Sex & the Immune Response: Why Taking Sex into Account is Essential to New Immunoregulatory Approaches for Treating Breast Cancer

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The immune system plays an important role in the development of cancer, and immune cells have recently become targets for treatments. The immune systems of males and females have important sex-based differences that depend, in part, on differential responses of immune cells to steroid hormones, such as estrogens, progesterone, and androgens. This essay, drawing from insights and advocacy from social scientists, argues that therapeutic interventions and research with animal models should take sex into account because there are many sex-based differences that affect immunocompetence, susceptibility to infection, and severity of illness. The development of therapies that target the immune cells in cancer patients should be sex/gender inclusive, considering differential immune responses in men and women.

The Immune System

The immune system detects and protects against disease by recognizing and responding to various stimuli (antigens), and it is affected by both gender and sex (Klein, 2012; Fish, 2008). The immune system receives regulatory signals from an extended network of cells

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8 Immunocompetence is the ability to produce an effective immune response following exposure to an antigen
9 Antigen is a toxin or other foreign substance that induces an immune response in the body
and tissues, which are affected differently by sex and gender. As therapies targeting the immune system are being developed to treat cancers, taking sex differences into account will be crucial to their success. This article aims to share with a broad social science audience some of the ways in which sex/gender and health concepts and research approaches—many of which have been spearheaded by social scientists—have been incorporated into, and are transforming, bench science fields such as neuroscience (Einstein, 2012) and immunology (Klein, 2010; Matzinger, 1994).

How is the immune system involved in cancer? The immune response is mediated by many types of cells that play important roles in anti-tumour immunity\(^{10}\), including B cells\(^{11}\), T cells\(^{12}\), natural killer (NK)\(^{13}\) cells, dendritic cells (DC)\(^{14}\), and granulocytes. These cells interact with each other to regulate inflammation, which could be useful for fighting harmful antigens, but may also harm the patient’s own tissues in an attempt to remove the injurious stimuli. On the one hand, inflammatory environment can suppress tumour growth by destroying cancer cells or inhibiting their outgrowth; on the other hand it can also promote tumour progression by selecting tumour cells that are more fit to survive under such conditions.

The presence of immune cells within tumours may lead to inflammation, which is an important factor in regulating tumour growth and metastasis\(^{15}\) (Schreiber, 2011). The immune cells within the tumour microenvironment\(^{16}\) communicate with each other through direct contact or by producing signaling molecules (cytokines & chemokines)\(^{17}\) that regulate and shape tumour growth (Grivennikov, Greten & Karin, 2010).

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\(^{10}\) Anti-tumour immunity is the ability of a patient’s immune system to eliminate a cancerous growth

\(^{11}\) B cells are white blood cells that recognize antigens and secrete specific antibodies to destroy them. Antibodies are blood proteins produced by B cells in response to specific antigens

\(^{12}\) T cells are white blood cells that orchestrate the immune system’s response to infected or cancerous cells

\(^{13}\) Natural killer (NK) cells are immune cells that provide rapid responses and kill cells undergoing a cancerous transformation without requiring help from other immune cells

\(^{14}\) Dendritic cells (DC) are immune cells that process antigens and present these to other cells

\(^{15}\) Metastasis is the spreading of cancer cells away from the primary tumour to form new secondary malignant growths

\(^{16}\) The tumour microenvironment is the area surrounding tumours, consisting of immune cells, stromal cells, blood vessels, soluble molecules, and tumour cells.

\(^{17}\) Cytokines and chemokines are proteins secreted by cells to communicate with each other and to recruit immune cells to sites of inflammation
B cells produce specific tumour-associated antigens to activate other immune cells, and produce antibodies\(^{18}\) and cytokines in response to signals of danger. They also play a key role in the activation of the complement system\(^{19}\), which helps clear pathogens from the organism. T cells scan the body for foreign invaders and can directly kill infected or cancerous cells. T cells recognize specific targets through their T cell receptor after being alerted by an antigen presenting cell (like a B cell or DC), and produce cytokines to regulate inflammation; they are also important because they activate other immune cells, such as B cells. NK cells provide rapid responses to cells infected with a virus or undergoing a cancerous transformation; they can directly kill these cells and release cytokines that signal other immune cells to control a cancerous growth or infection. DC are the most important antigen-presenting cells; they shape the immune response by directly interacting with other cells and by producing cytokines. Other cells, including macrophages, monocytes, and neutrophils, provide a rapid and non-specific response to antigens by clearing the cellular debris from sites of inflammation, engulfing and digesting infected cells (phagocytosis), producing cytokines, and presenting antigens to T cells.

