Parallels between cancer and preeclampsia: functional mechanisms and therapeutic approaches

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Abstract

Preeclampsia is a pregnancy complication with risks for both mother and fetus, arising from multiple etiologies, one of its causes being abnormal placentation. Successful embryo implantation and development rely on processes such as tightly controlled transcription regulation, angiogenesis, immune evasion, and remodeling of the extracellular matrix, which are also frequently associated with the behavior of malignant cells. A better understanding of the molecular pathways that are shared between preeclampsia and cancer can provide valuable insight into the mechanisms that lie at their foundation, and give rise to new therapeutic strategies. The present study aims to draw a parallel between the two conditions, in terms of functional mechanisms and therapeutic approaches. In this sense, this paper focuses on five processes and three potential therapeutic strategies that have been demonstrated to be relevant in these conditions.

Some studies offer contradicting conclusions on the nature of the associations between preeclampsia and cancer, but a clear connection exists between the molecular mechanisms of placental growth and invasion and metastatic cancer. Moreover, statins, beta blockers and PARP inhibitors have all demonstrated beneficial effects on both pathologies, although they may be not be acting through the same mechanisms in both diseases. Further research is required for a better understanding of the underlying causes of preeclampsia and placental dysfunction, as uncovering novel origins of the disease would provide a new appreciation for the reasons behind malignant transformation.

Introduction

Although frequently overlooked, the placenta is a highly complex organ in its own right, for both mother and baby. In the early stages of pregnancy, it mimics the functions of all the major organ systems which the fetus has not yet developed: lungs, liver, kidney, and others, ensuring its appropriate nutrition and oxygenation. The exchange of nutritional and other resources at the level of the placenta is facilitated by the interaction between the fetal membranes and the maternal endometrium of the uterus. The degree of invasion of the placenta into the uterine wall depends on the species and has broadly been classified into three forms (reviewed in Mossman, 1987). In species with epitheliochorial placentation (for example, ungulates including whales, lemurs, pangolins, and others) the epithelium of the uterine lining is in close apposition with the surface of the placenta, but maternal blood is retained within the uterine blood vessels and does not come into direct contact with the fetal tissue. In species with endotheliochorial placentation (for example, all Carnivora, and some Afrotherian mammals), the placenta errodes into the endometrium, removing epithelium and connective tissue, so that the fetal tissues come into direct contact with the endothelial wall of maternal uterine blood vessels. The most invasive form of placentation is found in species with hemochorial placentation (for example, monkeys and apes, most rodents), in which the endothelial wall of uterine blood vessels is breached by the invading fetal tissue, causing maternal blood to wash directly over fetal tissue. A lesser degree of variation in the invasiveness of placentation also exists between members of the same species (Burton et al, 2015).

In humans, implantation and placentation are highly invasive processes where the placenta becomes deeply embedded in the lining of the uterus. Invasion of syncytiotrophoblast cells starting at 8 weeks of gestation involves the endothelial cells of maternal vessels deep in the myometrium being replaced by cells of fetal origin, such that the spiral arteries are converted into low-impedance, non-contractile tubes (Southcombe et al, 2011). This increases the rate of blood passage through the uterine vasculature and prevents maternal control of the local blood pressure. Eventually the spiral arteries break open to release maternal blood directly onto the fetal surface of the placenta in order to supply resources to the developing fetus. When this process of placental invasion fails, it results in poor placentation (Redman & Sergeant, 2010) associated with poor fetal growth and development, and a range of other negative obstetrical outcomes.

Preeclampsia is a pregnancy complication that can affect between 2 to 8% of all pregnancies. It is usually characterized by maternal hypertension, proteinuria, and organ failure, leading to severe fetal and maternal complications including death (Ghosein-Doha et al, 2018; Hahn et al, 2019). Dysfunctional placentation, especially inadequate invasion of the placental tissues into the uterus, lies at the foundation of this syndrome. It arises from an imbalance between factors produced by the placenta, like trophoblast-derived factors, and maternal adaptation to them, leading to immunologic dysfunction and inappropriate responses of the mother's body (Redman & Sergeant, 2010). Several different areas of research are being utilized for the study of preeclampsia, including genetics and epigenetics, feto-maternal microchimerism, immunological interactions between paternal antigens and the maternal immune system, oxidative stress, and cardiovascular health. Figure 1 illustrates the differences between normal placentation and defective placentation, as is in the case of preeclampsia.

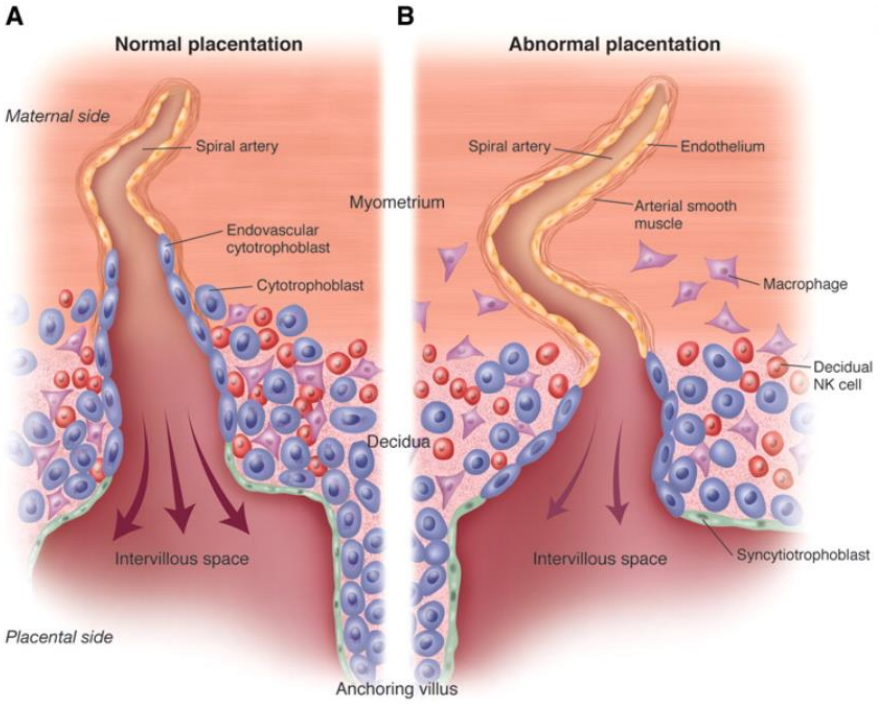

Figure 1. Comparison between normal and abnormal placentation. Extracted from Redman & Sargent, 2005.

