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WJMER

World Journal of Medical Education and Research

An Official Publication of the Education and Research Division of Doctors Academy

DOCTORS ACADEMY

BETTER EDUCATION. BETTER HEALTH.

ISSN 2052-1715

Literature Review
DAUIN 20230206

World Journal of Medical Education and Research:
An Official Publication of the Education and Research Division of Doctors Academy

Why Does the Body Attack Rapidly Dividing Cancer Cells but Not a Fast-Growing Foetus?

Borrelli N[1], Stephens S[1]

Institution
[1]*School of Biosciences, Cardiff University, Cardiff CF10 3AT, United Kingdom*

WJMER, Vol 29: Issue 1, 2023

Abstract:
The foetus is semi-allogenic so contains expression of foreign antigens like cancer cells as well as self-antigens. However, unlike most cancer cells the foetus is not recognised as foreign so is not attacked by the mother. This is because during pregnancy the environment switches from pro-inflammatory to anti-inflammatory. Sex hormones released through pregnancy are thought to help maintain this immune tolerance and induce protective effects against women developing cancer.

Aims:
1. To examine the role of the maternal immune system in protecting the foetus from rejection and how this can be used for future treatments of tumour rejection.
2. To investigate the role of hormones in pregnancy and how they protect the foetus.
3. To explore if women are protected from cancer during pregnancy.

Methods/Results: The databases used for the literature search were Scopus, Web of Science and Medline via OVID. After screening the papers and looking at their eligibility eight were selected. Four investigated the maternal immune system and tolerance, three investigated how hormones during pregnancy maintain a tolerogenic state and one investigated pregnancy induced protection against breast cancer.

Conclusions: There have been new discoveries regarding the immune cells involved in promoting the anti-inflammatory and tolerogenic environment seen in a successful pregnancy but the full extent of this across the entire gestation period is still not completely understood. There are continuous findings that support the idea that sex hormones during pregnancy do play a role in promoting this environment however there are controversies as to whether they induce protection against cancer specifically breast cancer.

Key Words:
Foetus; Pregnancy; Hormones; Tumour; Tolerogenic

Corresponding Author:
Miss Naomi Borrelli ; E-mail: BorrelliN@cardiff.ac.uk

Introduction:

Shared characteristics between trophoblast cells and cancer cells:

At the point of fertilisation, a human zygote forms consisting of two primary cell lines known as the embryoblast (inner cell mass) and the trophoblast (outer cell mass). These trophoblasts rapidly proliferate and invade the maternal endometrial decidua at around day 7. The ability of these trophoblast to proliferate, migrate and form their own blood supply makes them very similar to cancer cells[1].

Foetus vs cancer cells:

Although cancer cells and a foetus appear to be phenotypically similar the main thing that distinguishes them is that cancer cells proliferate and grow uncontrollably whereas in the foetus this process is highly regulated. This was demonstrated by Lui et al in 2010[2] which found that there was a highly conserved juvenile multiorgan genetic program that down regulated many genes required for rapid proliferation in early life. Lui et al did further investigations in this and in 2013[3] looked at the mechanisms that caused the down regulation after birth of an important foetal growth factor that is involved in the juvenile multiorgan genetic program called Insulin-like growth factor 2 (IGF2) which is also commonly upregulated in many cancers. They found that the expression of IGF2 was controlled by the E2f transcription factor family specifically E2f3. The E2f3 positively regulates the expression of IGF2 so when it binds to the IGF2 promoter it activates its transcription. Therefore, the downregulation of the E2f3 is what helps drive the downregulation of IGF2 seen post-natal. In many cancers this process is reversed and overexpression of this E2f3 is what leads to the oncogenic expression of IGF2. It is thought that this occurs in cancers because they lose the retinoblastoma

protein (Rb) which binds to this E2f3 and supresses its activity.

Maternal immune system during pregnancy:
During pregnancy the growing embryo is semi-allogenic because it has half of its genetic material from the mother and the other half from the father. This means that there is expression of antigens that are both foreign and self to the mother. Therefore, for the pregnancy to be successful the foreign antigens coming from the father need to be tolerated and not destroyed by the maternal immune system. This occurs by immune suppression and the mechanisms by which this happens are very similar to cancer with the main difference being that in cancer this process is continuous whereas in pregnancy the immune suppression is precisely timed as it follows an "immune clock of pregnancy"[4].

