológicos em todo o corpo [14].

A disfunção do ritmo circadiano durante o envelhecimento é um processo complexo que envolve múltiplos fatores dos sistemas biológicos. Alguns dos principais mecanismos envolvidos na disfunção do ritmo circadiano durante o envelhecimento inclui o declínio em número e eficiência dos fotorreceptores retinianos [15]. O próprio SCN sofre alterações estruturais e funcionais ao longo do envelhecimento. Outro fator associado a desregulação do ritmo circadiano é a redução na produção de melatonina, um hormônio associado à regulação do sono e ao ritmo circadiano. Isso pode resultar em uma redução na eficiência do sistema circadiano em sincronizar

os processos biológicos com os ciclos diurnos e noturnos [16]. Mudanças no estilo de vida, como padrões irregulares de sono, exposição inadequada à luz durante o dia e hábitos alimentares desregulados, podem contribuir para a disfunção do ritmo circadiano em pessoas idosas [17]. Assim, todas essas alterações produzem a perda de ritimicidade e desencadeia alterações na atividade de proteínas como REV-ERBα [14]. A REV-ERBα exerce influência na regulação de genes envolvidos nas respostas metabólicas e inflamatórias [18,19]. Como resultado direto, a desregulação dessa proteína pode desencadear modificações significativas nas respostas hormonais, no funcionamento mitocondrial, no metabolismo celular e no equilíbrio energético [20]. Portanto, a disfunção do ritmo circadiano, especialmente durante o processo de envelhecimento, revela a complexidade intrínseca das interações entre os ritmos biológicos e os sistemas regulatórios do corpo. A compreensão mais profunda desses mecanismos não apenas lança luz sobre os fundamentos da regulação biológica, mas também oferece perspectivas promissoras para intervenções terapêuticas destinadas a mitigar os efeitos do envelhecimento e melhorar a saúde e o bem-estar ao longo da vida.

Nessa premissa o exercício físico poderia ser utilizado como método não-farmacológico para a prevenção e tratamento das alterações prostáticas associada ao processo de envelhecimento. Em síntese, o exercício físico sistematizado é caracterizado por atividades que aumentam significativamente a demanda energética modulando positivamente o perfil metabólico, hormonal e imunológico. Pouco se sabe sobre o efeito do exercício físico na regulação do ritmo circadiano prostático durante o processo de envelhecimento [21,22]. No entanto, o exercício físico pode modular proteínas e genes CLOCK no musculo estriado esquelético, hipotálamo e fígado e parece estar envolvido nas alterações no metabolismo mitocondrial. Apesar de diversos estudos mostrarem ação circadiana no controle de vias proliferativas, ciclo celular e apoptose na tecidos prostáticos [23–26], esse é o primeiro estudo no qual mostra efeito das proteínas do ritmo circadiano com influência do exercício físico combinado em tecidos prostáticos em animais idosos.

CONSIDERAÇÕES FINAIS

As doenças prostáticas são originadas principalmente durante o envelhecimento. O qual é um processo natural e fisiológico, interfere em diversos mecanismos celulares, hormonais, metabólicos e imunológicos de maneira sistêmica. Modificações nesses processos, favorecem o desenvolvimento de alterações inicialmente intracelulares prostáticas, que evoluem para alterações teciduais e lesões pré-neoplasicas, sendo consideradas precursora de câncer prostático. Com isso, podemos dizer que o envelhecimento leva ao desenvolvimento de câncer de próstata, principalmente em idades avançadas.

Inicialmente, a carcinogênese prostática pode ser identificada através de modificações morfológicas nas células prostáticas, com núcleo alterado, epitélio disfuncional, estroma ativado, e presença de infiltrado inflamatório. A fim de caracterizar o perfil histopatológico prostático durante o processo de envelhecimento em camundongos jovens e camundongos idosos, verificamos a incidência de lesões na próstata ventral, e verificamos que apesar de não haver alteração no peso prostático, os animais com idade mais avançadas, principalmente os animais de 24 meses de idade, possuem maiores incidências de lesões pré-neoplásicas, associadas a metaplasia nuclear e focos inflamatórios teciduais. Essas alterações estão relacionadas com os fenótipos associados a senescência celular que possivelmente podem estar interferindo na manutenção da resposta ao dano no DNA, bem como sinalização carcinogênica em tecidos prostáticos.

Posterior a esse resultado hipotetizamos que o controle saudável das células prostáticas pudesse sofrer interferência da modulação do ritmo circadiano no envelhecimento. O que poderia ser um alvo promissor na prevenção e tratamento do alterações prostáticas que levam a carcinogênese. Com isso, verificamos que o envelhecimento promove redução nos níveis gênicos de *Bmal1* e aumento dos níveis de *Nr1d1* e valores proteicos de REV-ERBα. E observamos que o exercício físico combinado realizado durante o envelhecimento promove efeitos contrário ao processo do envelhecimento, como o aumento nos níveis gênicos de *Bmal1* e redução dos níveis de *Nr1d1* e valores proteicos de REV-ERBα. Ainda, observamos que esse mecanismo associados ao exercício físico promovem a redução de proteínas relacionados ao funcionamento e biogênese mitocondrial como AMPK/SIRT1/PGC1α, onde ambas estão reduzidas com o protocolo de treinamento físico combinado e apresentam correlação positiva com a REV-ERBα. A fim de entender como a REV-ERBα pode modular as vias intracelulares prostáticas, verificamos que a REV-ERBα tem correlação positiva com o receptor androgênio e com AKT1 e caspase 3. Ainda animais idosos treinados apresentaram maiores valores proteicos dos supressores tumorais PTEN e p53/p21, proteínas de checkpoint importantes no desenvolvimento carcinogênico prostático, pelo mecanismo de controle de progressão ou parada do ciclo celular em uma célula com alto teor mutagênico. Por outro lado, os animais idosos sedentários não apresentam esse mesmo fenótipo molecular. Dessa forma podemos dizer que o envelhecimento leva a alterações moleculares

circadianas, modificando todo o microambiente prostático para o desenvolvimento tumoral, e a prática de exercício físico combinado mesmo em animais já considerados idosos, é capaz de reverter os danos associados ao envelhecimento.

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