It has been hypothesized that the maternal immune response to fetal cells may influence the course of the placentation process (Redman & Sergeant, 2010). Immunological incompatibility between mother and fetus or mother and sexual partner has been associated with pregnancy complications such as preeclampsia (Lokki et al, 2018). Fetal tissues need to be protected against the maternal immunological response, so in a healthy pregnancy, a number of immunosuppressive processes take place to protect the fetus. For example, fetal tissues only express a single HLA molecule, HLA-G, which is virtually monomorphic across individuals. The absence of paternal classical class I and II HLA antigens on the placenta prevents recognition of fetal tissue as "other" but the presence of HLA-G prevents a "missing self" reaction (Yokoyama, 1997). However, immunosuppression is not the sole contributor to a successful pregnancy. In fact, maternal immune cells, especially uterine natural killer cells, accumulate at the maternal-fetal interface, where they appear to play an important role in facilitating uterine tissue remodeling by the placenta by the production of various cytokines, chemokines and angiogenic factors (Gaynor and Colucci, 2017).

A large number of genetic alterations have also been associated with preeclampsia or other pregnancy hypertension disorders, but a root cause has not yet been determined. Different genes have been associated with different manifestations of preeclampsia, but a central pathway shared among all patients is the angiogenesis-regulating PlGF-sFLT1-endoglin axis (Oudejans et al, 2006). The characteristic endothelial dysfunction may be mediated by excess placenta-derived soluble VEGF receptor 1 (sVEGFR1 or sFlt1). Preeclampsia patients also present a placenta-derived soluble TGF-beta coreceptor (sEng) which inhibits the formation of capillaries and induces vascular permeability (Venkatesha et al, 2006). Both maternal and fetal genes may play a part, making it difficult to pinpoint a single cause of the syndrome. Genes involved in thrombophilia, endothelial function, vasoactive proteins, and oxidative stress are among the most commonly investigated factors (Williams & Broughton Pipkin, 2011). The genetics behind reduced placental invasion have been investigated, with one study concluding that a core set of genes underlying eutherian placental invasiveness are associated with the pathogenesis of human preeclampsia, including genes for placentally-expressed transcription factors (Elliot & Crespi, 2015).

Upon analyzing the main players in the pathology of preeclampsia, it can be noticed how the same mechanisms play a role in the development of cancer. Growth and metastasis of tumors involves many of the same processes that regulate placental growth and invasion of uterine tissue, including angiogenesis, immune evasion, and degradation of the local extracellular matrix, suggesting a potential link between placentation and malignancy (Chiang et al, 2008). As increased placental invasion in mammalian species has been associated with increased aggressiveness of the cancers that they suffer (D'souza et al 2014), understanding the underlying mechanisms and response of the host may provide relevant insight into how tumors may behave and interact with the body. So far, few associations have been made between healthy pregnancies and future risks of cancer. Breast cancer is the predominant malignancy that has been studied in this context, associated with a 37% increased risk of preeclampsia (Calderon-Margalit et al, 2009). A study has also found that preeclampsia is associated with a 1.23-fold increased risk in all cancers, and a more than a doubling of the risk of ovarian cancer (Calderon-Margalit et al, 2009). Other studies, however, identified a reduced breast cancer risk of patients who have suffered from preeclampsia (Yang et al, 2018, Wright et al, 2018), or no association with cancer risk at all (Bellamy et al, 2007). These differences in study outcomes could be explained by the different etiologies of preeclampsia, which may affect different processes in different populations, causing the same disease but having different effects on its correlation with cancer risk.

Clearly, both preeclampsia and cancer are pathologies caused by a wide variety of factors, not all known yet. Through gaining insight into the overlapping areas between their mechanisms, it is possible that our understanding of one disease can be improved by understanding the other. The present study aims to review the main modes of action behind preeclampsia and investigate whether they may uncover relevant insights in the context of cancer. First, the main functional mechanisms of preeclampsia will be analyzed and compared to their counterparts in cancer. Second, therapeutic approaches which have been found to be relevant in both diseases will be discussed and compared to offer insight into their therapeutic potential.

Functional Mechanisms

Placental invasion

A set of associations can be drawn between cancer risks and pregnancy complications based on the pre-existing connections between cancer and normal pregnancy processes. Holtan et al. (2009) provides an overview of the parallels in growth, invasion, and immune modulation between cancer and pregnancy. Focusing on extravillous trophoblast cells (EVT), which are the aggressive and invading subtype of cytotrophoblasts, a number of significant similarities can be identified between the two conditions. EVT cells invade the uterine wall to anchor the placenta, and behave similarly to tumor cells regarding proliferation, migration, and angiogenesis. Among many different shared attributes, both cell types activate pathways such as MAPK and TGFb, stimulating proliferation and survival, evade apoptosis and antigrowth signals through CDK and BCL2, and sustain angiogenesis through VEGFR and PGF/FGF signaling (Costanzo et al, 2018). Tissue invasion and immune evasion are also similar in both conditions, which display several different common mechanisms described below.