Anti-tumour Immunity: In the context of the immune system, anti-tumour immunity means that the patient responds effectively and eliminates a cancerous growth. In contrast, immune tolerance means the inability to respond to a cancer. Effective engagement of the immune system is a crucial first step in tumour elimination: although some tumours express immunogenic\(^{20}\) antigens that activate the immune system and may make tumours susceptible to treatments with antibodies or cancer vaccines, this kind of treatment has yielded limited success. Additionally, the immune system is rarely able to eliminate tumours that have already established over time.

Researchers have offered various explanations for the failure of treatments involving antibodies or vaccines, including the possibility of active immune suppression occurring within the tumour microenvironment (Zou, 2005). Tumour cells may evade an immune system response by exploiting natural immunosuppressive mechanisms, because they can limit an individual’s ability to eliminate the cancer cells by blocking the action of immune cells. Interestingly, research has shown that mice can successfully fight tumours and can effectively eliminate a secondary graft of the same tumour cells that is injected far from the

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\(^{18}\) Antibodies are blood proteins produced by B cells in response to specific antigens  
\(^{19}\) The complement system helps antibodies and other immune cells clear pathogens from an organism  
\(^{20}\) Immunogenic cancers can elicit tumour-specific immune responses in patients, which may help a patient’s body to rid itself of a developing tumour
primary tumour site (Woglom, 1929; Hanahan & Weinberg, 2011). Cells that regulate the immune response within the microenvironment of a primary, established tumour may suppress local inflammation but permit immune responses in other parts of the body. This means that eliminating a cancerous growth may require targeting mediators of immune suppression in the tumour.

**Sex/gender Differences in Immunity**

There are sex/gender differences in the immune systems of males and females. For example, male mice and male humans are more likely than females to have more severe and more frequent bacterial, viral, fungal, and parasitic infections (Klein, 2000). In contrast, females tend to have more robust immune responses to antigenic challenges, such as infection and vaccination (Klein et al., 2010). Consequently, women consistently report more frequent and severe reactions to viral and bacterial vaccines than men (Klein et al., 2010; Cook, 2008). Although females may have a superior immune response, which can result in faster infection clearance, they are often more likely to develop *immune-mediated pathology* (Meier et al., 2009). For example, women worldwide are 2–6 times more likely to die from H5N1 avian influenza, partly due to heightened immune responses (Klein, 2012). Females are also more at risk for developing many autoimmune and inflammatory diseases than males; 80% of patients with autoimmune diseases are women (Voskuhl, 2011). In contrast, men are 1.6 more likely than women to die from all malignant cancers (Cook et al., 2011).

**Genes & steroid hormones affect the immune system:** Differences in both gene expression and sex steroid hormones help establish variability in immune responses between males and females. Genetic differences between males and females affect the immune system by the different genes present on the X and Y chromosomes. The X chromosome contains many genes that are involved in immune responses (Candore et al., 2010). It also contains 10% of all *microRNAs* (miRNAs)21 in the human genome, while the Y chromosome does not contain any (Pinheiro et al., 2011). miRNAs are critical regulators of the immune response, affecting the expression of molecules involved in immunity.

Steroid sex hormones also affect the quantity and functioning of immune cells, and these effects may differ in males and females. Table 1 lists some of the known effects of sex hormones, such as estrogens, progesterone, and androgens on immune cells.

