Metabolismo lipídico en la activación polarizada de los macrófagos

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January 15, 2025

Los macrófagos, células cruciales de la inmunidad innata, defienden contra patógenos y resuelven la inflamación, manteniendo el equilibrio tisular; realizan fagocitosis, presentan antígenos a las células T y conectan la inmunidad innata con la adaptativa a través de varios estados de activación. La activación clásica está asociada con respuestas Th1 y producción de interferón-γ, mientras que la activación alternativa, inducida por interlequina-4, se caracteriza por un aumento de la endocitosis, una menor secreción de citocinas proinflamatorias y funciones en la inmunorregulación y la remodelación tisular. Aunque estos representan extremos opuestos observados in vitro, la notable plasticidad de los macrófagos permite un amplio espectro de fenotipos de activación que son complejos de caracterizar experimentalmente. Si bien la aplicación de técnicas ómicas ha dado como resultado avances significativos en la caracterización de la polarización de los macrófagos, los estudios lipidómicos han recibido menor atención. Más allá de su papel como componentes estructurales y fuentes de energía, los lípidos funcionan como moléculas de señalización que regulan la activación y polarización de los macrófagos, dando forma así a las respuestas inmunitarias. En este trabajo se analiza la interacción entre la señalización lipídica y la polarización de los macrófagos, y explora cómo el metabolismo lipídico influye en el fenotipo y la función de los macrófagos. Estos conocimientos ofrecen posibles estrategias terapéuticas para enfermedades relacionadas con la inflamación.

Financiación: Ministerio de Ciencia e Innovación (PID2022-140764OB-I00)

Los macrófagos son células residentes en los tejidos que actúan como centinelas del sistema inmunitario, regulando un delicado equilibrio entre la defensa contra los patógenos y la iniciación/resolución de la inflamación, manteniendo así la homeostasis tisular. Los macrófagos presentan un alto grado de plasticidad y diversidad. Está ampliamente reconocido que estas células se originan de progenitores a partir de la embriogénesis y continúan durante toda la vida de un individuo. Muchos macrófagos residentes en los tejidos derivan de progenitores embrionarios y son capaces de autorrenovarse sin depender de los monocitos sanguíneos adultos. En condiciones habituales, los macrófagos derivados del feto y los derivados de los monocitos coexisten, y ambos contribuyen a la homeostasis tisular. Durante la inflamación, los monocitos son reclutados para generar macrófagos que desempeñan un papel crucial en la promoción de la inflamación local o en la facilitación de su resolución. Esto garantiza una presencia permanente de macrófagos en los tejidos adultos a través de la autorrenovación y aumenta su número durante las circunstancias inflamatorias.

El concepto de activación clásica de los macrófagos fue introducido por primera vez para describir la actividad microbicida mejorada, dependiente de antígeno pero no específica, de los macrófagos tras la exposición secundaria a patógenos. Esta actividad, posteriormente vinculada a las respuestas Th1 (linfocitos T colaboradores CD4+) y a la producción de interferón γ (IFNγ), también se asoció con propiedades citotóxicas y antitumorales. Por el contrario, se descubrió que el IFNγ inhibe la expresión del receptor de manosa de los

macrófagos, mientras que la interleuquina 4 (IL-4) mejora su expresión e induce una activación alternativa, caracterizada por un mayor aclaramiento endocítico y una menor secreción de citoqiinas proinflamatorias. Posteriormente, Mills y colaboradores propusieron la clasificación M1/M2, observando que los macrófagos de cepas de ratones Th1 resistentes a *Leishmania major* producían más óxido nítrico cuando eran activados por IFNγ o lipopolisacárido bacteriano (LPS) en comparación con los macrófagos de cepas Th2, que metabolizaban la arginina a ornitina. Dado que el óxido nítrico inhibe la división celular y la ornitina la promueve, se planteó la hipótesis de que los fenotipos M1 y M2 tenían funciones opuestas en la inflamación. Con el tiempo, la investigación ha revelado un espectro de estados de activación de macrófagos entre M1 y M2, que dependen en gran medida del tipo de estímulo. Hoy día, los macrófagos M1 se reconocen como células proinflamatorias clásicamente activadas (LPS más IFNγ) que expresan la óxido nítrico sintasa inducible (iNOS) y producen citoquinas proinflamatorias, lo que inicia la inflamación. Por el contrario, los macrófagos M2 son células antiinflamatorias/reparadoras activadas alternativamente (IL-4 o IL-13), que expresan altos niveles de arginasa y producen citocinas antiinflamatorias, lo que promueve la resolución de la inflamación.

