citocromo c y Smac/Diablo desde las mitocondrias al citosol en las células Caco-2. En el citosol, el citocromo c forma un complejo (apoptosoma) con la proteína Apaf-1 (factor activador de la proteasa apoptótica) y la procaspasa-9, lo que permite la activación de esta caspasa, que a su vez es capaz de activar a las caspasas efectoras -3, y -7, responsables del clivaje de varias proteínas provocando los cambios morfológicos y bioquímicos característicos de la apoptosis (Robertson et al., 2000). Por su parte Smac/Diablo en el citosol promueve la activación de caspasas inhibiendo a la familia de proteínas inhibidoras de la apoptosis (IAP) (Verhagen et al., 2000; Verhagen et al., 2002).

Las caspasas son una familia de cisteína-aspártico-proteasas que se expresan ubicuamente como pro-enzimas inactivas (Boatrightn y Salvesen, 2003). Luego de la señal apoptótica, se produce el procesamiento de las pro-caspasas generando la enzima activa. El clivaje de la proenzima no es siempre un requerimiento obligatorio para la activación de las caspasas, pero todas las caspasas activadas pueden ser detectadas como fragmentos clivados en células apoptóticas (Degterev et al., 2003; Fuentes-Prior y Salvesen, 2004). La caspasa-3 es la principal caspasa efectora que cliva la mayoría de los sustratos celulares en las células apoptóticas. Se activa por el clivaje de la caspasa-8 ó -9 pero no por la -2 (Porter y Janicke, 1999). En las células Caco-2 se demostró por Western Blot que PTH genera las formas clivadas, activas y pro-apoptóticas de caspasa-3 y además se observó, mediante un ensayo de luminiscencia, que la hormona incrementa la actividad de esta enzima. El clivaje de PARP por la caspasa-3 genera dos fragmentos inactivos de 24 y 89 KDa. El fragmento amino-terminal (p24) permanece en los nucléolos, retiene su habilidad de unirse al ADN inhibiendo la actividad catalítica de PARP no clivada, y de esta manera alterando la reparación del ADN (D'Amours et al., 2001). En la apoptosis tardía con avanzada fragmentación nuclear el fragmento p89 migra del núcleo al citoplasma (Soldani et al., 2001). En correlación con la activación de caspasa-3, en las células Caco-2 el análisis por Western Blot demostró que PTH también induce el clivaje del sustrato PARP con su consecuente inactivación.

Los experimentos presentados en esta tesis también revelan que PTH disminuye la fosforilación de Akt en la línea celular intestinal Caco-2. La vía Akt es reconocida como una de las vías críticas en la regulación de la supervivencia celular y su activación provee una señal de supervivencia que les permite a las células contrarrestar el estimulo apoptótico (Yao y Cooper, 1995). Existen numerosas investigaciones elucidando el importante rol de Akt en la supervivencia de varios tipos de cánceres (Bao et al., 2004; Shi et al., 2004; Gupta et al., 2004; Wendel et al., 2004). Una proteína secretada llamada periostina que está sobreexpresada en tumores puede activar a Akt inhibiendo la apoptosis inducida por stress, favoreciendo el crecimiento del cáncer y la supervivencia de células endoteliales e incrementando dramáticamente la metástasis del colon (Bao et al., 2004). Por otro lado, el tratamiento de células con ceramida, un lípido intermediario crítico que está involucrado en señales de muerte (Basu y Kolesnick, 1998) bloquea la actividad de Akt en distintos tipos celulares (Summers et al., 1998; Zhou et al., 1998; Zundel y Giaccia, 1998). Akt también puede ser clivada selectivamente durante etapas tempranas de la apoptosis (Widmann et al., 1998). Estos datos sugieren que una característica importante de la iniciación de la apoptosis es la regulación negativa de la actividad de Akt.