Epithelial-mesenchymal transition is a cellular program which promotes invasion by inducing changes in cell adhesion, enhancing motility and degrading the extra-cellular matrix. It is involved in developmental processes like mesoderm and neural tube formation and wound healing, and pathological conditions like organ fibrosis and cancer metastasis. Both malignant cells and trophoblasts secrete ECM degrading proteases and growth factors to stimulate motility (such as epidermal growth factor), and present changes in integrins and loss of E cadherin, leading to reduced polarity and increased cell motility. Switches in such invasion programs are not yet fully

understood, but this mechanism illustrates how common ground exists between cancer and placental invasion and embryo development (Holtan et al, 2009).

During replacement of maternal vascular endothelium of the spiral arteries, trophoblasts can change their phenotype to become endothelial cells in order to form flaccid vascular structures with low elasticity and high blood flow, the processes being termed “vasculogenic mimicry”. It has been studied in both cancer and pregnancy, and results indicate that malignant tumor cells acquire an embryonic-like phenotype (Fernandez-Cortes et al, 2019). Tumor cells display a diverse genotype, with characteristics from epithelial, fibroblast, or endothelial cells, with some gene expression profiles and signaling pathways being common with EVT cells, including angiogenesis.

To support the growth of fetuses and tumors, blood supplies are generated by neoangiogenesis, a process that has many common points in cancer and pregnancy. Growth factors such as angiopoietins and VEGF are involved in both situations, with VEGF being an important target for cancer therapy (Shibuya et al, 2011). The mTOR pathway is a well-known regulator of proliferation, autophagy, apoptosis, and vascularization in cancer (Zou et al, 2020), but also plays a role in the early post-implantation decidual reaction in pregnancy, in which the cells of the endometrium proliferate rapidly to generate a nutrient-rich and immunologically suitable substrate for rapid embryonic growth (Roberti et al, 2018). Inhibition of mTOR is a common target in neoplasia but in pregnancy, it results in reduced placental nutrient transport and restricted fetal growth. A study has suggested that inhibition of mTOR signaling is caused, in part, by maternal folate deficiency (Rosario et al, 2017). Maternal folate serum levels have been consistently associated with preeclampsia. Supplementation with folic acid has been found to have protective effects against preeclampsia, possibly by interacting with homocysteine, which in increased concentrations, can damage the placenta’s vasculature (Liu et al, 2018; Serrano et al, 2018). Supplementation with folate may also activate the mTOR pathway, providing adequate nutrition to the embryo. Figure 2 illustrates the similarities between the fetomaternal interface and tumor microenvironment, as described in the work of Holtan et al (2009).

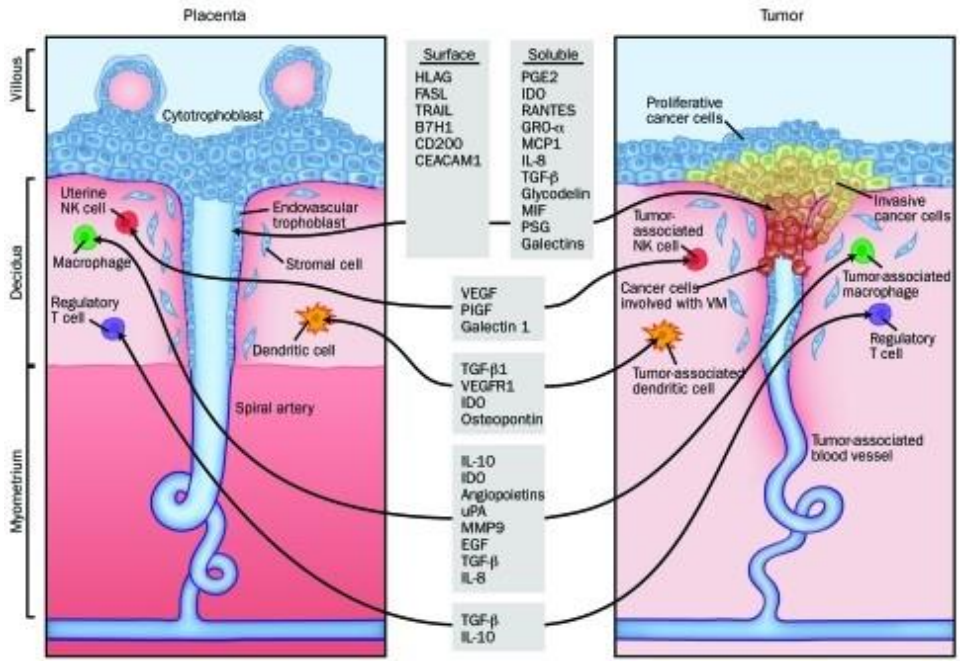

Figure 2. “Similarities between the fetomaternal interface and tumor microenvironment” extracted from Holtan et al, 2009

In the context of placental invasiveness and malignancy, antagonistic pleiotropy has been proposed as the main hypothesis for shared mechanisms between the two conditions. Simply put, the fitness benefits of genetic systems that allow rapid angiogenesis, rapid growth and proliferation, and switching between cell types, are so substantial for the fetus that they are favoured by natural selection even though they may incur fitness costs later in life, should these systems become misregulated and result in cancer. An alternative hypothesis is that the link between placentation and neoplasia originates from mechanisms that promote cancer survival by lowering malignancy rates, in the secondary evolution of less invasive placentas. As metastasis originated prior to the origin of eutherian type of invasive placentation, and the molecular mechanisms of malignant or placental invasion also play roles in evolutionary older processes, such as wound healing, it is possible that the mechanisms they share build a different relationship between cancer and placenta than previously thought. This line of reasoning would suggest that mammals with decreased placentation have evolved mechanisms to suppress trophoblast invasion, which in turn also decrease malignancy rates as an unintended but beneficial side-effect (D'Souza et al, 2014).