**Table I. The Effects of Steroid Sex Hormones on Immune Cells that Play an Important Role in Anti-cancer Responses**

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21 MicroRNAs are small RNA molecules that regulate the transcription of genes
<table>
<thead>
<tr>
<th>Hormones</th>
<th>Estrogens</th>
<th>Progesterone</th>
<th>Androgens</th>
</tr>
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<tbody>
<tr>
<td><strong>B cells</strong></td>
<td>↓ B cell production in bone marrow</td>
<td>↓ antibody production</td>
<td>↓ antibody production</td>
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<tr>
<td></td>
<td>↑ antibody production</td>
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<td>↑ escape from negative selection</td>
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<td>↑ stimulation of antibody production</td>
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<td></td>
<td>↑ # of regulatory T cells</td>
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<td>↑ recruitment of T cells</td>
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<td><strong>T cells</strong></td>
<td>↓ # of developing T cells</td>
<td>↑ differentiation of regulatory T cells</td>
<td>↑ pro-inflammatory T cell responses</td>
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<td></td>
<td>↑ escape from negative selection</td>
<td>↑ stimulation of antibody production by B cells</td>
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<td></td>
<td>↑ recruitment of T cells</td>
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<tr>
<td><strong>Natural killer (NK) cells</strong></td>
<td>↓ cytotoxicity of NK cells</td>
<td>↓ NK cell activity</td>
<td>↓ NK cell activity</td>
</tr>
<tr>
<td><strong>Dendritic cells (DC)</strong></td>
<td>↑ differentiation of DC</td>
<td>↓ DC cell activity</td>
<td></td>
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<tr>
<td></td>
<td>↑ development of regulatory, tolerogenic DC</td>
<td></td>
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</tr>
<tr>
<td><strong>Macrophages, monocytes, neutrophils</strong></td>
<td>↓ neutrophil ability to travel to sites of inflammation</td>
<td>↓ macrophage cell activity</td>
<td>↓ activity of macrophages and monocytes</td>
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<tr>
<td></td>
<td>↑ nitric oxide synthesis</td>
<td>↑ neutrophil ability to migrate to sites of inflammation</td>
<td></td>
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<tr>
<td></td>
<td>↓ production of proinflammatory cytokine by macrophages and monocytes</td>
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</table>

*The summarized points in this table are compiled from various studies that are referenced throughout the paper*

Estrogens are associated with inflammation, but they may have different effects in males and females (Candore et al., 2010). The reactivity of T cells, which are important in anti-cancer immune responses, is suppressed by 17β-estradiol (a type of estrogen), and this effect is more prominent among T cells in women than in men (Moulton et al., 2012). Estrogens also increase antibody production by B cells and increase the number of self-reactive B cells, which may make an
individual more susceptible to autoimmune diseases\textsuperscript{22} (Grimaldi et al., 2005).

Progesterone is another steroid sex hormone that has immunoregulatory effects. It has been implicated in modulating the development of DC toward a more regulatory, suppressive function, but this inhibitory effect is different in male and female rodents. For example, progesterone has a stronger anti-inflammatory effect on mature DC from female rats compared with male rats, as measured by pro-inflammatory cytokine production (Butts et al., 2008). Progesterone also decreases antibody production by B cells (Lu et al., 2002) and enhances immunoregulatory responses during pregnancy (Bouman et al., 2005).

Androgens, such as testosterone and dihydrotestosterone, are thought to mainly suppress the activity of immune cells. Androgens reduce the production of antibodies by B cells and decrease the activity of NK cells, as well as macrophages and monocytes. For example, men with Klinefelter’s syndrome\textsuperscript{23} have low testosterone levels and increased antibody levels (Sakiani, Olsen & Kovacs, 2012, Tanriverdi et al., 2003).

Together, these findings confirm that sex hormones affect the kinetics and magnitude of differential immune responses between males and females (Klein, 2012).

Life stages affect the immune system: Immune responses also differ during different female reproductive phases. Variations in estrogen and progesterone levels during the menstrual cycle influence populations of T cells. Hormonal changes just prior to ovulation lead to suppression of the immune system (Fish, 2008). Over the course of the menstrual cycle, estrogen increases the number of regulatory T cells, which are important for suppression of immune responses. When estrogens are rising and high (follicular and ovulation phases) regulatory T cells are high in number; when estrogens are falling and low (luteal phase and menses), regulatory T cells are low in number (Pennell et al., 2012). Shifts in reproductive hormone levels during pregnancy can also alter the immune response (Klein et al., 2010), and immune cells express progesterone receptors during pregnancy (Bouman et al., 2005). Autoimmune diseases such as rheumatoid arthritis and multiple sclerosis often enter remission during pregnancy, and treatments for autoimmune disorders involving estrogens have shown promise (Fish, 2008). For example, estriol (E3), the estrogen made only during

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\textsuperscript{22} Autoimmune diseases develop when the body’s immune response is inappropriately targeting the body’s own substances and tissues

\textsuperscript{23} Klinefelter’s syndrome is a genetic disorder where there is at least one extra X chromosome to a standard male karyotype (XY)
pregnancy, promotes the generation of tolerogenic, regulatory DC that may protect against autoimmunity (Papenfuss et al., 2011).