Como muchos procesos fisiológicos, la apoptosis es regulada por la fosforilación reversible de proteínas involucradas en la señalización apoptótica y controlada por el balance entre la actividad de quinasas y fosfatasas, tales como las fosfatasas PP1 y las subclases de fosfatasas PP2/4/6. Se sabe que en células intestinales la unión de PTH a su receptor lleva a eventos de fosforilación en tirosina, tales como en la activación de MAPKs y quinasas de la familia Src, resultando en la activación de vías de señalización “downstream”, que involucran varias serina/treonina quinasas (Gentili et al., 2001b; Gentili et al., 2000; Gentili et al., 2002; Gentili et al., 2006). Sin embargo se desconoce la regulación de tirosina o serina/treonina fosfatasas por PTH en células intestinales y la contribución de estas fosfatasas en la apoptosis inducida por la hormona.

PP2A es una serina/treonina fosfatasa capaz de formar complejos estables con numerosas proteínas quinasas, como Akt provocando su desfosforilación e inactivación (Ivaska et al., 2002). En esta tesis se muestra que PTH activa PP2A, induce su asociación física con Akt y consecuentemente modula la fosforilación de esta quinasa.

Estudios previos en células neuronales PC12 (Dagda et al., 2005) sugieren la existencia de una holoenzima PP2A/Bβ2 que se encuentra en equilibrio entre el citosol y la superficie de la mitocondria promoviendo la desfosforilación de proteínas asociadas con la membrana mitocondrial externa hasta ahora no identificadas, sensibilizando a las neuronas a la apoptosis (Dagda et al., 2008). Otras subunidades regulatorias pro-apoptóticas de PP2A parecen sustituir a Bβ2 en células no-neuronales. Ruvolo y colaboradores (Ruvolo et al., 1999; Ruvolo et al., 2002) reportaron que la desfosforilación de Bcl-2 inducida por ceramida en una línea celular linfocítica involucra la redistribución subcelular de PP2A que contiene una subunidad regulatoria B' α. En concordancia con estas observaciones, en esta tesis se muestra que, en las células Caco-2, PTH induce la translocación de PP2A desde el citosol hacia la mitocondria.

La caspasa-9 es un sustrato de Akt (Cardone et al., 1998) y su fosforilación por esta quinasa inhibe su función pro-apoptótica, promoviendo la supervivencia celular (Liu et al., 2003). Se demostró que en las células Caco-2 estimuladas por PTH, PP2A modula la degradación del sustrato de caspasa-3, PARP, sugiriendo que luego del tratamiento con PTH, la desfosforilación e inactivación de Akt por PP2A revierte la inhibición de caspasa-9, promoviendo su función pro-apoptótica y la activación de caspasa-3, con el consiguiente clivaje de su sustrato PARP. También se observó que el ácido okadaico revierte la disminución de la viabilidad celular inducida por la hormona, lo que sugiere que la activación de PP2A media la apoptosis inducida por PTH en las células Caco-2.

Estudios previos mostraron que PP2A es blanco de p38 MAPK en las células endoteliales cuya apoptosis es inducida por el Factor de Necrosis Tumoral (FNT) (Grethe et al., 2006). Además se ha reportado que p38 MAPK regula a PP2A en neutrófilos y miocitos (Liu y Hofmann, 2004; Avdi et al.,