Oxidative stress

Oxidative stress is one of the most prominent features of preeclampsia. The placenta is the main source of reactive oxygen species (ROS) synthesis, but maternal leukocytes and endothelium may also contribute. ROS contribute to cellular stress by damaging the DNA, proteins, and lipids, which may have effects on numerous cellular processes such as proliferation, growth, senescence, and apoptosis. They arise from mitochondrial activity under hyperoxia or are formed by the endoplasmic reticulum by the NADPH oxidase enzyme. During a normal pregnancy, the embryo requires low oxygen levels to drive development and promote placental angiogenesis (Elliot, 2016; Kim et al, 2014). Following the first trimester, the maternal blood vessels breach and supply the placenta, resulting in a dramatic increase in oxygen concentration, and thus a burst in oxidative stress. The presence of antioxidants that suppress the ROS is also relevant in this context, as the failure or absence of antioxidant defenses could contribute to the pathogenesis of preeclampsia through its effects on cell turnover rate, proliferation and necrosis in the trophoblast tissue (Jauniaux et al, 2000). Similar to the association between cancer and placental invasion, it has been hypothesized that less invasive placentas, which separate fetal tissues from maternal blood, have evolved as means of protection against oxidative stress. The unique presence of preeclampsia in humans may therefore represent a consequence of the failure of human evolution to evolve non-invasive placentation (Elliot, 2016).

The DNA mutations and damage caused by ROS have been linked with cancer initiation and progression. While ROS are pro-tumorigenic, excessively high levels of ROS induce cytotoxicity, and cancer cells develop coping mechanisms, such as increasing NADPH production and antioxidant enzymatic pathways (Perillo et al, 2020; Hayes et al, 2020; Reuter et al, 2010). ROS production can be increased by oncogenes that affect mitochondrial metabolisms, such as RAS, Rac1, STAT3, BCL-2, and MYC, or through loss of tumor-suppressor mediated regulation of antioxidant genes, such as SOD2, GPX1, SESN1/2 following the inactivation of TP53. The increase in ROS promotes proliferation and cell survival, activating MAPK-ERK and NF-kB signaling cascades. The participation of oxidative stress clearly plays a significant role in cancer development and progression, and it affects a multitude of pathways. In many situations, the effect of ROS on anti-apoptotic and pro-survival pathways is indirect, activating Ca2+ signaling which in turn activates MCL-1 or TRPA1, contributing to oxidative stress tolerance of the malignant cells (Hayes et al, 2020). Cancer cells thrive on moderately increased levels of ROS and balance them with enhanced antioxidant systems. Therefore, disrupting this balance through increasing ROS, decreasing antioxidants, and targeting mitochondrial metabolism may lead to novel therapeutic approaches in the treatment of cancer (Perillo et al, 2020).

Although antioxidants are heavily implicated in maintaining cell function in both cancer and preeclampsia, their effects are limited in both conditions. A review of fifteen studies concluded that the available evidence does not support the use of antioxidants in the treatment or prevention of preeclampsia, although some studies revealed a reduced occurrence of preeclampsia in the group on antioxidants compared to those on placebo (Salles et al, 2012; Kent et al, 2010). The situation is different in cancer treatment, where it is uncertain whether antioxidants are beneficial or detrimental. On one hand, higher levels of antioxidants could protect patients against chemotherapy-induced ROS. On the other hand, the use of antioxidants may interfere with ROS-inducing anti-neoplastic agents and reduce the cellular damage and necrosis of the targeted malignant cells. An extensive review of 174 studies performed on patients, animals, or in vitro models concluded that antioxidant supplementation has therapeutic potential and increases survival times in patients receiving chemotherapy (Singh et al, 2018). This means that increasing antioxidant activity through supplementation may not have a significant direct effect on the pathology of either cancer or preeclampsia, but may help by supporting the main treatment and preventing ROS-related side effects.

MMPs

The behavior of cancer cells during metastatic invasion exhibits similarities to the behavior of placental trophoblast cells during invasion of the uterine lining. The invasion cascade is made possible by the degradation of the extracellular matrix by members of the matrix metalloproteinases (MMP) family. The regulation of ECM degradation consists of the balance of MMPs and tissue inhibitors of metalloproteinases (TIMP), and aberrant expression of either of those factors may lead to dysregulated invasion in conditions like preeclampsia. In a healthy pregnancy, the expression of multiple MMPs (MMP2,3,7,9,13, and others) is increased, active forms of the proteins being observed in the early stage placental tissue, and in small renal and mesenteric arteries (Raffetto et al, 2008).

While the connection between MMPs and preeclampsia is apparent, there is an ongoing debate on how MMP and TIMP expression is changed. Most studies focus on MMP 2 and 9, but MMP1, 7, and 13 have also been investigated in this context. Decreased levels of MMPs would limit the remodeling potential of the spiral arteries and may cause buildups of collagen in the arterial walls. Several studies have reported low expression of MMP2 and 9, in preeclampsia, confirming the participation of these enzymes in spiral artery transformation and endothelial function (Chen et al, 2017; Rahat et al, 2016; Espino Y Sosa et al, 2017). However, other studies have associated high expression of MMP2 and low expression of MMP9 in the plasma of women with hypertension and preeclampsia (Narumiya et al, 2001; Laskowska et al, 2017; Timokhina et al, 2020). This finding could be explained by the presence of nitric oxide (NO) and ROS in preeclampsia, which has the ability to activate MMPs, being positive stimulators of MMP activity (Pustovrh et al, 2005). The action of NO may be through the MAPK pathway or through VEGF activation, which in turn enhances the expression and activity of MMPs (Reuter et al, 2010). It is not yet fully understood how this mechanism would work, as VEGF in preeclampsia is reduced by the presence of excess sFlt-1, as previously discussed, which should inhibit VEGF and thus, MMPs. The differences between these studies arise from the different models that were used, and possibly different stages of the pregnancy.

