Metabolismo y regulación de los plasmalógenos en inmunidad innata e inflamación. Papel de la lipina-2 – R

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La lipina-2 es una fosfatasa de ácido fosfatídico dependiente de Mg^{2+} que participa en la ruta de novo de la biosíntesis de fosfolípidos. Esta enzima está ocupando en los últimos tiempos un lugar central en investigación inflamatoria debido a su participación en la regulación del ensamblaje del inflamasoma NLRP3, es decir, la plataforma multiproteica que media el procesamiento de la interleuquina-1β (IL-1β) en respuesta a agentes infecciosos y factores de estrés celular. En experimentos preliminares, hemos encontrado que los niveles de una clase de fosfolípidos relativamente menor, los plasmalógenos de etanolamina, están elevados en las mitocondrias de las células deficientes en lipina-2 en comparación con las células normales. Estos aumentos son específicos de las mitocondrias, ya que no se observan cuando se utilizan homogeneizados de células enteras para los análisis lipidómicos. Por lo tanto, parece claro que existe algo único en los plasmalógenos de etanolamina de las mitocondrias que lo vincula directamente con las funciones reguladoras de la lipina-2. Desentrañar este algo, es decir, los mecanismos y acciones moleculares que involucran a los plasmalógenos de etanolamina y su relación con las respuestas mediadas por la lipina-2, constituye el objetivo principal de la presente propuesta. Los plasmalógenos han recibido en general poca atención en comparación con muchas otras clases de lípidos a lo largo de los años. Sin embargo, esto está cambiando recientemente debido a la posible asociación del metabolismo de los plasmalógenos con varios trastornos metabólicos y degenerativos, así como con el envejecimiento. Es muy importante tener en cuenta que el enlace éter vinílico que es característico de esta clase de fosfolípidos es un excelente eliminador de oxidantes. Esto podría proporcionar una base molecular para explicar los niveles elevados de plasmalógenos mitocondriales en las células deficientes en lipina-2, ya que el aumento de la producción de oxidantes en estas condiciones podría desencadenar una elevación de plasmalógenos como mecanismo de respuesta para contrarrestar el daño oxidativo. La presente propuesta de investigación se articula en torno a tres objetivos específicos, todos ellos explorando territorios completamente desconocidos, que proporcionarán información clave para comprender cómo la lipina-2, al modular el metabolismo de los plasmalógenos, actúa como un freno que reduce los efectos deletéreos de los factores de estrés que activan el inflamasoma. Dichos objetivos se formulan de la siguiente manera: (i) establecer los principios reguladores de la biosíntesis y degradación de plasmalógenos en macrófagos; (ii) definir el impacto del metabolismo de los plasmalógenos en la activación proinflamatoria de los macrófagos; y (iii) evaluar el papel de los plasmalógenos en modelos animales de enfermedades donde la activación del inflamasoma es clave. 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. (20.22-140.764-I).

La inflamación crónica de bajo grado, que constituye una característica distintiva de la obesidad, está directamente relacionada con el desarrollo de una serie de enfermedades que comúnmente se diagnostican en personas obesas, incluidas, entre otras, la diabetes de tipo 2, enfermedades cardiovasculares y algunos tipos de cáncer (…)

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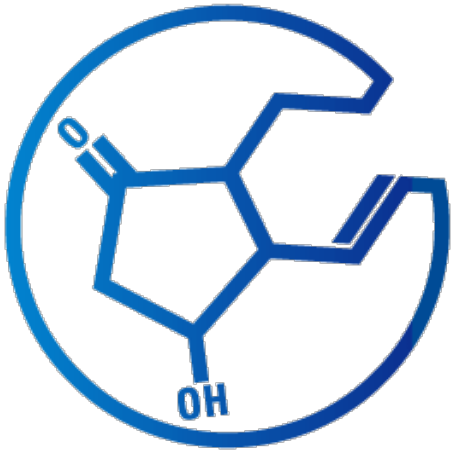

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