



Revisión

Antitumor effect of oleic acid; mechanisms of action. A review

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Abstract

Introduction: The beneficial effects of oleic acid in cancer processes can no longer be doubted, but little is known about the mechanisms of action behind this phenomenon.

Aim: The aim of the present review is to clarify whether oleic acid has an effect on important mechanisms related to the carcinogenic processes.

Methods: We searched electronic databases and bibliographies of selected articles were inspected for further reference. We focused our research on two cellular transformations characterizing cancer development: proliferation and cell death or apoptosis.

Results: Numerous studies have reported an inhibition in cell proliferation induced by oleic acid in different tumor cell lines. Herein, oleic acid could suppress the over-expression of HER2 (erbB-2), a well-characterized oncogene which plays a key role in the etiology, invasive progression and metastasis in several human cancers. In addition, oleic acid could play a role in intracellular calcium signaling pathways linked to the proliferation event. Regarding cell death, oleic acid has been shown to induce apoptosis in carcinoma cells. The mechanisms behind the apoptotic event induced by oleic acid could be related to an increase in intracellular ROS production or caspase 3 activity. Several unsaturated fatty acids have been reported to induce apoptosis through a release of calcium from intracellular stores. However, evidence regarding such a role in oleic acid is lacking.

Conclusions: Oleic acid plays a role in the activation of different intracellular pathways involved in carcinoma cell development. Such a role could be the root of its anti-tumoral effects reported in clinical studies.

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Key words: *Oleic acid. Apoptosis. Proliferation. Intracellular signaling.*

EFECTO ANTITUMORAL DEL ÁCIDO OLEICO;
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CIENTÍFICA

Resumen

Introducción: Los estudios epidemiológicos atribuyen un papel protector al ácido oleico frente a determinados tipos de cáncer. Sin embargo, el conocimiento relativo al mecanismo por el cual tal ácido graso ejerce sus efectos es escaso.

Objetivo: La presente revisión bibliográfica tiene como objetivo recopilar aquellos trabajos que centran su atención en los mecanismos intracelulares que podrían explicar los efectos clínicos atribuidos al ácido oleico.

Métodos: Se ha realizado una búsqueda bibliográfica a través de bases de datos electrónicas y las referencias de los artículos de interés han sido utilizadas como fuente de búsquedas más avanzadas. Nuestra revisión se ha centrado en la descripción de dos de las transformaciones celulares que caracterizan el desarrollo de cáncer: proliferación y muerte celular.

Resultados: Numerosos estudios atribuyen un papel inhibitorio de la proliferación de células tumorales al ácido oleico. Entre los mecanismos de acción, se encuentran su capacidad para suprimir la expresión de HER2 (erbB-2), un oncogén bien conocido por su implicación en la etiología, progresión y metástasis de distintos tipos de cáncer. Además, el ácido oleico podría jugar un papel en la activación de la señalización de calcio intracelular, rutas igualmente ligadas a la proliferación celular. En cuanto a su papel en los fenómenos de muerte celular, el ácido oleico puede inducir apoptosis en células tumorales describiéndose como mecanismos implicados la producción de intracelular de especies reactivas o la activación de la actividad caspasa 3. Aunque muchos estudios relacionan la apoptosis inducida por los ácidos grasos insaturados con la liberación de calcio de los depósitos intracelulares, faltan estudios que aclaren el papel del ácido oleico a este respecto.

Conclusión: El ácido oleico juega un papel en la activación de diferentes rutas intracelulares implicadas en el desarrollo de células tumorales. Estos mecanismos podrían ser la base de los efectos protectores que le atribuyen los estudios clínicos.

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Palabras clave: *Ácido oleico. Apoptosis. Proliferación celular. Señalización celular.*

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Abbreviations

OA: Oleic acid.
PUFA: Polyunsaturated fatty acids.
MUFA: Monounsaturated fatty acids.
SOC: Store-operated channels.
SOCE: Store-operated Ca²⁺ entry.
ROS: Reactive oxygen species.
DHA: Docosahexaenoic acid.

Introduction

General evidence of the antitumor effect of oleic acid

Epidemiological studies have suggested a positive association between the total fat intake and the risk of cancer, particularly breast, colorectal and prostate cancers.¹ Carcinogenesis models have also provided evidence for a lipid specific action beyond their caloric supply, thus suggesting that the type of fat and its unique composition are of greater importance than overall fat intake.²⁻⁷

Whereas a high intake of n-6 polyunsaturated fatty acids (PUFA) has tumor-enhancing effects, n-3 PUFA have inhibitory effects. However, there are few experimental studies addressing the role of monounsaturated fatty acids (MUFA) of the n-9 family, such as oleic acid (OA), on cancer, if compared to the investigations about the role of other dietary lipids.