In cancer, MMP disregulation is in part responsible for cellular disruption, tumor vascularization, and metastasis. MMPs are required for the epithelial-mesenchymal transition, where they break down the intercellular relationships or cell-matrix interactions, allowing the cancer cells to become motile and invasive. MMPs participate in metastatic neoangiogenesis, playing a crucial role in a rate-determining step of cancer development (Quintero-Fabian et al, 2019). MMP2, 8, and 9 have been implicated in the regulation of angiogenesis in cancer. MMP2 expression and activity are induced by various factors, such as IL-8 or VEGF. Some MMPs also likely play

antagonistic roles in the regulation of metastasis, being involved in the inhibition of angiogenesis by cleaving plasminogen and insulin-like growth factor-binding protein 2 (IGFBP-2), thus showing adverse effects in cancer. Given its involvement in MMP activity, VEGF is a candidate to be blocked out to prevent MMP9 activation. TIMPs/MMPs have also been targeted with MMP inhibitors in order to reestablish balance and control the spread of malignancy (Quintero-Fabian et al, 2019).

The expression pattern of MMPs must be further investigated in order to confirm precisely through what mechanisms it is implicated in both preeclampsia and cancer. Additional studies should be performed on different models and at different stages of preeclampsia. In order to obtain accurate and replicable data, there is a need for large sample sizes to test for intra-species variability, as the levels of MMPs may vary even within the species. Before experimenting with therapies targeted for MMPs and TIMPs, a consensus must be reached regarding the expression levels of the enzymes and how they are involved in preeclampsia. With the current knowledge, MMP-2 inhibitors in particular could prove useful in the treatment of preeclamptic patients which present high levels of MMP-2.

MTHFR

PESNPdb is a database designed for the centralization of SNPs and other mutations associated with preeclampsia (Tuteja et al, 2012). According to this database, MTHFR is one of the most commonly identified genes that present variants that are significantly associated with recurrent pregnancy loss. It catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a co-substrate for homocysteine remethylation to methionine (Burda et al, 2015), ensuring the availability of methyl groups for genome-wide methylation processes. As such it is necessary for, and regulates, epigenetic modification during embryonic development. Parental MTHFR genotypes have been associated with the modulation of chromosome abnormalities, such as the production of aneuploidy embryos (Enciso et al, 2016). Moreover, embryonic MTHFR knockdown has been shown to reduce blastocyst rates and number of total, trophectoderm and inner cell mass, the gene being indispensable for blastocyst maturation (Ishitani et al, 2020).

MTHFR SNPs have been linked to preeclampsia, increasing the risk of developing this condition by 20-30% (Wang et al, 2013). So far, the influence of epigenetic modifications in MTHFR has led to conflicting information in the context of preeclampsia and associated pregnancy complications. Several studies have correlated the methylation of the promoter region of this gene with preeclampsia (Ge et al, 2015; Shaker et al, 2021), but not with genome-wide disruption in placental DNA methylation (del Gobbo et al, 2018), as would be expected based on the gene's function.

In cancer, different MTHFR SNPs have been linked to different cancers and risks. The A1298C allele has been associated with increased cervical cancer risk (Gong et al, 2018), hepatocellular carcinoma (Su et al, 2019), and colorectal cancer (Xu et al, 2017).

sFlt-1/VEGF axis

sFlt-1 is a soluble VEGF receptor that has been found to be overly expressed in preeclamptic placentas, acting as an antagonist for VEGF and placental growth factors by preventing them from binding with the endothelial cell receptor Flt1. During pregnancy, maternal and fetal blood vessels may sprout and fuse if VEGF signaling is excessive. Through this mechanism, sFlt-1 acts as a barrier against extreme VEGF signaling, limiting angiogenesis. As sFlt-1 is not only expressed in mammals, but in numerous vertebrates, and the length and homology of the amino acid sequence are similar between species, it may have other biological roles (Shibuya et al, 2011).

As the soluble receptor has been found to be upregulated in the weeks before the manifestation of preeclampsia symptoms, it may be involved in the pathogenesis of the disease (Roberts et al 2009). Induced or exogenous expression of sFlt-1 in animal models caused them to present preeclampsia-like symptoms such as hypertension and proteinuria. Although it is clear that sFlt-1 is involved in angiogenesis and the pathology of preeclampsia, it is yet unknown how the gene's expression is regulated (Shibuya et al, 2011).

In cancers, the production of sFlt-1 is suppressed (Sasagawa et al, 2020), and tumors treated with the soluble factor have shown reduced proliferation, migration, and angiogenesis (Jinjun et al, 2017; Shibuya et al, 2011) and increased cytotoxicity (Miyake et al, 2016). In cancer cell lines transfected with sFlt-1, some cells presented disturbed cell membranes and cell adhesion, suggesting that the cytotoxic activity is achieved through induction of necrosis.

Given the important role sFlt-1 plays in preeclampsia, a better understanding of its mechanisms is required before it can be targeted for treatments. It would be interesting to determine the expression of sFlt-1 in cancers of pregnancy, or follow-up cancer patients who later become pregnant, as well as preeclamptic patients who later develop cancer. Observing sFlt-1 expression across time and in different conditions may provide insight into a patient's risk of developing either cancer or preeclampsia.

Therapeutic Strategies

Statins

Statins are a class of drugs used in cardiovascular treatments for the reduction of LDL cholesterol through inhibition of the HMG-CoA reductase enzyme, which is crucial for cholesterol synthesis. These molecules have also been found to exhibit anti-cancer properties, influencing the proliferation, migration, and survival of tumor cells (di Bello et al, 2020). Through the mechanisms that are involved in cholesterol biosynthesis, downstream signaling of Ras, Rho, or Rac proteins is also affected. The use of statins to reduce cholesterol levels has been shown to improve outcomes in cancer (Gupta et al, 2019).

Statins also present cholesterol-independent effects which broaden their therapeutic potential. They have been shown to improve endothelial function by protecting and stimulating the regeneration of vascular endothelium. Their antioxidant effects are associated with vasodilation and decreased production of reactive oxygen species (ROS). Furthermore, angiogenesis at the site of ischemia, reduced inflammatory response, and anticoagulant activities are among the effects of statins which make them suitable for the treatment of preeclampsia. In this context, studies on animal models indicate that pravastatin reduced PE pathology, and in 2015, pravastatin was successfully used in preventing fetal death of a patient with severe PE, demonstrating its potential use in the treatment of vascular pregnancy disorders (Chaiworapongsa et al, 2015).