**Social & environmental factors affect the immune system:** Social and cultural factors are also important determinants of disease susceptibility, because gender influences patterns of exposure to infections and treatments. Gender roles influence where and how men and women spend their time and the healthcare they receive (Anker, 2007). For example, in certain societies, fatality rates from measles are higher among females than among males, because girls are more likely to stay at home, thereby increasing their exposure to diseases of siblings and increasing their risk of infection (Fish, 2008). The World Health Organization (WHO) has also reported important gendered differences in access to healthcare, which can affect the level of care given to males and females. A study conducted in Kolkata, India, for instance, revealed that boys with diarrhoea were more likely than girls to be rehydrated and taken to qualified health professionals (Anker, 2007).

Therefore, sex and gender differences affect how the immune system responds to infection (immunocompetence), susceptibility to infection, and severity of any resulting illness (Fish, 2008), underscoring the need for therapeutic interventions and research with animal models to take sex into account.

**Breast Cancer**

*Sex/gendering breast cancer:* Breast cancer is a malignancy with a strong female bias. It is the most common cancer among Canadian women, accounting for 28% of all newly diagnosed cancer cases. It affects one in nine women over their lifetime (Canadian Cancer Society, 2012). This realization has led to some of the most significant progress in women’s health as a social cause since the 1970s (Schulzke, 2011). Many concrete advances emerging from this activism include the use of women’s bodies in clinical trials and research, as well as women gaining autonomy to make healthcare and treatment decisions (Sweeney, 2012).

However, some diseases are more embedded in cultural meaning than others (Conrad, 2010), and breast cancer patients may be pressured to conceal their disease, because it attacks one of the stereotypical signs of femininity (Schulzke, 2011), threatening a woman’s sense of her gender. In spite of this – or, perhaps, because of this - breast cancer has been relatively ignored in men. Although one in every 150 breast cancers occurs in males. Because breast cancer is gendered, treatments for men are currently founded on extrapolations and assumptions based on the trends observed in female breast cancer patients (White et al., 2011). Most male breast cancers have estrogen and progesterone receptors, so as in women, treatment usually involves hormonal therapies (e.g., tamoxifen), thereby threatening their gender, undermining masculinities. Most men
report adverse effects of this treatment and, in fact, there are no conclusive data available about the efficacy of this treatment for men (Nahleh & Girnius, 2006). In spite of the fact that breast cancer is thought to be a woman’s disease, it must be studied in males as well as females in order to optimize treatments for men.

The development of breast cancer, in both females and males, is affected by the patient’s immune response. Sex-specific aspects of the immune system appear to play a role in cancer progression. As well, treatments targeting the immune systems of patients may prove beneficial, but to develop successful immunotherapies it will be necessary to consider the differences in immune responses between males and females and between different female reproductive phases. For example, current hormonally based therapies affect the relative abundance of various biologically active estrogen metabolites that are involved in the regulation of inflammation (Islander et al., 2011). Therefore, it is important to investigate how existing breast cancer treatments affect immune cells in both sexes. Unfortunately, it is still rare in animal and cell-based research to use females as experimental subjects (Beery & Zucker, 2011). Despite the fact that 99% of breast cancer occurs in women, male mice are often used in breast cancer models used to inform the treatment of female breast cancer patients.

Thus, we have the double edged problem: the disease is gendered female so males are excluded from the development of therapies, but the basic animal model used for research is male, thereby excluding female biologies from the early research into the disease.

