Prostaglandins & other Lipid Mediators 125 (2016) 100–107

Contents lists available at ScienceDirect

Prostaglandins and Other Lipid Mediators

Review

Reducing the burden of obesity-associated cancers with anti-inflammatory long-chain omega-3 polyunsaturated fatty acids

Subreen A. Khatib, Emily L. Rossi, Laura W. Bowers, Stephen D. Hursting*

Department of Nutrition, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, United States

ARTICLE INFO

Article history:
Received 18 March 2016
Received in revised form 21 June 2016
Accepted 18 July 2016
Available online 19 July 2016

Keywords:
Obesity
Cancer
Omega-3 PUFAs

ABSTRACT

Today's world population has an unprecedented risk of dying from the consequences of being overweight and obese. Chronic diseases such as cardiovascular disease, type 2 diabetes, and cancer are often accelerated because of excessive adiposity. Various biological mechanisms are implicated in the obesity-cancer link, particularly local and systemic inflammation as well as altered growth factor signaling pathways. In order to combat obesity-induced inflammation and the resulting increases in cancer risk and progression, the identification of safe and effective mechanism-based interventions is imperative. Notably, long chain omega-3 polyunsaturated fatty acids (PUFAs) modulate the secretion of pro-inflammatory cytokines, prostaglandins and other inflammatory mediators, restore insulin sensitivity, and can prevent or delay tumorigenesis. Delineating the precise mechanisms by which omega-3 PUFAs suppress obesity-induced inflammation will help identify promising key mechanistic targets and intervention strategies to break the obesity-cancer link.

Contents

Abbreviations: GPR120, G-protein coupled receptor 120; Barr2, beta-arrestin2; TAB1, TGF-beta activated kinase 1/MAP3K7 Binding Protein 1; LPS, lipopolysaccharide; TAK1, transforming growth factor beta-activated kinase 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; JNK, c-Jun N-terminal kinases; IKK-β, I-kappaB kinase-beta; IL–6, interleukin-6; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; Gq/11, Gq protein; PI3K, phosphoinositide 3-kinase; IRS–1, insulin receptor substrate-1; IGF–1, insulin growth factor-1; Akt, protein Kinase B; mTOR, mammalian target of rapamycin; HIF-1α, hypoxia inducible factor-1 alpha; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor.

* Corresponding author at: Department of Nutrition CB #7461, The University of North Carolina, Chapel Hill, NC, 27599.
E-mail addresses: skhatib@live.unc.edu (S.A. Khatib), emilylro@live.unc.edu (E.L. Rossi), lwbowers@email.unc.edu (L.W. Bowers), hursting@email.unc.edu (S.D. Hursting).

http://dx.doi.org/10.1016/j.prostaglandins.2016.07.011
1098-8823/

1. Introduction

The prevalence of obesity has risen dramatically within the past 30 years. Today nearly 40% of adults in the United States (U.S.) are considered obese [1]. The World Health Organization (WHO) estimates that 1.9 billion of the world's population is overweight, including nearly 700 million obese, and these numbers continue to increase [2]. Overweight and obesity are characterized by excessive fat accumulation and classified by a weight-for-height index, commonly known as body mass index (BMI), with obesity defined as a BMI $\geq 30\,kg/m^2$. Must et al. [3] demonstrated a strong correlation between obesity and mortality risk that increases with advancing age. Given that life expectancy in the U.S. and other industrialized countries is on the rise, the now heavier and older population has a greater chance of experiencing the adverse health consequences of being overweight and obese [4].

Obesity engenders a state of chronic, low-grade inflammation characterized by excessive secretion of inflammatory mediators by adipocytes, macrophages, and other cells, including the gut microbiota. These pro-inflammatory factors disrupt metabolic homeostasis and thereby promote insulin resistance, type 2 diabetes, cardiovascular disease, genome instability and cancer [5]. The disparity in mortality between obese individuals and their lean counterparts is attributed, at least in part, to this aberrant pro-inflammatory signaling and the resulting metabolic dysfunction [6]. Unfortunately, significant and sustained weight loss is difficult to achieve in obese individuals. Thus, anti-inflammatory interventions may be needed to reduce the inflammatory burden imposed with morbid adiposity levels. Numerous clinical and epidemiological studies have shown beneficial health effects with increased long chain omega-3 polyunsaturated fatty acids (PUFAs) consumption, including reductions in inflammation, hyperlipidemia and improved insulin signaling (Table 1) [7–9]. The anti-inflammatory and metabolic reprogramming properties of omega-3 PUFAs have been shown to delay the onset of cancer in several animal models, negating the pro-tumorigenic effects of obesity. This review will discuss how omega-3 PUFAs suppress obesity-associated pro-inflammatory adipokine secretion and growth factor signaling, as well as consider issues related to translating these mechanistic insights to decrease cancer development and progression.