Immune suppression during pregnancy:
Regulatory T-cells (Tregs) are one of the important immune cells that permit this immune tolerant environment during pregnancy. Tregs are a subset of CD4+ T-cells that have high expressions of an Interleukin (IL) 2 receptor subunit on their cells surface known as CD25+. By having the CD25+ on their cell surface it allows the Tregs to absorb IL-2 from the microenvironment. This inhibits the proliferation of effector T-cells that rely on IL-2 for this and triggers their apoptosis reducing the immune response[5]. The Tregs are highly expressed during pregnancy specifically in the first and second trimester and are essential for normal gestation. Since the Tregs behave similarly in pregnancy and in cancer the deletion of Tregs could be potentially used as a therapeutic treatment in the future for tumour rejection. Another mechanism that prevents the maternal rejection of the foetus is the switch from type 1 T-helper cells (Th1) to type 2 T-helper cells (Th2) cells which are both groups of activated effector T lymphocytes. Th1 cells produce pro-inflammatory cytokines such as IL-2, IFN-γ (interferon gamma), and TNF-α (Tumour necrosis factor alpha) which are mainly involved in killing external pathogens. Th2 cells produce interleukins such as IL-4, IL-5, IL-10, IL-13 and IL-25 that increase an antibody-specific response. Therefore, Th1 can cause damage to the body and Th2 can protect the body. When pregnancy starts the microenvironment is Th1-dominant, but as the pregnancy progresses this quickly shifts to a Th2 environment to allow immunological tolerance which allows the pregnancy to continue. This shift is important because a more dominant Th1 microenvironment has been observed in women with a history of recurrent spontaneous miscarriages. However, this shift does increase the risk of maternal infection which is why it is important that at post-partum the Th1/Th2 balance is restored. This shift is also seen in tumours and malignancies such as melanoma and glioma which favour a Th2 microenvironment[6].

Sex hormones:
During pregnancy there is a systemic rise of sex hormones such as progesterone (P4), oestradiol (E2), estrone (E1) and human chorionic gonadotropin (hCG). These hormones not only play a role in controlling and coordinating anatomical modifications in the foetus but also facilitate the maintenance of immune tolerance in pregnancy. hCG is a glycoprotein hormone which is synthesised by the syncytiotrophoblast straight after embryo implantation and is key for maintaining the E2 and P4 hormones during pregnancy before the placenta is developed. But it has recently been suggested that it also drives IL-10 producing regulatory B cells during pregnancy so controls undesired immune activation. Progesterone is a steroid hormone that is required for the development of the uterine structure to maintain pregnancy. It also influences the activity of different types of immune cells such as dendritic cells (DCs), monocytes and macrophages. It also impacts the levels of galectin-1 which acts as a negative regulator of Th1 immune response and recruits suppressive uterine DCs[7].

Protective effects of pregnancy:
The influence of pregnancy on maternal health has been an important focus on research. It has been shown that an early first full-term birth is the most effective way of preventing breast cancer with the potential of reducing the risk up to 50%. In spontaneous mice carcinoma models the protective effects of pregnancy were investigated by using hormone doses at levels that were like pregnancy. It was found that E2 alone decreased the tumour burden in mice and together with P4 enhanced this protective effect. But the stage of the pregnancy cycle that is most important in reducing cancer risk is still unclear[8].

Aims and Objectives:

1. The role of the maternal immune system in protecting the foetus from maternal rejection and how this can be used for future treatments of tumour rejection.
2. The role of hormones in pregnancy and how they protect the foetus.
3. If women are protected from cancer during pregnancy.

Methods and Results:
Before starting the literature search several scoping searches were done to provide an overview of the literature. After this a research question was

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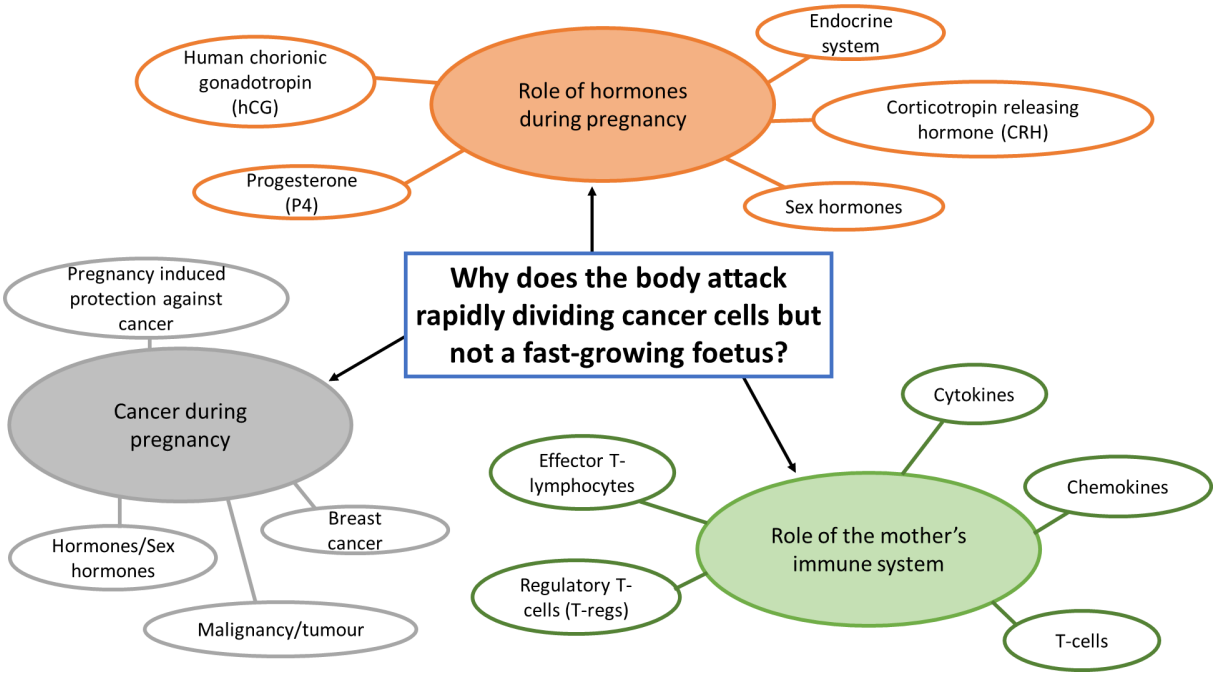

