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Minireview

Fatty acid-induced angiogenesis in first trimester placental trophoblast cells: Possible roles of cellular fatty acid-binding proteins

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ABSTRACT

Angiogenesis is involved in the growth of new blood vessels from the existing one. Consequently, angiogenesis plays an indispensable role in tissue growth and repair including early placentation processes. Besides angiogenic growth factors (vascular endothelial growth factor (VEGF), angiopoietin-like 4 (ANGPTL4), placental growth factor (PlGF), platelet derived growth factor (PDGF), fibroblast growth factors (FGF)), dietary fatty acids (c>16) also directly or indirectly modulate angiogenic processes in tumors and other cell systems. Usually n−3 fatty acids inhibit whereas n−6 fatty acids stimulate angiogenesis in tumors and other cells. Contrary to this, docosahexaenoic acid, 22:6n−3 (DHA) and other fatty acids including conjugated linoleic acid stimulate angiogenesis in placental first trimester cells. In addition to the stimulation of expression of major angiogenic factors such as VEGF and ANGPTL4, fatty acids also stimulate expression of intracellular fatty acid-binding proteins (FABPs) FABP-4 and FABP-3 those are known to directly modulate angiogenesis. Emerging data indicate that FABPs may be involved in the angiogenesis process. This paper reviews the fatty acid mediated angiogenesis process and the involvement of their binding proteins in these processes.

Contents

Introduction

Angiogenesis is involved in the growth of new blood vessels from existing vessels. This is an important natural process in the body used for growth and development, and tissue repair (Adams and Alitalo, 2007). Although blood vessels attain a non-angiogenic state in the adult body, angiogenesis still occurs under certain conditions such as in the cycling ovary and in the placentation processes (Albrecht and Pepe, 2010). Angiogenesis is also involved in the pathogenesis of several disorders, including tumor growth and metastasis where the newly formed vasculature provides nutrients and oxygen to sustain tumor cell function and survival (Carmeliet and Jain, 2011). The angiogenic process is a highly complex, dynamic process regulated at every stage by several pro- and anti-angiogenic molecules. Several growth factors such as vascular endothelial growth factor (VEGF), angiopoietin-like 4 (ANGPTL4), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF), and placental growth factor (PlGF) are involved in angiogenesis (Aiello and Wong, 2000; Folkman and Klagsbrun, 1987; Gealekman et al., 2008). These factors are responsible for promoting

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and sustaining angiogenesis. VEGF causes dilation of blood vessels and endothelial cell proliferation/migration. PDGF, recruits smooth muscle cells to stabilize new vessels whereas FGF, promotes endothelial cell proliferation. and the physical organization of endothelial cells into tube-like structures. Matrix metalloproteinase (MMP), causes breakdown of the basement membrane, and angiopoietin, mediates vascular remodeling and maintains vascular integrity (Morisada et al., 2006). Most growth factors, including VEGF, PDGF, and angiopoietins, are receptor tyrosine kinases. Binding of the growth factor to its receptor activates signal transduction, ultimately causing transcription of the growth factor in the nucleus. Some pro-angiogenic molecules regulate the production of angiogenic growth factors such as tumor necrosis factor-alpha (TNF-α). Interleukin (IL)-8 also upregulates pro-angiogenic factors such as MMP-2 and MMP-9. Therefore, molecules that regulate expression of growth factors, production, or down-stream effects will likewise impact angiogenesis. In general, n−3 fatty acids have anti-inflammatory and anti-cancer effects, whereas n−6 fatty acids promote inflammation and carcinogenesis (Dutta-Roy, 2000b; Sapieha et al., 2011; Sterescu et al., 2006). n−3 long chain polyunsaturated fatty acids (LCPUFAs) such as eicosapentaenoic acid, 20:5n−3, (EPA) and docosahexaenoic acid, 22:6n−3, (DHA) inhibit whereas n−6 LCPUFA such as arachidonic acid, 20:4n−6(AA) promotes angiogenesis (Belury, 2002; Chen, 2010; Sapieha et al., 2011; Spencer et al., 2009; Sterescu et al., 2006). These fatty acids influence angiogenesis via several mechanisms such as expression of angiogenic factors, VEGF, ANGPTL4 and other modulators such as eicosanoids, cyclooxygenase (COX), fatty acid-binding proteins (FABPs), and NO (Spencer et al., 2009).

Adequate placental angiogenesis is critical for the establishment of the placental circulation and thus for normal fetal growth and development despite the fact that angiogenesis is a hallmark of the malignant process. Whether reduced placental vascularity is secondary to placental insufficiency, or conversely, whether inadequate placental vascularization is a cause of placental dysfunction is not well established yet. However, there is no doubt that inadequate placental vascular development, secondary to reduced VEGF or VEGF receptor expression, can cause lethal embryonic defect. It is therefore reasonable to suggest that inappropriate placental expression of angiogenic factors may contribute to placental vascular defects and placental dysfunction and therefore this is an important cause of infertility and fetal growth retardation. With the recent spate of clinical work on regulators of angiogenesis, these observations lead us to believe that regulation of placental angiogenesis could become a novel and powerful method for ensuring positive outcomes for most pregnancies. Since supplementation of n−3 fatty acids are recommended in pregnancy for optimal feto-placental growth and development (Innis, 1991; Uauy et al., 2001) it is therefore important to investigate the effects of these fatty acids in placental angiogenesis.

