Nuevos fosfolípidos implicados en la activación metabólica de macrófagos por ácidos grasos saturados – Regulación de la actividad del inflamasoma por lípidos anti-inflamatorios

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La inflamación crónica de bajo grado que es característica de la obesidad, está directamente relacionada con el desarrollo de una serie de enfermedades frecuentemente diagnosticadas a individuos obesos, tales como la diabetes de tipo 2, enfermedad cardiovascular y algunos tipos de cáncer. En obesidad, los adipocitos estresados liberan altas cantidades de ácidos grasos saturados, debido a una lipolisis desregulada. Los macrófagos presentes en el tejido se activan por la sobrecarga de ácidos grasos, produciendo citoquinas proinflamatorias, lo que resulta en un estado de inflamación crónica de bajo grado. Existe en la actualidad el acuerdo de que los inflamasomas, es decir, máquinas multiproteicas intracelulares que generan interleuquina-1β madura, desempeñan un papel fundamental en la aparición de las enfermedades asociadas a la obesidad, como diabetes de tipo 2 y las enfermedades cardiovasculares. Sin embargo, los mecanismos moleculares que controlan la activación del inflamasoma en un contexto de inflamación metabólica no se conocen aún con el suficiente detalle. En trabajos previos de nuestro grupo, hemos descrito que una enzima clave del metabolismo lipídico, la ácido fosfatídico fosfatasa lipina-2, restringe la activación clásica del inflamasoma NLRP3 en macrófagos. En experimentos preliminares hemos observado que la lipina-2 también restringe la activación del inflamasoma en un entorno de inflamación metabólica durante la sobrecarga de ácidos grasos, lo que sugiere que esta enzima puede funcionar como un freno celular para reducir los efectos nocivos de estreses celulares que, como la sobrecarga de ácidos grasos saturados, activan vías proinflamatorias en macrófagos. Por tanto, las estrategias destinadas a mejorar los efectos nocivos de la inflamación se beneficiarán en gran medida de un conocimiento más profundo de los entresijos moleculares subyacentes a los procesos de regulación celular mediados por lipina-2 en las células del sistema inmune innato. La presente propuesta de investigación se articula en torno a cuatro objetivos específicos, todos ellos explorando un territorio completamente desconocido, que pueden proporcionar información de gran interés para entender cómo el metabolismo desregulado de los lípidos y la aparición de nuevas especies de lípidos en las células estresadas activa las rutas proinflamatorias convergentes en el inflamammoma NLRP3 en macrófagos, y el papel antagónico desempeñado por la lipina-2. Estos objetivos se formulan de la siguiente manera: (i) analizar por espectrometría de masas los lípidos que cambian como consecuencia de la activación inflamatoria metabólica de macrófagos; (ii) identificar y caracterizar las vías enzimáticas implicadas en la generación de esos lípidos y evaluar su impacto en la activación del inflamasoma; (iii) sintetizar lípidos potencialmente interesantes como herramienta para revelar su impacto en la producción de interleuquina-1β; y (iv) evaluar la implicación de especies moleculares específicas de los lípidos identificadas en objetivos anteriores en modelos animales de activación de inflamasomas y obesidad. La finalización exitosa de esta propuesta sentará una base sólida para comprender, a nivel molecular, nuevos conceptos sobre el metabolismo de los lípidos durante la inflamación, y sobre los mecanismos mediados

por lipina-2 para reducir la inflamación que pueden abrir la puerta a futuras intervenciones terapéuticas (20.19-105.989-I).

El inflamasoma es un complejo multiproteico intracelular encargado de producir interleuquina 1β (IL-1β) y participar en la destrucción de microorganismos patógenos. Puede ser activado tanto por moléculas procedentes de estos microorganismos como por moléculas endógenas generadas por el organismo frente a situaciones de peligro o de daño. Debido a estas diferentes formas de activación, el inflamasoma, además de formar parte de la maquinaria celular de eliminación de patógenos, también provoca el agravamiento de enfermedades no infecciosas tales como la diabetes tipo 2, la artritis reumatoide o la aterosclerosis. Por ello, es importante conocer los mecanismos que inhiben la activación del inflamasoma, ya que dicho conocimiento podría ayudarnos en el desarrollo de tratamientos para la cura de las enfermedades mencionadas anteriormente. Recientemente se ha descrito que los ácidos grasos omega-3 pueden inhibir la activación del inflamasoma, si bien los mecanismos moleculares implicados no han sido bien definidos. Experimentos preliminares realizados en nuestro laboratorio sugieren que la incorporación de estos ácidos grasos en los lípidos celulares constituye un paso necesario para ejercer su efecto protector en la generación de IL-1β. También se ha observado que una enzima del metabolismo lipídico conocida como lipina-2 ejerce un efecto inhibitorio sobre la activación del inflamasoma. De hecho, mutaciones en esta enzima producen en humanos una enfermedad autoinflamatoria (Síndrome de Majeed) cuyos síntomas son aliviados por terapia anti IL-1β. Esta enzima posee actividad ácido fosfatídico fosfatasa y podría, por tanto, participar en la generación de posibles lípidos inhibidores del inflamasoma. Basados en estos antecedentes, el objetivo central del presente proyecto es identificar las especies lipídicas que contienen ácidos grasos omega-3 esterificados y que inhiben el inflamasoma, y determinar si la lipina-2 participa en la generación de estas moléculas. Los objetivos específicos del proyecto se dividen en cuatro: (i) definir mediante aproximaciones lipidómicas por espectrometría de masas el total de lípidos presentes en células fagocíticas humanas que tienen en su composición un ácido graso omega-3; (ii) generar por síntesis orgánica derivados estables de los lípidos más representativos del apartado anterior y desarrollar protocolos para su introducción en las células; (iii) estudiar los posibles mecanismos por los que estos lípidos inhiben la activación del inflamasoma, por ejemplo, efectos sobre las rutas de transducción de señal; (iv) definir nuevas rutas antiinflamatorias gobernadas por la lipina-2 y su participación en la generación de los lípidos inhibidores antes descritos, tanto en células humanas en cultivo como en modelos animales de enfermedad. Con todo ello se pretenden definir nuevas estrategias para inhibir el inflamasoma en células humanas, así como desvelar posibles mecanismos por los que la falta de actividad de la lipina-2 genera una enfermedad autoinflamatoria. Los resultados podrían ayudar a idear nuevas herramientas para el tratamiento de enfermedades en las que la activación del inflamasoma tiene un papel clave (20.21-141.P20).

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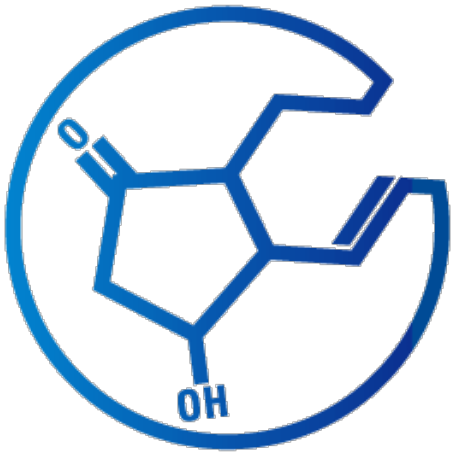

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