Figure 1: *Mind map that was done to prepare for the literature search*

formulated with a stepwise approach by using the FINERMAPS (feasible, interesting, novel, ethical, relevant, manageable, appropriate, potential value, publishability, and systematic) criteria to ensure that it was original, answerable and addressed gaps in the field[9]. A mind map (figure 1) was created to identify and isolate key topics in the research question.

Information Sources:
Papers abstracts and titles were screened based on a pre-defined inclusion/exclusion criterion (table 1). This allowed for quick removal of obvious irrelevant studies bringing the total number of potential papers down to 59. For these papers the full text was obtained so that they could be further examined in much more detail using the inclusion/ exclusion criteria.
As a result, **8 papers were selected:** 4 studies looked at the maternal immune system and its effect on maternal-foetal tolerance, 3 studies looked at how hormones during pregnancy prevent the body from attacking the foetus and 1 study looked at pregnancy induced protection against breast cancer (see figure 4 for an overview of the search process).

Literature Review and Synthesis:
The research question posed in this literature review was "Why does the body attack rapidly dividing cancer cells but not a fast-growing foetus?" Understanding what mechanisms are in place that allow the mother to tolerate the alloy-antigens expressed by the father can help predict what conditions are required for a successful pregnancy. This can help develop novel strategies that can help prevent spontaneous abortion in high risk patients [10].

Inclusion Criteria	Exclusion Criteria	Justification
Published peer-reviewed literature	Unpublished or non-peer-reviewed literature.	Only published peer-reviewed literature was considered because unpublished literature may be unrepresentative of the wider population and validity of the results has not been confirmed so could not be very accurate or repeatable.
Primary randomised or non-randomised studies	Secondary resources such as reviews or chapters in a book/ textbook.	Secondary resources were used for background research and only primary studies were selected to make sure that the data collected was relevant and accurate.

Inclusion Criteria	Exclusion Criteria	Justification
Prospective studies	Retrospective or case-based studies.	Retrospective studies analyse pre-existing data so are more prone to bias and scientists have not originally collected the data themselves so important evidence could be missing. Case-based studies are also prone to bias as researcher may allow their feelings to influence the study and are very difficult to replicate because they are not representative of the wider population.
Literature published in the last 10 years (2012-present)	Literature published more than 10 years ago (before 2012).	Studies that had been published in the last 10 years were included to make sure that the sources being used in the review were up to date and more credible.
English Language	Foreign Languages.	Due to time constraints could not translate papers. Also, information could be misinterpreted via translations causing key messages/findings of a paper to be lost. However, there was no restriction in place as to where the candidates in the study came from to ensure research was as inclusive as possible.
Human studies either in vivo or in vitro	Studies that were non-human i.e., using animals.	Only studies that looked at human patients or samples were included to make sure that the data obtained from the papers was relevant and answered the research question and aims in a representative way.
Studies done on women with a "normal healthy pregnancy"	Studies involving woman that have uterine abnormalities such as polycystic ovaries or woman that have health or obstetric complications.	By looking at papers that only used woman with a "normal healthy pregnancy" as their patient sample it made sure that the results obtained were more representable of the wider society and repeatable. It also made sure that the results obtained were more relevant to the research questions and more controlled as there are no other factors apart from the topics researched that could have affected them.
Adult participants over the age of 18 years old but younger than 45	Paediatric participants (younger than 18 years old) and adults' participants older than 45.	Pregnancy in children/teenagers is more likely to be associated with obstetric complications that could affect the outcome which is why they were excluded. Women who are 45 years old and older are much less likely to get pregnant or have a successful pregnancy due to a decline in fertility. Therefore, they were also excluded from the study.
Study done more than 2 years ago was cited by other research papers.	Study done more than 2 years ago was not cited by any research papers.	If a paper has been cited by other research paper it is a good indication that it has impacted the field and is of good quality. This may not be feasible for research papers released in very recent years because ongoing studies may not have been carried out which is why the criteria was for papers published more than 2 years ago. However, the number of citations was not included as a criterion as this could have led to bias.