Essential fatty acids and their metabolites

Essential fatty acids (EFAs) belong to the n−6 (omega-6) and n−3 (omega-3) families, starting with the precursors, linoleic acid,18:2n−6 and alpha-linolenic acid, 18:3n−3. The n−6 series of EFAs contain two or more double bonds, with the first double bond on the sixth carbon from the methyl end of the molecule; the n−3 EFAs contain three or more double bonds, with the first double bond on the third carbon atom from the methyl end. n−3 fatty acids and n−6 fatty acids play crucial biological roles that include altering the properties of cell membranes, providing substrates for the production of signaling molecules or functioning mediators, and modulating gene expression (Dutta-Roy, 1994; Innis, 1991; Smith, 1989). The primary n−6 fatty acid is linoleic acid (LA), which can be converted to AA. The three main n−3 fatty acids are α-linolenic acid (ALA), DHA, and EPA. Through the same desaturase and elongase enzymes, the n−3 fatty acids, ALA can be converted into EPA and DHA. The enzymes responsible for the metabolism of both n−6 fatty acids and n−3 fatty acids are the COX, lipooxygenases (LOX), and cytochrome P450 (CYP 450). Several eicosanoids derived from the n−6 fatty acids promote tumor angiogenesis, such as the prostaglandins (PGH_2, PGE_2, PGI_2), leukotrienes (4-series LTs), thromboxanes (TXA_2), and hydroxyeicosatraenoic acids (12-HETE, 15-HETE) (Bagga et al., 2003; Hoagland et al., 2001; Jin et al., 2009; Kamiyama et al., 2006; Nie et al., 2000; Pai et al., 2001; Pola et al., 2004; Smith, 1989). These eicosanoids make the tumor microenvironment more favorable for neoplasms and metastasis by encouraging the transcription of angiogenic growth factors, increasing the rate of endothelial cell migration and proliferation, and increasing the rate of vascularization. In contrast, n−3 fatty acids metabolism produces leukotrienes and prostaglandins that attenuate excess vascularization. n−3 and n−6 fatty acids compete each other for incorporation into the cell membrane in addition to enzymes for eicosanoid production, including COX-2 and 5-LOX. Thus, high levels of tissue n−3 fatty acids can reduce angiogenesis through decreased production of pro-angiogenic AA-derived eicosanoids, membrane receptor–ligand interactions, and through n−3 fatty acid's intrinsic antitumor properties (Bagga et al., 2003; Kamiyama et al., 2006; Nie et al., 2000; Pai et al., 2001; Pola et al., 2004; Yuan et al., 2009). Furthermore, n−3 fatty acids have been found to down- regulate expression of angiogenic growth factors such as VEGF, PDGF, IL-6, and MMP-2 (Kang and Weylandt, 2008; Spencer et al., 2009). n−3 fatty acids are only found in marine fish and certain vegetables and nuts whereas corn and soybean oils, processed foods containing these oils, and grain-fed meat contain high levels of n−6 fatty acids. Now, the ratio of n−6/n−3 fatty acids is approximately 15:1 or higher; our bodies may not be accustomed to utilizing such high levels of n−6 fatty acids. This is considered to be one of many factors responsible for the relatively recent rise in chronic diseases, predominantly those associated with inflammation including cancer, heart disease, arthritis, and diabetes (Simopoulos, 2002).

The maternal, fetal, and neonatal EFAs/LCPUFAs status is an important determinant of health and disease in infancy and later life (Innis, 1991; Uauy et al., 2001). In fact, fetal brain and retina are very rich in AA and DHA (Innis, 2007). The deposition of DHA and AA to the fetus is critically important during the last trimester in order to accomplish brain and retinal growth and development (Innis and Friesen, 2008). Because the developing fetus cannot efficiently produce its own DHA, it must obtain this vital nutrient from its mother through the placenta during pregnancy and from breast milk after birth. DHA is a critically required nutrient for the development and function of infant cognition and vision (Innis, 1991; Uauy et al., 2001). The numerous studies have demonstrated a positive effect of supplementation with DHA in pregnant women in terms of less premature birth and in the child, in terms of complex brain performance, like visual acuity, attention spans, and intelligence, and mother overall health. In addition, DHA may reduce the incidence of pre-eclampsia and postpartum depression by stimulating placental angiogenesis (discussed later). All these indicate a critical need for DHA for fetal growth and development and for early placentation processes such as invasion of first trimester trophoblasts. Evidence from various studies suggests that learning ability may be permanently impaired if there is a reduction in the accumulation of sufficient DHA during intrauterine life (Carlson, 2009; Helland et al., 2003). The critical importance of LCPUFAs in the development of the feto-placental unit demands an efficient placental uptake system of maternal fatty acids. Pregnancy is associated with a reduction in maternal plasma DHA percentage and its possible depletion in the maternal store. Since the synthesis of LCPUFAs in the fetus and placenta is low, both the maternal LCPUFAs status and placental function are critical for their supply to the fetus. The essential role for DHA in fetal neurological development in mammalian species is well established. It is currently estimated that 67–75 mg/day of DHA are accumulated in utero during the last trimester of gestation. Maternal supplementation with DHA up to 1 g/d or 2 · 7 g n−3 LCPUFAs did not have any harmful effect. DHA supplementation studies demonstrate that slightly enhanced length of gestation may increase the birth weight at delivery.