La polarización de los macrófagos produce alteraciones notables en la expresión génica, lo que impide la definición de un estado de activación específico por un solo gen. Esta incertidumbre suele mitigarse mediante el uso de múltiples marcadores para caracterizar los resultados de la activación. Muchos laboratorios han ampliado las asignaciones de marcadores para incluir factores de transcripción, citocinas, quimiocinas y marcadores de la superficie celular, con el objetivo de lograr una comprensión integral de la activación de los macrófagos. Estos aspectos resaltan la complejidad de la polarización de los macrófagos y la necesidad de refinar nuestra comprensión de este paradigma más allá de los enfoques convencionales. El cambio de los marcadores genéticos y proteicos tradicionales hacia enfoques ómicos, como la transcriptómica y la proteómica, ha mejorado nuestra comprensión de la activación de los macrófagos. Sin embargo, la lipidómica ha recibido menos atención. Más allá de sus funciones tradicionales como componentes estructurales y fuentes de energía, los lípidos funcionan como moléculas de señalización que influyen en numerosos procesos celulares. De hecho, el metabolismo lipídico y las vías de señalización han surgido como reguladores clave de la activación y polarización de los macrófagos, lo que configura las respuestas inmunitarias y los resultados inflamatorios. En esta revisión, exploramos exhaustivamente la sofisticada interacción entre la señalización lipídica y la polarización de los macrófagos, centrándonos en cómo el metabolismo lipídico influye en el fenotipo y la función de los macrófagos y viceversa.

A pesar de los significativos avances en la biología de los macrófagos, aún quedan grandes desafíos para definir con precisión los estados de polarización de los macrófagos e identificar biomarcadores robustos más allá de los clásicos disponibles en la actualidad. La plasticidad característica de estas células implica una complejidad experimental adicional, ya que exhiben fenotipos muy diversos en condiciones normales y patológicas. Sin embargo, esta característica biológica representa al mismo tiempo una extraordinaria posibilidad de intervención terapéutica en un enorme número de patologías. Los análisis lipidómicos de los macrófagos destacan que, a lo largo del proceso de activación polarizada, varias enzimas clave involucradas en las vías de biosíntesis de lípidos son inducidas, expresadas y activadas en diferentes grados. Por lo tanto, los cambios en los niveles de las diferentes clases de lípidos son consecuencia de procesos enzimáticos altamente orquestados, muchos de los cuales aún no están completamente caracterizados o comprendidos. Claramente, se necesitará más investigación para comprender cómo las vías de señalización y los procesos enzimáticos coordinan la remodelación de la composición lipídica de los macrófagos con diferentes fenotipos bajo diferentes estímulos, lo cual es crucial para su función. Para ello, se deben realizar esfuerzos para integrar enfoques multiómicos, como la transcriptómica, la proteómica y la metabolómica, a fin de caracterizar de manera integral el metabolismo lipídico de los macrófagos dentro de todo el panorama de polarización e identificar biomarcadores adecuados. Estos avances mejorarán nuestra comprensión de la biología de los macrófagos y facilitarán el descubrimiento de terapias dirigidas a diversas enfermedades.

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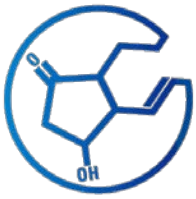

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