Table 1*: Inclusion/Exclusion criteria that was used when screening the studies that were obtained from the databases online and selecting them to include in the results section of the review.*

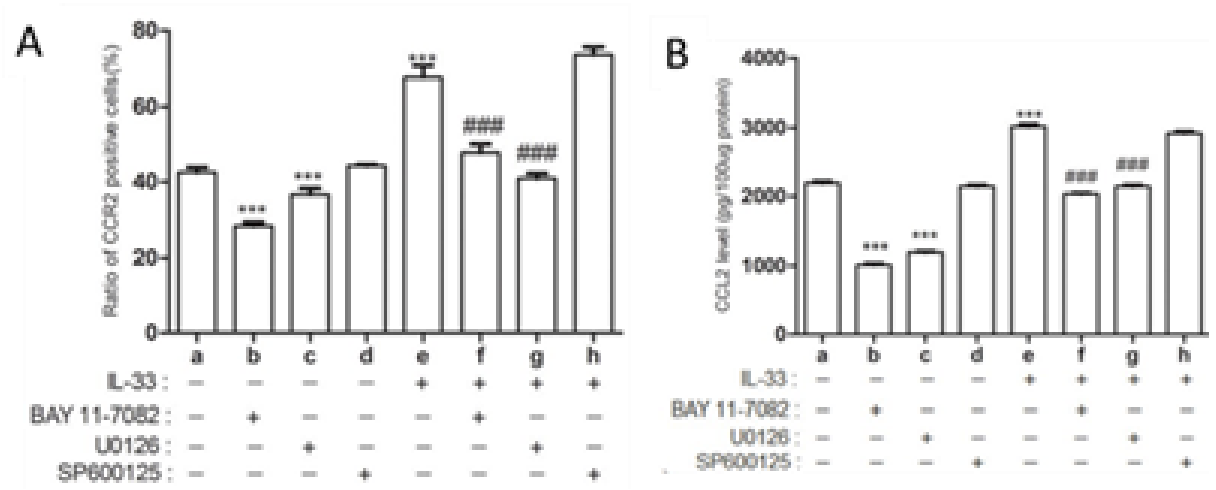

Figure 2: *The specific signalling pathways involved in CCL2/CCLR2 expression in DSCs.*

IL-33 as a potential novel factor in pregnancy success:

Interleukin-33 (IL-33) is a cytokine of the immune system and is part of the IL-1 (interleukin- 1) family and is normally expressed for optimal biological activity. In 2012 a study found that CCL2 (Chemokine (C–C motif) ligand 2) which was secreted from the decidual stromal cells (DSCs) interacted with CCR2 (chemokine (C–C motif) receptor 2) found on decidual leukocytes (DLs) and stimulated them to release Th2 associated cytokines. However, what was not clear was the stimulation of the secretion of the CCL2[11]. Hu et al[12] was one of the first studies to look at the role and mechanism of IL-33 on DSCs and to make a direct correlation between IL-33 and CCL2 in pregnancy. They found that when BAY 11-7082 (inhibitor of NF-κB) and U0126 (inhibitor of ERK1/2) where present and IL-33 was either absent or present the expression of both CCL2 and CCR2 was statistically significantly decreased in both cases. This suggested that these inhibitors not only had a direct effect on CCL2/CCLR2 expression but also reversed the effects of IL-33 as by itself IL-33 statistically significantly increased CCL2/CCR2 expression (figure 2). The JNK (Jun N-terminal kinase) inhibitor SP600125 had no effect which confirmed that IL-33 inducing CCL2/CCR2 expression depended on NF-κB and ERK (extracellular signal-regulated kinase) 1/2 signalling pathways. Therefore, their overall finding was that IL-33 can stimulate CCL2/CCR2 expression through activating NF-κB and ERK1/2 pathways which then stimulates Th-2 associated cytokine stimulation and can promote proliferation and invasion of DSCs. This finding is pivotal as it provides a pathway that enables foetal tolerance and scientist can study it further and come up with effective therapeutic approaches when treating miscarriages.

A limitation of the study is they only looked at the first trimester. A study done in 2011 found that a decoy receptor of IL-33 known as sST2 (soluble variant of ST2) increases in the third trimester so could cause IL-33 to decrease[13] Therefore, by limiting their samples to only the first trimester Hu et al fail to see what the true effects and levels of IL-33 are across the whole pregnancy.