OA has attracted much attention, especially in the last few years, as the “Mediterranean diet”, characterized by a high olive oil (rich in OA) consumption, has been traditionally linked to a protective effect against cancer.⁸ A wide range of studies have been conducted into breast cancer, where a potential protective effect of olive oil and OA has been described.⁹⁻¹¹ In addition, epidemiological studies suggest that olive oil may have a protective effect on colorectal cancer development.¹²⁻¹⁴ In this sense, some animal studies have also shown that dietary olive oil prevented the development of colon carcinomas in rats, corroborating that olive oil may have chemopreventive properties against colon carcinogenesis.¹⁵⁻¹⁷

Finally, a novel approach to chemotherapy has the potential to yield novel dietary-drug combinations that can provide additive or even synergistic protection against the progression of cancer and it is especially relevant when the etiology of disease development has varied mechanistic routes. With regard to this novel approach, OA has been reported to act synergistically with cytotoxic drugs, thus enhancing their antitumor effect.¹⁷⁻¹⁹

Thus, both epidemiological and animal studies have reported a protective role of oleic acid in several cancers. However, the mechanisms behind the antitumor effect of such a fatty acid are not well understood. The aim of the present review is to clarify where the knowledge concerning this topic is.

Materials and methods

Search strategy

We consulted studies published in electronic databases such as Pubmed or Medline. The bibliographies of selected articles were inspected for any further reference.

Firstly, we studied the title and abstract of all kind of papers (regular or review papers) with a potential interest to understand the role of oleic acid in cancer events. We mostly focused on those related to the mechanisms of action of such a fatty acid at the cellular level. Thus, the main key words used in the search were: “oleic acid”, “apoptosis”, “proliferation”, “carcinoma cells”, “intracellular signaling”. Then, the text of the main trials that met the criteria previously mentioned was fully examined to extract the specific data included in the review.

Results and discussion

Cancer development is characterized by specific cellular transformations involving changes in proliferation rates, inactivation of tumor-suppressor genes and inhibition of apoptosis. Thus, we will describe the ability of oleic acid to induce apoptosis and/or inhibit cell proliferation in cancer cell lines.

Oleic acid-proliferation

It has been recently shown that OA promoted the growth of non-malignant cells but, in fact, it had the opposite effect, in malignant cells.²⁰ Several researchers have also demonstrated that both oleic and α -linolenic acid showed a proliferation inhibition effect on prostate carcinoma cells.^{21,22} According to these results, numerous studies have also reported an inhibition in cell proliferation induced by OA in different tumor cell lines.^{23,24} However, other inconsistent results have been also obtained, including non-promoting, weak-promoting, and even promoting effects on tumor growth.²⁵⁻²⁹ Such contradictory observations may be in part the result of the different methods used in the determinations.

On the basis that OA and other fatty acids are good cellular fuels that can be degraded through β -oxidation when imported into the mitochondria, some researchers have designed a new synthetic OA analog, “minerval” with a modification that blocks the biological activity of fatty acids. Thus, enzymes involved in those processes may not recognize this modified fatty acid, so that its utilization as a source of energy would be decreased, and subsequently, its availability to modify cell signaling increased. Supporting the above-mentioned suggestion, they showed a markedly increase of the antiproliferative activity of minerval with respect to

Table I
Key studies evaluating the antitumor effect of OA

Reference	Key findings
<i>General evidences of the protective effect of oleic acid and olive oil</i>	
Chajes V et al., ⁹ Escrich E et al., ¹⁰ Martín-Moreno JM et al. ¹¹	OA has a protective effect in breast cancer
Macquart-Moulin et al., ¹² Stoneham M et al., ¹³ Bautista D et al. ¹⁴	Olive oil has a protective effect on colorrectal cancer development
Bartoli R et al., ¹⁵ Reddy BS and Maeura Y, ¹⁶ Schwartz B et al. ¹⁷	Olive oil prevents the development of colon carcinomas in rats
<i>Mechanisms involved: OA-proliferation</i>	
Zeng L et al. ²⁰	OA promoted the growth of non-malignant cells but has the opposite effect in malignant cells
Liu J et al., ²¹ Hughes-Fulford M et al., ²² Martíne J et al., ²³ Grao L et al. ²⁴	OA showed an inhibitory proliferation effect in different carcinoma cells
Hardy S et al., ²⁵ Soto-Guzmán A et al., ²⁶ Welsch CW, ²⁷ Ip C, ²⁸ Zusman I et al. ²⁹	OA has a non-promoting, weak-promoting, and even promoting effect on tumor growth
Martínez J et al. ³⁰	Minerval inhibits the growth of cancers in both animal models and cultured cells
Menéndez JA and Lupu R, ³⁶ Menéndez JA et al., ³⁷ Menéndez JA et al., ³⁸ Nelson R ³⁹	OA can suppress the over-expression of HER2 (erbB-2)
Gamberucci A et al. ⁵¹	OA can inhibit SOCE in Ehrlich tumor cells
Carrillo C et al. ⁵²	OA can inhibit SOCE in a colon adenocarcinoma cell line
<i>Mechanisms involved: OA-apoptosis</i>	
Menéndez JA et al. ⁵⁵	OA induces apoptosis in breast cancer cells
Puertollano MA et al. ⁶¹	ROS was substantially increased after YAC-1 tumor cell incubation with OA
Azevedo-Martins AK et al. ⁶²	OA reduced catalase activity in human leukaemia cell lines
Puertollano MA et al., ⁶¹ Cury-Boaventura MF et al. ⁶⁵	OA increases caspase 3 activity in different carcinoma cell lines