1.1. Omega-3 polyunsaturated fatty acids

Omega-3 and omega-6 PUFAs are essential nutrients, meaning they cannot be synthesized in the body and must be obtained from the diet. The three main dietary forms of omega-3 PUFAs are the marine-derived eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and the plant-derived alpha-linolenic acid (ALA). Omega-6 PUFAs include linoleic acid (LA), found in high concentrations in many vegetable oils. The ratio of omega-3 to omega-6 PUFAs is inversely associated with the pathogenesis of many diseases such as cardiovascular disease, rheumatoid arthritis, and many cancers [10]. Western diets have a particularly low omega-3:omega-6 PUFA ratio, thereby potentially increasing the risk of these chronic diseases. Clinical studies have shown that an omega-3:omega-6 PUFA ratio of 4:1 was associated with a 70% decrease in total mortality of CVD patients, a ratio of 2.5:1 suppressed cell proliferation in colon cancer, and a ratio of 2–3:1 decreased rheumatoid arthritis-associated inflammation [8].

Eicosanoids are the products of omega-3 and omega-6 PUFA cleavage from cell membrane phospholipids by phospholipase A_2. The enzymes cyclooxygenase (COX) and lipoxygenase (LOX) metabolize PUFAs to produce these eicosanoids, which include pro-inflammatory prostaglandins, leukotrienes and thromboxanes as well as anti-inflammatory resolvins and protectins. COX and LOX produce proliferative and pro-inflammatory eicosanoid mediators from arachidonic acid (AA), an omega-6 PUFA and a derivative of LA, whereas anti-inflammatory eicosanoid products are produced from the omega-3 PUFAs EPA and DHA, which can be derived from ALA. A difference between the effects of EPA and DHA has been shown with organ specificity. DHA is more readily incorporated in organs such as the brain, liver, and retina whereas EPA are seen at higher concentrations in red blood cells [10–12].

There may be an optimal omega-3:omega-6 PUFA ratio to be achieved in the blood and tissues in order to reduce enzymatic conversion of LA to AA and increase substrate availability of COX and LOX to act on EPA and DHA [13]. The absorption and incorporation of omega-3 PUFAs into phospholipid membranes serves to inhibit the COX and LOX pathway utilization of AA, thereby decreasing production of pro-inflammatory prostaglandin E_2 (PGE_2), thromboxane A_2, and leukotriene B_4 metabolites [14–16]. These anti-inflammatory actions are thought to be responsible for the beneficial health effects seen with higher omega-3 PUFA consumption, including a reduction in the risk of obesity-associated cancer incidence and mortality.

1.2. Obesity-associated inflammation and cancer

1.2.1. Obesity and cancer

Obesity promotes an increased risk of many cancers and a worse cancer outcome after diagnosis. Obesity is an established risk factor for endometrial, colorectal, breast (postmenopausal), esophageal (adenocarcinoma subtype), liver, kidney, gallbladder, pancreatic, uterine, and ovarian cancer [17]. Obesity also worsens the prognosis of each these cancers as well several others, including prostate cancer, premenopausal breast cancer, thyroid cancer, and some leukemias. Morbid obesity (BMI > $40\,kg/m^2$) is associated with a markedly higher risk of dying from cancer, increasing rates by 52% in men and 62% in women [18]. The exact mechanisms underlying the obesity-cancer link remain unclear, but abundant evidence suggests that they involve increased adipose tissue inflammation and metabolic dysfunction.

1.2.2. Adipose tissue inflammation

The local secretion of inflammatory adipocytokines from adipose tissue, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), resistin, and monocyte chemotactic protein-1 (MCP-1), is increased in obese individuals compared to their normal weight counterparts [19–21]. These pro-inflammatory cascades stem from an overabundance of immature pre-adipocytes, which recruit activated macrophages to the adipose tissue [22]. These adipose tissue macrophages (ATMs) are a primary source of pro-inflammatory cytokines, which are involved in paracrine and endocrine signaling and often have potent pro-tumor effects [22]. Cytokines promote tumor growth in the microenvironment by increasing angiogenesis and fostering an immunosuppressive environment, which works against the body's anti-tumor immunity. IL-6 inhibits the maturation of dendritic cells, thus reducing the population of cytotoxic T-cells, which kill cancer cells [23]. IL-1β promotes tumor growth by inducing angiogenic factors, including vascular endothelial growth factor, which support the tumor with a nutrient rich blood supply [24].

Activation of the transcription factor nuclear factor (NF)-κB through the phosphorylation of its upstream activator IkB kinase-β (IKK-β) induces increased gene expression pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β (Fig. 1).

TNF-α is known to increase tumor cell proliferation, tumor stage, and systemic metastatic growth [25,26]. In addition, TNF-α and IKK-β activate c-Jun NH2-terminal kinase (JNK), which promotes proliferation and survival of tumor cells [27,28]. TNF-α also contributes to insulin resistance by increasing insulin receptor substrate 1 (IRS-1) phosphorylation at serine 307, which impairs its