Role of Decidual Natural Killer Cells (dNK) in pregnancy:

In humans around 70% of dNK have the phenotype CD56brightCD16 which are essential at the maternal-foetal interface as they create a microenvironment that is favourable to pregnancy. There are two forms of CD56CD16- natural killer cells: CD56brightCD16− and CD56dimCD16− . CD56dimCD16− have a higher cytotoxicity whereas CD56brightCD16− have an immunoregulatory role and produce anti-inflammatory cytokines[14]. Yang et al[15] were the first study to look at the involvement of the cytokine IL-24 in this dNK conversion during early pregnancy. In their study they found that IL-24 triggers CD56dimuNK cells to differentiate into CD56brightCD16−dNK that had low cytotoxic activity, high immunomodulation, and angiogenic activities. This was highlighted by the fact that when IL-24 was neutralised killer and pro-inflammatory molecules such as CD16, Granzyme B and perforin were statistically significantly upregulated (figure 3A+B) whereas anti-inflammatory molecules IL-10, TGF-β, IL-8 and inhibitory receptors KIR2DL1 and KIR3DL1 were statistically significantly downregulated (figure 3C). In prostate cancer reduction of CD56bright cells has been observed which leads to dysfunctional natural killer cells and impaired cytotoxicity[16]. The above findings indicate that IL-24 could be used as a potential immunotherapeutic therapy against prostate cancer

as it may be able to increase the levels of CD56bright cells and rescue the cytotoxicity.

A limitation of this study is that they included women who underwent a myomectomy to remove fibroids in their endometrial tissue samples. Myomectomy can cause tissue trauma which leads to an inflammatory response and either a regenerative or fibrotic response to tissue healing. A study showed that during tissue/wound healing IL-24 was released suggesting that it could have a role in this process[17]. Therefore, the true conditions of the endometrial tissue are not accurately mimicked with these women.

Decidual CD8+ T-cells and progesterone:
Decidual CD8+ T-cells (CD8+dt cells) recognise and respond to foreign foetal, placental, and viral antigens as they are key cells in protecting the immune system from foreign infections. Therefore, it is crucial that their activation is regulated in order to maintain a healthy pregnancy[18]. Liu et al[19] performed an in vitro study that looked at the phenotype and transcriptional characteristics of decidual-derived CD8+ T-cells. They found that CD8+dt cells may undergo a specific type of TEM (effector T-cell) differentiation that causes them to be dysfunctional which was shown by their high expression of exhaustion-related molecules: Pd-1, Cd39 (figure 4A). They also showed residency because they had high expression of CD103 compared to peripheral CD8+ T-cells. These CD103+CD8+dT had low expression of Granzyme B suggesting compromised cytotoxicity (figure 4B) but showed higher levels of intracellular IFN-γ (figure 4C) which could indicate that that they are still capable of defending the foetus against pathogens. This confirmed the findings of a previous study that showed that although the activity of CD8+dt cells was reduced during pregnancy when they were activated produced pro-inflammatory cytokines so were not completely suppressed[18]. Overall Liu et al reemphasised previous findings and provided a novel understanding of the phenotype of CD8+ dt cells that previous papers failed to do. However, a limitation of this study is that the scientists did not provide a mechanism of what causes these CD8+dt cells to alter their function during pregnancy.