OA in human adenocarcinoma cells, with no apparent toxic effects. They additionally showed that exposure to minerval inhibits the growth of cancers in both animal models and cultured cells.³⁰

Several mechanisms have been proposed for the antiproliferative effect of unsaturated fatty acids. Among them, a reduction in the synthesis of eicosanoids derived from arachidonic acid could be considered to be involved in the growth inhibitory effect.³¹⁻³³ Specific changes in gene expression patterns have been also suggested.^{34,35} In this sense, OA can suppress the over-expression of HER2 (erbB-2), a well-characterized oncogene which plays a key role in the etiology, invasive progression and metastasis in several human cancers.³⁶⁻³⁹ Finally, different studies have reported that unsaturated fatty acids can modulate the activity of the components of intracellular signaling.⁴⁰⁻⁴² It is well established that Ca²⁺ is among the major intracellular factors involved in the signaling transduction pathways evoking cell growth and proliferation, and other key processes such as gene expression.^{43,44} Within Ca²⁺ mechanisms contributing to the increases in intracellular Ca²⁺ concentration ([Ca²⁺]_i), particular attention has been paid to the role of Ca²⁺ entry through store-operated channels (SOC).⁴⁵ Thus, store-operated Ca²⁺ entry (SOCE) has been involved in cell signaling occurring in non-excitable cells to evoke different cell processes including gene regulation and cell growth.⁴⁶ Entry in cell cycle is preceded by SOC activation.⁴⁷ In addition, the growth factor stimulation

of cell proliferation is accompanied by increased activity and/or expression of TRP channels that are related to SOCE.⁴⁸ Moreover, SOCE inhibition by different means abolishes tumor cell proliferation.^{49,50} It has been recently observed that the addition of PUFA to cells cultured *in vitro*, modifies the extent of SOCE.⁵¹ Thus, OA can inhibit SOCE in Ehrlich tumor cells, possibly because they intercalate into the plasma membrane and directly affect the activity of the channels involved.⁵¹ In addition, it has been recently reported a SOCE-inhibitory effect induced by oleic acid in a colon adenocarcinoma cell line.⁵²

Oleic acid-apoptosis

Unsaturated fatty acids have been widely reported to induce apoptosis in several cell lines.⁵³⁻⁵⁵ The mechanisms behind cell death are numerous and involve a complex set of pathways.

In the apoptotic pathway, the collapse of the mitochondrial membrane potential is a common event that leads to mitochondrial dysfunction and the production of reactive oxygen species (ROS). In fact, increased ROS production has been associated with the induction of apoptotic cell death in different cells.⁵⁶ According to these findings, exposure of neonatal cardiomyocytes to hydrogen peroxide or superoxide anion (O₂⁻) induces apoptosis.⁵⁷ Whether apoptosis induced by fatty acids is associated with an increased production of ROS

remains controversial and seems to depend on the type of fatty acid. Some researchers studied the role of ROS in palmitate-induced apoptosis in the neonatal rat cardiomyocyte and reported no evidence of ROS involvement.⁵⁸ By contrast, docosahexaenoic acid (DHA), a n-3 PUFA, is able to disrupt the mitochondrial membrane permeability and induce ROS production in tumor cells.^{59,60} Regarding the effect of the MUFA, some researchers have reported that the production of ROS was substantially increased after YAC-1 tumor cell incubation with OA and other unsaturated fatty acids.⁶¹

Moreover, fatty acid may disturb the redox state of the cells not only owing to an increase in ROS generation as previously shown, but also due to a reduction in antioxidant enzyme activities. Thus, some researchers demonstrated that OA reduced catalase activity in human leukaemia cell lines.⁶²

Apart from (and in line with) this increase in intracellular ROS production, unsaturated fatty acids-induced apoptosis has been reported to be mediated by an increase in caspase-3 activity in different carcinoma cell lines.^{59,61,63-65}

In addition, alterations in intracellular Ca²⁺ homeostasis are commonly observed during apoptosis.^{66,67} It has been demonstrated that the depletion of the endoplasmic reticulum Ca²⁺ stores can directly induce apoptosis.⁶⁸ Several reports have shown the ability of unsaturated fatty acids to induce Ca²⁺ release from the intracellular stores^{59,69,70} and to induce ROS generation with a subsequent cell death.^{59,71} This way, Aires et al. propose a model for the mechanism of action of DHA in which this fatty acid mobilizes Ca²⁺ from the intracellular pool and stimulates ROS production from the mitochondria, followed by downstream signaling, which will involve the activation of caspase-3, leading to chromatin fragmentation and apoptosis.⁵⁹ However, evidence regarding the role of OA in these pathways is lacking.

In summary, research has demonstrated the advantageous effects of olive oil and OA on health at both the epidemiologic and cellular level. However, as far as we are concerned, little is known about the mechanisms by which OA could affect cell proliferation and cell death of cancer cells. Thus, much research needs to be conducted especially at the cellular level, to more fully understand the pathways by which OA could reduce cancer risk.

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