However, previous literature remains conflicting, showing contradictory effects on blood pressure, soluble FMS-like tyrosine kinase-1 (sFlt1), and soluble endoglin (sEng). Statins demonstrate a dose-dependent reduction of sFlt1 and increased eNOS and secretion of sEng, indicating that they may be beneficial for patients with preeclampsia or HELLP (Vahedian-Azimi et al, 2021).

The positive effects of statins on both cancer and preeclampsia provide further insight into the common mechanisms between the two conditions. Moreover, the Flt-1 gene and the VEGF-VEGFR systems are heavily implicated (Shibuya et al, 2011). It would appear that the over-expression of sFlt-1 contributes to preeclampsia pathology, while in cancer, over-expression would lead to impaired proliferation. This relationship would suggest that due to the positive effects it has on preeclampsia and the negative impact it would have on cancer, sFlt-1 inhibitors could interfere

with antiangiogenic cancer treatments, such as Bevacizumab. However, a study found that in cancers co-occuring with preeclamptic pregnancy, only some sFlt1 drugs affect the anti-tumor efficacy of the Bevacizumab therapy. (Pan et al, 2019).

Following the same line of reasoning, if sFLT-1 inhibits VEGF and therefore angiogenesis, it could be expected that statins would allow for uncontrolled angiogenesis in cancer, thus benefiting the tumor and negatively impacting the progression of the disease. However, statins have been shown to have a positive effect on malignancy rates (di Bello et al, 2020). This suggests that the broad therapeutic potential of the statins encompasses a mechanism that outweighs the loss of anti-angiogenic effects of sFLT-1.

An important factor may be the type of statins used in the different conditions. In preeclampsia, many studies have successfully tested pravastatin (Costantine et al, 2014; Gajzlerska-Majewska et al, 2018), a hydrophilic statin with a decalin ring, but in cancer, the same drug showed little efficacy in suppressing tumor growth (Barbalata et al, 2020). This would be expected due to the functions of statins, but is in contradiction with other studies who proved that statins offer therapeutic benefits in cancer. One study claimed that pravastatin may induce cancer in elderly patients (Bonovas & Sitaras, 2007), but the correlation between the drug and malignancy remains unproven, as described in the work of Brophy (2007). Simvastatin is one of the mainly investigated lipophilic statin subtypes in cancer. It may function by inhibiting enzymes required for cell growth, interfering with Hedgehog, p53, NF-kB, and other pathways (di Bello et al, 2020). In preeclampsia, simvastatin has been shown to have potent effects on sEng secretion and sFlt-1 inhibition (Vahedian-Azimi et al 2021).

Beta-Blockers

Beta-blockers are an important category of molecules used in the treatment of cardiovascular disease, including high blood pressure. They act by blocking the adrenergic beta receptors and mediating the fight-or-flight response, resulting in relaxation of the smooth muscles. As can be expected based on their function, some beta-blockers are used in the treatment of preeclampsia. Moreover, this class of drugs has been associated with improvement of response to therapy in cancer patients. This section aims to make the connection between the common mechanisms of beta-blockers in cancer and preeclampsia in order to determine how this knowledge can be used to understand more about the workings of both conditions.

One of the most commonly used beta-blockers in the treatment of hypertension in preeclampsia is labetalol. This is an alpha-blocker and non-selective beta-blocker and is commonly used as first-line therapy. However, anti-hypertensive drugs only alleviate one of the symptoms and do not address the root cause of preeclampsia (Odigboegwu et al, 2018). When studied for its effects in cancer, labetalol demonstrated intermediate antiproliferative effects (Pasquier et al, 2013). A meta-analysis study found that non-selective beta-blockers such as labetalol were associated with disease-free survival and overall survival in ovarian cancer and melanoma (Yap et al, 2018).

Beta-adrenergic receptors, the target of beta-blockers, have been suggested to play important roles in the pathology of cancers by promoting proliferation (Ji et al, 2013; He et al, 2017), or interfering with the processes of immune cells. These receptors do not only play a role in the cardiovascular processes they are associated with but affect a variety of different processes which may end up influencing the course of different pathologies. For example, in hemangioma, activation of beta-adrenergic receptors in the ERK-MAPK pathway is important for tumor growth, the pathway being stimulated either directly, or through the release of VEGF-A (Ji et al, 2013). Increased p38 MAPK levels have also been associated with severe hypoxia in HELLP syndrome (Lukas et al, 2019), and inhibition of MAPKs has been found to result in oxidative stress, which contributes to the defective trophoblast invasion present in preeclampsia (Alese et al, 2019). Another mechanism of action that has been proposed in the context of beta-adrenergic receptors

is the involvement of matrix metalloproteinases, which are highly relevant in vascular and uterine remodeling. In glioblastoma, activation of beta-adrenergic receptors increased the expression of MMPs 2 and 9 through ERK ½ activation and in turn increased cell proliferation (He et al 2017). MMPs' function has made them an attractive research topic in both preeclampsia and normal pregnancy, with a decrease in MMP-2 and 9 levels being associated with hypertensive pregnancy, preeclampsia, and decreased vasodilation (Chen et al, 2017). In contrast, other studies have found that MMP2 and MMP13 are increased in preeclamptic patients when compared to controls (Timokhina et al, 2020; Laskowska 2017). Although not fully understood, the effects of MMP expression and activity are clearly relevant. Abnormal expression of MMPs may lead to reduced uterine perfusion pressure, which in turn may lead to the imbalances in sFlt-1 and sEng previously discussed. By blocking the beta-adrenergic receptors which are responsible for increasing expression of MMPs, a reduction in cell proliferation may be achieved. In the case of the decreased levels of MMP-9 in preeclampsia, it is possible that the effects of beta-blockers on other mechanisms compensate for the further decrease of this metalloproteinase.