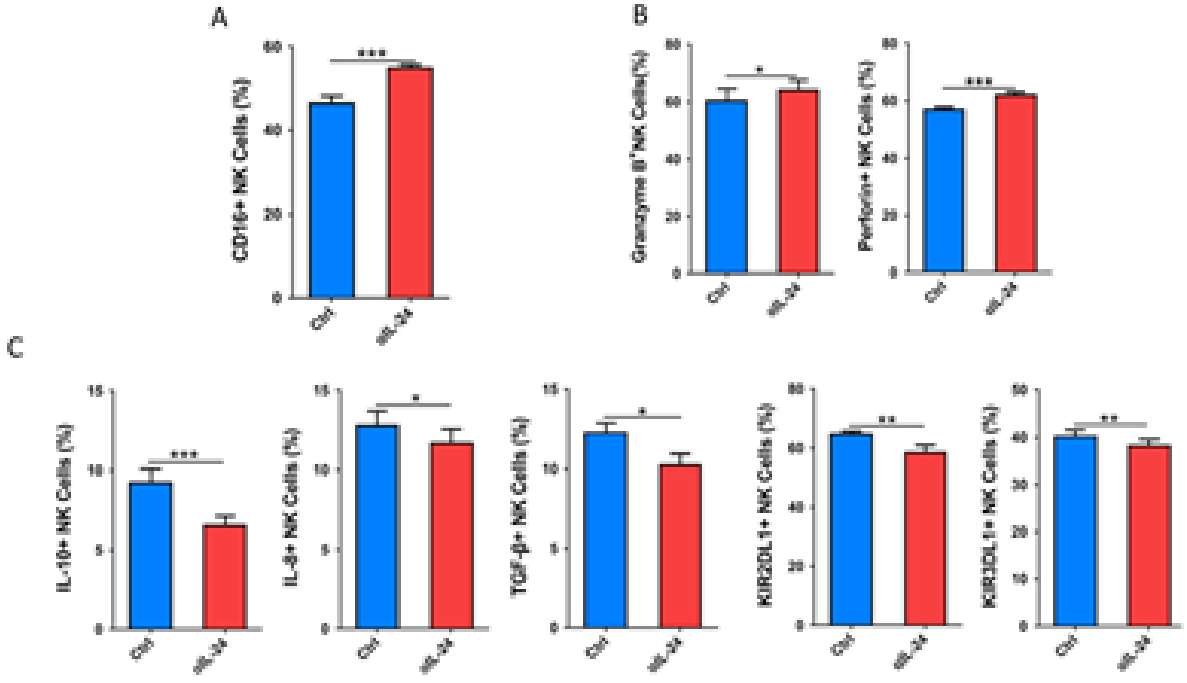

***Figure 3**: IL-24 derived from DSCs influence the differentiation of dNK.*

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Lissauer et al[20] previously highlighted that the potential mechanism that gives CD8+dt cells this unusual profile that enables maternal-foetal tolerance was progesterone. They found that with administration of progesterone at concentrations like pregnancy (10um) the polyfunctional cytokine profile of CD8+ cells and their proliferation rate were statistically significantly reduced causing the T-cells to be in a mature state. This could suggest that progesterone is what triggers the CD8+dt cells to undergo the specific type of TEM differentiation suggested by Liu et al which causes them to become less polyfunctional and more exhausted. Lissauer et al also found that progesterone decreases the level of pro-inflammatory cytokines released by CD8+dt cells in a dose-dependent manner. This could indicate that where the levels of progesterone are lower the CD8+dt cells retain their cytotoxicity and are able to fight away infections during pregnancy, but closer to the foetus where the levels of this hormone are higher the profile of this T-cell changes to permit foetal tolerance. Therefore, this may provide an explanation as to why high levels of INF-γ were seen in the Liu et al study.

Taken together Lissauer et al and Liu et al provide a more comprehensive mechanism that explains how the phenotype of CD8+ t-cells changes during pregnancy.