2002). Sin embargo PP2A puede desfosforilar el residuo de treonina de p38 MAPK alterando la actividad de esta proteína (Keyse et al., 2000). Por otro lado, la actividad de PP2A es importante en el arresto celular inducido por PKC/PKCα en células epiteliales intestinales (Guan et al., 2007). Con el objetivo de caracterizar los mecanismos involucrados en la desfosforilación de Akt en las células Caco-2 expuestas a PTH, se investigó la participación de PKC, p38 MAPK y AMPc. Los inhibidores específicos de PKC y de p38 MAPK, Ro-31-8220 y SB 203580 respectivamente, no revirtieron la disminución en la fosforilación de Akt inducida por PTH, descartando la participación de estas enzimas en el mecanismo de regulación de Akt por la hormona. Sin embargo se demostró que el Rp-AMPc, un antagonista competitivo altamente específico de los activadores de la vía de señalización del AMPc, aumenta la fosforilación de Akt en serina 473 y disminuye el incremento en la actividad de PP2A inducida por PTH sugiriendo que Akt es desfosforilada por la fosfatasa PP2A, que a su vez es activada por el AMPc. El AMPc puede estimular (Bommakanti et al., 2000; Filippa et al., 1999; Fujita et al., 2006) o inhibir (Brennesvik et al., 2005; Lou et al., 2002; Poser et al., 2003) la actividad de Akt. PP2A no es un blanco clásico del AMPc, sin embargo existen trabajos que describen la activación de PP2A dependiente de este segundo mensajero (Feschenko et al., 2002; Moon et al., 2003). El AMPc puede activar PP2A mediante la fosforilación dependiente de PKA de la subunidad regulatoria B (Ahn et al., 2007; Usui et al., 1998). Además, Hong y colaboradores (Hong et al., 2008) mostraron que la inhibición de Akt dependiente del AMPc en las células tiroideas PCCL3 es mediada por PP2A. Identificaron un complejo de señalización novel y estable, Epac-PP2A, y observaron la modulación de su actividad fosfatasa por Rap-GTP y PKA.

La homeostasis de los tejidos requiere un balance entre la proliferación celular y la muerte. La apoptosis y la proliferación celular están vinculados por ciertos reguladores del ciclo celular y un estímulo apoptótico puede afectar tanto la proliferación como la supervivencia. La proteína p53 es un regulador de la fase G1 del ciclo celular que en condiciones normales es rápidamente degradado, pero luego de un stress celular, como la exposición a agentes que

dañan al ADN, la vida media de la proteína p53 se incrementa y se acumula en el núcleo de las células (Chen et al., 2000). Por otro lado, hay varios trabajos que sustentan la hipótesis de que la apoptosis espontánea es independiente de p53: en ratones normales y ratones *nulos (*"knockout") de p53 el nivel de apoptosis espontánea fue similar, indicando que el gen de p53 participa poco en el control de la eliminación del exceso de células no dañadas (Merritt et al., 1994); además se observó un desarrollo normal de los embriones de ratones nulos de p53 (Donehower et al., 1992). Consistente con estos datos, hay poca expresión de p53 en el epitelio intestinal normal. En el cáncer, incluyendo los cánceres del tracto gastrointestinal, el gen p53 está frecuentemente mutado (Levine et al., 1991; Watson et al., 1996). Acorde con estas observaciones, en las células Caco-2, el gen p53 tiene alelos mutados (Ray et al., 2001; Djelloul et al., 1997). En este trabajo de tesis se observó que la hormona no afecta los niveles de expresión de p53, sugiriendo que PTH induce la apoptosis en las células Caco-2 por un mecanismo independiente de la expresión de p53. No obstante, se necesitaría profundizar las investigaciones respecto a si PTH afecta la fosforilación de residuos claves para la activación de p53.

La familia de las proteínas 14-3-3 comprende una serie de proteínas diméricas de 30 KDa encontradas en todas las células eucariotas (Aitken, 1996; Fu et al., 2000; Tzivion et al., 2001; Van Hemert et al., 2001; Wilker y Yaffe, 2004). Esta familia de proteínas altamente conservadas consiste de 7 productos génicos distintos en células humanas así como una variedad de formas modificadas post-translacionalmente (Aitken et al., 1995; Dubois et al., 1997; Megidish et al., 1998; Powell et al., 2003). Múltiples isoformas de 14-3-3 parecen estar involucradas en una amplia variedad de procesos de transducción de señales, incluyendo activación mediada por Ras-Raf de la vía de las MAPKs, regulación de la apoptosis, adhesión dependiente de la señalización de las integrinas, y control del ciclo celular en respuesta a stress genotóxico (Aitken, 1996; Fu et al., 2000; Tzivion et al., 2001; Wilker y Yaffe, 2004). En células epiteliales, una isoforma particular de 14-3-3, la 14-3-3 σ, presenta un rol importante en la proliferación celular, el control del ciclo celular y la tumorogénesis humana (Wilker y Yaffe, 2004; Nguyen et al., 2004; Manke

