Papel de la cascada del ácido araquidónico en el control de la proliferación de las células epiteliales intestinales humanas

Marisol Cabral Salvadores

5 CONCLUSIONES

Las principales conclusiones de esta tesis doctoral son:

- las células intestinales epiteliales (Caco-2) sintetizan eicosanoides a partir del AA a través de la vía de las COXs y de las LOXs, alcanzando concentraciones entre 1–10 nM, mientras que no producen cantidades cuantificables de eicosanoides derivados de la vía del CYP450.

- la PGE_2 y la PGE_3, a través de la interacción con sus receptores EP_1 y EP_4, activan de forma similar diversas vías de señalización como ERK, CREB y p38 e inducen la síntesis de DNA y la proliferación de las células Caco-2.

- el LTD_4 interacciona con el $CisLT_1R$ y activa ERK, CREB y β-catenina, provocando la proliferación de las células epiteliales intestinales. Estos efectos, a excepción de la desfosforilación de β-catenina, son PGE_2-dependientes.

- el LTB_4, al interaccionar con el receptor BLT_1 y BLT_2 y activar ERK, induce la proliferación de las células Caco-2, efecto que también es PGE_2-dependiente. Sin embargo, el LTB_5, derivado del EPA, no tiene este efecto mitogénico.

- HETES como el 5-, 12- y 15-HETE, al interaccionar con el receptor BLT_2, activan la proliferación de las células Caco-2. El 12-HETE activa p38 y su efecto proliferativo es PGE_2-dependiente. Un efecto similar tiene el 12-HEPE, derivado del EPA.

- los enantiómeros del 9- y 13-HODE tienen efectos contrarios sobre la proliferación de las células Caco-2. Así, mientras los enantiómeros R inducen la proliferación a través de la interacción con los receptores BLT_1 y BLT_2 y la activación de la síntesis de PGE_2, los enantiómeros S son ligandos del PPARγ y tienen efectos antiproliferativos y proapotóticos.

Teniendo en cuenta el conjunto de resultados que conforman esta tesis doctoral proponemos que el papel de la cascada del AA en la regulación de la proliferación de las células epiteliales intestinales es complejo, ya que hay diversos eicosanoides y receptores de eicosanoides implicados directa e indirectamente en el control del crecimiento de estas células (Figura 5.1). Además, existen metabolitos que presentan efectos opuestos, incluso enantiómeros de un mismo eicosanoide que tienen efectos contrarios sobre el control del crecimiento celular y de la apoptosis. No obstante, proporcionamos evidencias de que la acción mitogénica de todos estos metabolitos podría converger principalmente en

la activación de la vía COXs y la subsecuente síntesis de PGE_2, que por tanto jugaría un papel central en el control de la proliferación de las células epiteliales intestinales.

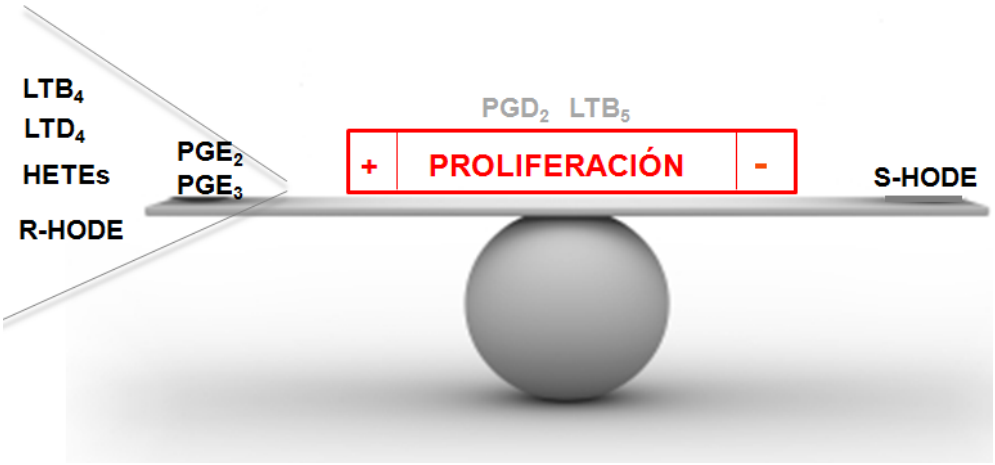

Figura 5.1. Metabolitos de la cascada del AA que tienen efecto proliferativo y anti-proliferativo en las células epiteliales intestinales no diferenciadas.

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