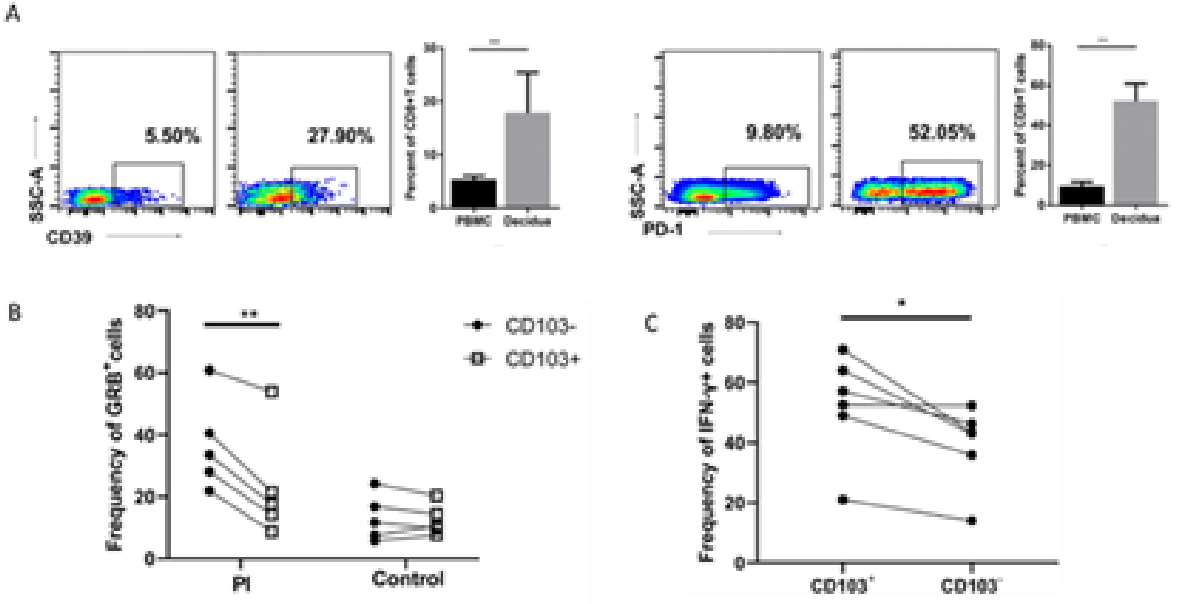

Figure 4*: : How CD8+dt cells change during pregnancy.*

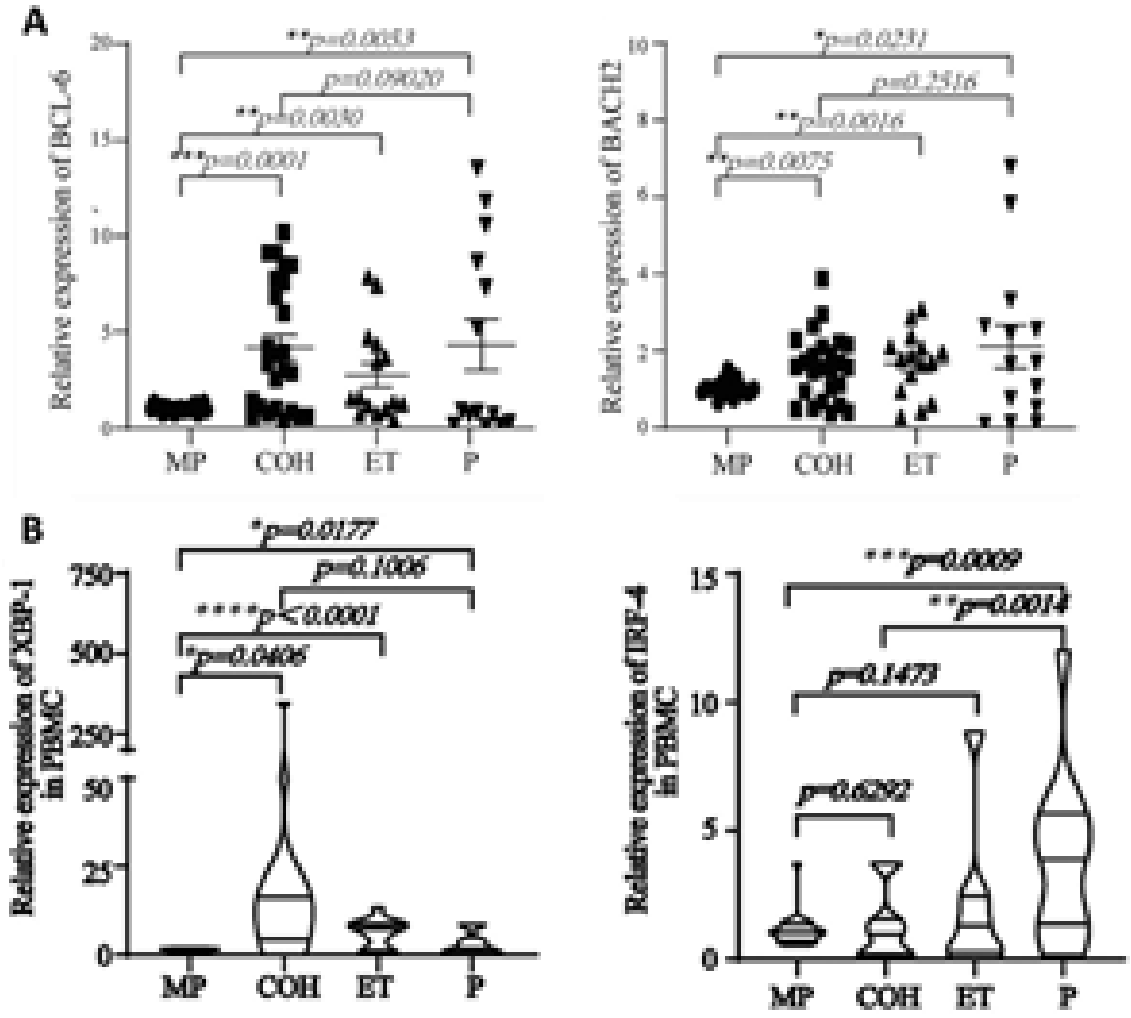

Figure 5*: How oestrogen can manipulate the function of Tfh cells.*

Oestradiol can manipulate Tfh cells:

T follicular helper cells (Tfh) are a subset of CD4+ T-cells so help promote B cell antibody production. During pregnancy it has been found that its essential that the accumulation of Tfh cells (which favours Th2 and balances Th1/Th2 immunity) is done in a timely manner for the pregnancy to be successful. This is because excessive or lack of accumulation could result in a miscarriage[21]. Hu et al[22] wanted to investigate if the function of Tfh could be manipulated by oestradiol in humans. They found that upon E2 exposure, a forward loop was formed in which GPER1 (G Protein-Coupled Oestrogen Receptor 1) was activated to increase BCL6 and BACH2 (functional genes for Tfh cells) and XBP1 and IRF4 (transcription factors involved in stages of B cell differentiation) therefore driving Tfh and plasma cell augmentation (figure 5).

Overall, the findings from this study[22] emphasise the need to add Tfh to the paradigm of T-cells that are crucial in pregnancy and illustrate how hormones work together with immune cells to maintain foetal tolerance.

A limitation of this study[22] was that they only looked at the expression of Tfh and the effects of oestrogen up to 9 weeks of gestation. Tfh cells have shown to be present abundantly in mid and late pregnancy. However, enhanced Tfh cell accumulation in the uterus and placenta has also been correlated with increased foetal reabsorption that is caused by PD1 blockade which enhances foetal rejection[23]. This shows how the expression of Tfh cells changes at the different stages of pregnancy and illustrates what could happen if this expression is not controlled. Therefore, by limiting their study to only 9 weeks of gestation Hu et al do not demonstrate whether the manipulative effects oestrogen has on Tfh cells are beneficial throughout the entire pregnancy.