Blocking beta-adrenergic receptors has been associated with a reduction in tumor growth, making beta-blockers attractive therapeutic strategies in the treatment or support of the treatment of cancer. Their effects should be further investigated and compared in order to determine the most important mechanisms of action through which beta-blockers affect pregnancy and cancer, and offer additional insight into the pathology and therapeutic options of these conditions.

PARP inhibitors

Poly (ADP-ribose) polymerase (PARP) is a family of proteins that plays important roles in multiple cellular processes, such as DNA repair, apoptosis, and gene expression. As PARP molecules exert their function at the DNA level through single-strand break repair, they offer a wide therapeutic potential, as they may play important roles in diverse pathologies. If single-strand break repair is inhibited and other repair mechanisms, such as homologous recombination, are defective due to pre-existing pathologies, PARP inhibitors cause the cells to lose their repair functions and are therefore lethal for those cells. This has significance in cancers that present mutations in DNA repair mechanisms like homologous recombination, such as BRCA1/2 breast and ovarian cancers. Overactivation of PARP proteins due to oxidative stress also leads to cell death and the expression of pro-inflammatory genes, which may contribute to the pathology of other diseases. PARP inhibitors are also being investigated for non-oncologic applications, in conditions like stroke, myocardial infarction, septic shock, severe asthma, or chronic diseases like Parkinson's or multiple sclerosis (Curtin et al 2013, Berger, 2017).

PARP 1 and 2 act as DNA damage sensors and signal transducers, with PARP1 transferring an ADP from NAD+ to target proteins which recruit repair proteins. When this process is inhibited, the repair process cannot move forward, and double-strand breaks are ensured, leading to cytotoxicity. PARP inhibition alone cannot kill a cell that has functional repair mechanisms, but it is suitable for targeting cells with mutations in their repair mechanisms. BRCA1/2 proteins are important in homologous recombination, and cancers with defective or absent BRCA1/2 are significantly more sensitive to PARP inhibitors.

In the context of cancer, PARP inhibitors have been approved for use in HR-defective ovarian and breast cancer, but clinical trials are ongoing to extend their use to other types of malignancies as well. They are often used in combination therapies, which could enhance their efficacy in patients without dysfunctional HR. BRCA mutations have also been associated with prostate or gastrointestinal cancers, making them suitable for PARP inhibitor clinical trials (Sachdev et al, 2019). Ongoing clinical trials are testing PARP inhibitors in combination with other treatments in melanoma, non-small cell lung cancer, or other solid tumors (Berger et al, 2017).

PARP proteins have been implicated in important posttranslational modifications and cell signaling, thereby affecting multiple key cellular functions. These functions may depend on PARP's catalytic activity or the protein-protein interactions it is involved in. As PARP activation consumes the NAD+ substrate, it has been hypothesized that due to NAD+ depletion in cells exposed to DNA-damaging agents, cell viability decreases as PARP activation increases. Hyperactivation of PARP can be caused by reactive oxygen species, nitric oxide, and other triggers relating to oxidative stress (Berger et al, 2017), and may lead to endothelial dysfunction (Crocker et al, 2005). Reactive oxygen species have been associated with preeclampsia, as previously described. For this reason, the management of PARP activation could prevent unwanted cell death in cells affected by oxidative stress. A study found that the loss of endothelial function in preeclampsia is dependent on PARP overactivation and that a PARP inhibitor reversed the oxidative stress and reduction of cellular ATP, suggesting that PARP inhibitors may reverse the biochemical process of preeclampsia (Crocker et al, 2005). Another study performed on endothelial nitric oxide synthase knockout mice revealed that PARP inhibition reduced blood pressure and protected uterine artery function in the pregnant mice (English et al, 2012). PARP inhibition has also been found to prevent the development of endothelial dysfunction and hypertension in reduced uterine perfusion pressure rat models of preeclampsia (Walsh et al, 2012).

Discussion

Preeclampsia is a severe and potentially life-threatening pregnancy complication with multiple etiologies. Just as there are multiple pathways and causes of cancer, there are multiple defective processes that lead to the development of preeclampsia. It is entirely possible that there are several different diseases which present clinically as preeclampsia, similarly to how there are multiple diseases involving abnormal cell growth with the potential to invade the rest of the body, which are grouped together as cancer. Defective placentation lies at the foundation of the development of many symptoms, like hypertension, proteinuria, and organ failure, through host adaptation to imbalances between various factors. Numerous pathways are involved in this process, from vascular growth factors and oxidative stress to methylation regulation and extra-cellular matrix remodeling. The same processes have also been repeatedly implicated in cancer, many of the imbalances contributing to the pathology of the disease. The more that is understood about them in either preeclampsia and cancer, the more that can be inferred about the underlying mechanisms of the other. For this reason, the present study aimed to draw a comparison between preeclampsia and cancer by investigating their parallels in functional mechanisms and therapeutic approaches.

Upon evaluating the research on some of the most important features of preeclampsia, many mechanisms have been identified that play important roles in both preeclampsia and cancer. These include evolutionary development of less invasive placentation as means of protection against cancer mechanisms, involvement of matrix metalloproteinases, the sFlt-1/VEGF axis, and oxidative stress. For several processes, literature is contradictory or incomplete, so more research needs to be performed to accurately determine their role in the pathology of the diseases. Some act in similar ways in both conditions, but some act through opposite effects in preeclampsia versus cancer. Since preeclampsia can manifest in two different forms with different etiologies (early and late onset), the different underlying mechanisms could account for these contradictions.