et al., 2005). En células Caco-2, 14-3-3 σ se encuentra mayoritariamente en el núcleo pero cuando las células se exponen a PTH, esta proteína también es detectada en el citoplasma. En concordancia con estas observaciones, estudios previos revelaron que 14-3-3 se encuentra principalmente en el citoplasma, pero puede también ser detectada en la membrana plasmática, el aparato de Golgi y el núcleo de células eucariotas (Tzivion et al., 2001). Sin embargo, hasta el momento no se sabe la importancia para su función de la localización diferencial de 14-3-3. Al respecto, Tazawa y colaboradores demuestran que la co-expresión de RPTH1 con 14-3-3 resulta en la co-localización de ambas proteínas en membrana y en la región perinuclear (Tazawa et al., 2003). Sin embargo, en las células Caco-2 no se detectó la asociación entre 14-3-3 σ y RPTH1 en condiciones basales ni luego del tratamiento con PTH, sugiriendo que, a los tiempos estudiados, 14-3-3 no regularía la localización subcelular del RPTH1 en estas células intestinales.

Estos resultados demuestran que PTH desencadena efectos pro-apoptóticos en las células de adenocarcinoma de colon humano Caco-2, activando la vía mitocondrial de la apoptosis e inhibiendo la vía de supervivencia de Akt mediante la acción concertada de la fosfatasa PP2A y la vía del AMPc.

La acción pro-apoptótica de PTH en estas células sería de potencial interés en medicina para generar nuevas estrategias terapéuticas en el tratamiento del cáncer de colon humano

CONCLUSIONES

- ✓ Se demostró, por primera vez, la localización y expresión del receptor de PTH tipo 1 (RPTH1) en las células epiteliales Caco-2, derivadas de adenocarcinoma de colon humano. El RPTH1 se localiza en la membrana plasmática, el citoplasma y el núcleo de estas células.

- ✓ Se evidenció, mediante ensayos de supervivencia celular, que en las células Caco-2 el tratamiento con PTH 10^{-8}M, en ausencia de suero, disminuye el número de células viables.

- ✓ PTH provoca cambios morfológicos típicos de células apoptóticas: alteración de los filamentos de actina y consecuentemente de la forma celular, pérdida de las uniones intercelulares, cambios en la membrana plasmática con externalización del fosfolípido fosfatidilserina, picnosis de las mitocondrias con distribución perinuclear, fragmentación del ADN y condensación nuclear.

- ✓ Induce la desfosforilación de Bad, su disociación de la proteína 14-3-3 y su translocación hacia las mitocondrias y causa la liberación de los factores pro-apoptóticos citocromo c y Smac-Diablo desde las mitocondrias al citosol. Estas observaciones sustentan la idea de que la hormona activa la vía mitocondrial de la apoptósis en las células Caco-2.

- ✓ Provoca la activación de la enzima caspasa-3 y el clivaje de su sustrato PARP.

- ✓ La hormona no afecta los niveles de expresión proteica de Bad, Bcl-2 y Akt.

- ✓ PTH induce la desfosforilación de Akt mediante la serina/treonina fosfatasa PP2A, que a su vez es activada por el AMPc.

- ✓ Promueve la asociación de Akt con PP2A y la translocación de esta fosfatasa hacia las mitocondrias.

- ✓ PKC y p38 MAPK no participan en la desfosforilación de Akt inducida por PTH.

- ✓ PP2A participa en la disminución de la viabilidad celular y en el clivaje de PARP inducidos por la hormona.

- ✓ PTH no modifica los niveles proteicos de p53.

- ✓ La hormona induce la expresión de la proteína 14-3-3 y su localización citoplasmática pero no promueve la interacción de esta proteína con el RPTH1.

- ✓ Estos resultados demuestran que PTH desencadena efectos pro-apoptóticos en las células Caco-2 y contribuyen al conocimiento de los mecanismos moleculares de señalización que son estimulados por la hormona en estas células intestinales.

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