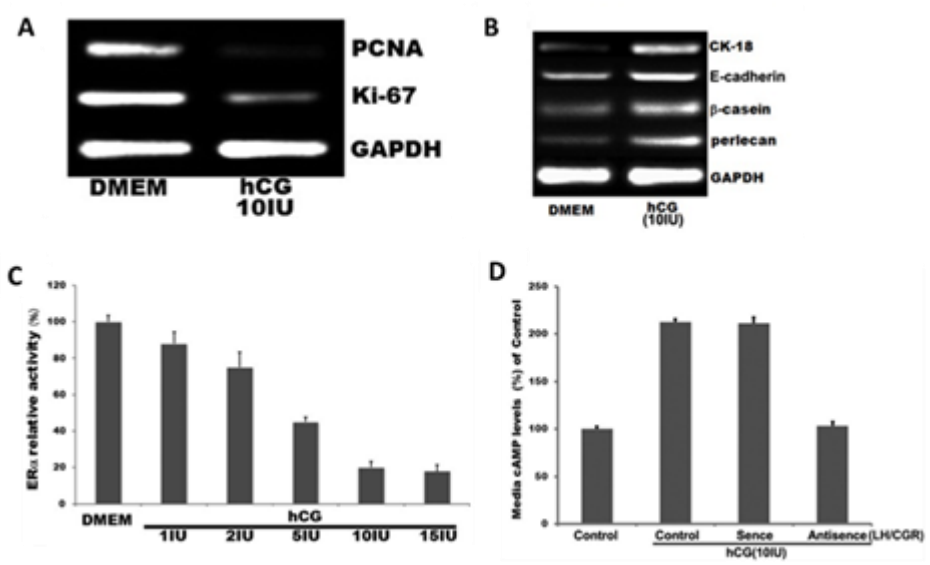

***Figure 6**:The role hCG has on human breast cancer cell line.*

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hCG may regulate human breast cancer cells:

Liao et al[24] wanted to investigate what affect hCG had on human breast cancer cell lines (MCF-7 cells) and its mechanism. They found that hCG inhibits the growth of MCF-7 cells and promotes cell differentiation by suppressing the expression of proliferation markers, PCNA and Ki-67 (figure 6A) and increasing the expression of differentiation markers, β-casein, perlecan, CK18, and E-cadherin (figure 6B). MCF-7 cells with high expression of hCG had reduced Erα (Oestrogen receptor alpha) expression (which can promote breast cancer cell motility and invasion) and increased cAMP expression (figure 6C+D), suggesting that hCG may control the breast cancer progression by stimulating the LH/hCGRs (luteinizing hormone/hCG receptors) to activate the cAMP signalling pathway.

A limitation of the study done by Liao et al was that they used a medium containing both hCG and LH (luteinising hormone) which activate the same signal transduction pathway. Therefore, it makes it hard to distinguish if the results obtained in the study were due to only the effects of hCG. In fact, a study down in 2021 that tested the effects of hCG without serum on MCF-7 breast cancer cell lines found that the hormone had the opposite effects as it stimulated their cell proliferation rendering the cancer cells more prone at colonizing primary organs and metastasize[25]. Since there are conflicts in the literature regarding the role of hCG in breast cancer further studies need to be done.

Conclusion:

Advancements in the field of research have provided more understanding to the different mechanisms in place that allow for a successful pregnancy. But there are still gaps in the literature that need addressing. Below are two future experiments that could help address some of the gaps there are in the literature and provide a more robust answer to the literature question posed in this review.

Looking at the whole gestation period:

PBMCs could be obtained by collecting blood samples from a large cohort of pregnant women and a control group (non-pregnant/pre-pregnant women) and single-cell RNA sequencing could be used to identify the PBMCs. Single-cell RNA would be more useful than traditional RNA-sequencing in this case because RNA-sequencing is used on bulk cells whereas single-cell RNA sequencing of PBMCs can provide a more in-depth analysis of the gene

expression of individual immune cells. Thus, revealing any new immune cells that are involved in maintaining maternal-foetal tolerance that have not yet been identified and providing a more accurate picture of the expression of these individual cells at various stages of pregnancy[26]. To increase the accuracy of the results it would also be important to make sure that this is the women's first pregnancy so that it eliminates the possibility of the women having had previous pregnancy complications and to exclude any women that have any uterine abnormalities or immune system diseases that could affect the pregnancy[27]. To reduce cohort heterogeneity, it would be beneficial to collect the blood samples of the patients at various stages of their pregnancy. To further validate the results post-partum blood samples should also be collected. This is because it has been recently suggested that there is existence of long-term immunological memory of pregnancy (IMOP) which may provide evolutionary advantage for future successful pregnancies[28].

Role of pregnancy hormones in breast cancer:

To address this scientist could use patient derived xenograft models. This means extracting human breast tumour and injecting it into the mouse. The advantage of using this model is that it can represent the biology and heterogeneity of breast cancer and can recreate the tumour microenvironment[29]. The sex hormones could be injected separately into separate mouse models at similar concentrations as to what they are in pregnancy. The effects the hormones each have on the breast cancer could be determined by measuring the tumour burden in the mice and comparing them to the control group. However, the disadvantage of this is that the mouse models are immunocompromised which means they don't truly mimic the conditions that are present in humans[30].

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