In the context of placental invasion, vasculogenic mimicry, the process through which cells exhibit a phenotype similar to endothelial cells, is common in both trophoblast cells and malignant cancer cells. Furthermore, mTOR is a pathway that regulates proliferation, apoptosis, and vascularization, and its inhibition has a positive impact on cancer treatment, but a negative impact on pregnancy and preeclampsia. Also, the previous theory that the mechanisms of invasive

placentation gave rise to the mechanisms for cancer metastasis is now being challenged. It has been hypothesized that less invasive placentas have developed as means of protection against cancer-promoting mechanisms, such as oxidative stress. This model of positive pleiotropy could explain the relationship between non-invasive placentation and metastatic cancer in animals who lack invasive placentation and have a low incidence of cancer, like sheep.

Oxidative stress is increased in both preeclampsia and cancer, either due to dysfunctional antioxidants or the production of ROS due to mutations in the responsible mechanisms. Although antioxidant supplementation does not provide significant effects in limiting ROS caused by the pathology of the disease, they may be used in supporting treatment. In the case of preeclampsia, the limitations in the delivery of antioxidants across the placental interface may damper their effects. However, this would be difficult to study from both a practical and an ethical perspective, but a treatment that successfully targets ROS could be beneficial for both conditions.

MMPs are crucial for the remodeling of the extracellular matrix, playing important roles in tumor metastasis and placental invasion. Currently, literature presents contradictory information in the case of preeclampsia, as some studies found low levels of MMP 2, and others found an increase in the protein levels. In cancer, several MMPs, such as 2 and 8 are induced by various factors and play a role in angiogenesis, while MMP 7 and 9 may play a role in blocking it. Before any antioxidants or MMP inhibitors can be investigated, more research should be performed on different models to reach a consensus regarding the expression of MMP2 and related matrix metalloproteases.

sFlt-1 has a protective role, in both pregnancy and cancer, against extreme VEGF signaling. Over-expression of sFlt-1 is representative of the pathology of preeclampsia, while cancer is marked by its under-expression. A better understanding of sFlt-1 implications in either of the disease will undoubtedly offer insight into how it may act in the other. Therapies aimed at reducing sFlt-1 in preeclampsia and inducing its expression in cancer may provide beneficial outcomes.

In this thesis I have investigated three therapeutic strategies: statins, beta-blockers, and PARP inhibitors. Although they are not the first treatments that come to mind for either preeclampsia or cancer, they have been explored as potential treatment options in both conditions. Statins have been found to be beneficial for both pathologies through cholesterol-independent mechanisms. Further experimentation should be performed to understand what mechanisms are implicated, and how they can be efficient in preeclampsia and cancer although they affect a mechanism that acts antagonistically. Multiple types of statins could have different effects and activate different pathways, therefore their individual characteristics and modes of action should be elucidated. Beta-blockers also have a positive effect on preeclampsia and cancer, as the blockade of beta-adrenergic receptors affects different processes that reduce hypertension. The processes and their interrelations should be further investigated, as the effects of beta-blockers seem to be beneficial even if some of the mechanisms through which they act may suggest otherwise. For example, the reduction of MMPs through blocking the beta-adrenergic receptors could be unwelcome in preeclampsia, where MMPs are already reduced, but beta-blockers are still used for their anti-hypertensive properties and they alleviate preeclampsia symptoms. The different mechanisms through which this class of molecules acts needs to be identified and classified, as some effects outweigh others. PARP inhibitors have been researched in the treatment of preeclampsia and cancer, where they show promising results. Like statins and beta-blockers, PARP inhibitors need to be further studied in order to determine the precise mechanisms through which they bring benefits in the treatment of the two diseases.

As it is often the case, more research is needed to understand the overlaps between pregnancy complications, like preeclampsia, and cancer. Current knowledge is limited by the disease models and computational approaches that are being used. As new studies are beginning to support the

hypothesis that less invasive placentation leads to the development of anti-cancer mechanisms, the processes discussed in this paper should be investigated in different mammalian species. It would be of interest to look at oxidative stress, MMPs, genetic mutations like MTHFR and other processes in animals with placentation types different from humans, like dogs, pigs or sheep. A knowledge of the molecular and genetic maternal defense mechanisms against placental invasion and proliferation that are employed by these organisms could help us understand how to most effectively approach treatment of cancer and limit tumor metastasis. However, these mechanisms should be investigated in species with non-invasive placentation that do present metastatic cancers, such as marsupials, as a comparison between different species with different predispositions to malignancy would offer valuable insight into how relevant these processes actually are and what interactions are most significant.

Ethical considerations must be taken into account in studies surrounding this topic, as it is difficult to verify many potential hypotheses when they involve embryos, fetuses or the still developing placenta. Novel in vitro experimental setups and techniques, such as organoids, may provide new openings for such research.

Moreover, while it is known that malignant cells regain embryonic characteristics, such as invasive growth, increased cell mobility, and secretion of factors, it is unclear how this is achieved and how they are stimulated. They clearly exhibit numerous features in common with the placenta, but the processes of the formation of placenta and how it drives embryonic development remain poorly understood. The study of placenta-specific genes re-expressed in cancer cells may provide new therapeutic targets. By understanding how the maternal body naturally prevents the negative impacts of placental invasion, new therapies could have fewer side-effects.

The present study has analyzed a number of different processes, but many more comparisons can be drawn between cancer and preeclampsia. The immunology of these conditions represents and entire field of study in itself, and was not within the scope of this analysis, but would require a literature review of its own. Many more interesting aspects could be further discussed, such as feto-maternal microchimerism, genetic profiles, syncytotrophoblast migration, and others. An extensive review of all such potential relationships between cancer and preeclampsia and placentation could offer a "bird's-eye" view of the issue and allow for new connections to be drawn.

Conclusion

Metastatic cancer shares many common molecular mechanisms with placenta growth and invasion, and thus with the associated condition, preeclampsia. A better understanding of the different etiologies of preeclampsia may provide valuable insights into the workings of different cancers. The processes that limit the harmful effect of placental invasion and protect against cardiovascular diseases may become adequate target therapies in cancer, but further research is needed to determine the etiologies of both diseases.

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