**Using the Immune System to Fight Cancer**

*Cancer immunotherapy*: Immunotherapy is a kind of treatment that uses the body’s own immune system to help fight cancer by stimulating immune cells to attack tumour cells. One approach is to immunize the patient with cancer vaccines, which trains the immune system to recognize cancer cells as targets. Another approach is administering therapeutic antibodies, which help activate immune cells and target them to tumour sites. Cell-based immunotherapies involve isolating immune cells, activating them outside the body, and then transfusing them back into the patient with the goal of enhanced killing of tumour cells (Waldmann, 2003). Recent research has focused on removing the ability of growing tumours to suppress and inhibit the actions of immune cells.

*Immune inhibitory receptors*\(^\text{24}\): One approach to breast cancer treatment would be through enhancing immune function by removing the biological factors in the tumour microenvironment that suppress the

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\(^{24}\) Immune inhibitory receptors are molecules that regulate many types of immune responses by suppressing the action of immune cells.
action of immune cells and prevent them from destroying cancer cells. One type of such biological factors is the family of inhibitory receptors of the immune system. These *immune inhibitory receptors* are the “brakes” of the immune responses, and they are important for the maintenance of *tolerance*\(^{25}\) to various antigens; they prevent immune cells from becoming over-activated, which could damage the body’s own tissues and lead to chronic inflammation and autoimmunity. Tumour cells can hijack these immune system inhibitory pathways for their own benefit, forcing the immune cells in the tumour microenvironment to remain inactive and ignore the cancer cells. (Pardoll, 2012). Stopping this exploitation of natural immune inhibitory pathways by tumour cells has become an important target in the fight against cancer.

Clinical trials involving antibodies that block immune inhibitory receptors, such as Cytotoxic T-lymphocyte antigen 4 (CTLA4) and Program Death 1 (PD-1), have already yielded promising results for the treatment of various cancers. For example, CTLA4 blockade is being used successfully to treat melanoma patients in advanced stages of the disease (Pardoll, 2012). Many other inhibitory immune interactions remain to be characterized and could be useful for breast cancer in both females and males, but in developing them as treatments, it will be necessary to take sex differences in the anti-tumour immune responses into account.

**Role of the CD200-CD200R interaction in cancer:** One immune inhibitory receptor is CD200R, which interacts with the CD200 biomolecule to regulate immune responses. CD200 levels are elevated in patients with various cancers including: renal, colon, and ovarian carcinomas; melanoma; multiple myeloma; acute myeloid leukemia (AML); and chronic lymphocytic leukemia (CLL) (Moreaux *et al.*., 2006; Siva *et al.*, 2007; Tonks *et al.*, 2007). Elevated CD200 has a negative effect on likelihood of survival; expression of CD200 on cancer cells has been correlated with poor chances of recovery among AML patients (Tonks *et al.*, 2007). Clinical trials of a molecule that blocks CD200 (an antibody to CD200; anti-CD200) reduced tumour size in leukemia-lymphoma patients (Mahadevan, 2010).

CD200 interacts with its receptor, CD200R; activation of this receptor has a dampening effect on the immune response to cancer (Wright *et al.*, 2003). Injecting CD200 molecules into mice with thymoma tumours increased tumour growth (Gorczynski *et al.*, 2001), and anti-CD200 antibodies have reduced the growth of RAJI and Namalwa cancer

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\(^{25}\) Immune tolerance is the process by which the immune system does not attack an antigen
cells in immunodeficient mice (Kretz-Rommel et al., 2007). These findings suggest that the presence of CD200 on tumour cells may identify cancer cells that are better able to evade the patient’s immune system (Kawasaki et al., 2007).

A Model for Breast Cancer Immunotherapies that Takes Sex Differences Into Account

We are currently investigating the role and mechanisms of action of CD200 in breast cancer using female mice; our goals are a) to clarify how CD200 regulates cancers in females, and b) to provide a knowledge base that is biologically appropriate for the affected population. In our mouse model, EMT6 breast cancer cells are injected into healthy female mice, where they grow into established tumours after a 16–18 day period. In the absence of an immune system (i.e., in cell culture) EMT6 breast tumour cells do not express CD200 on their surface. However, when EMT6 cells are injected into mice with intact, healthy immune systems, these cells begin to produce CD200 molecules on their surface (Gorczynski et al., 2010). As in the absence of an immune system, in the presence of a compromised immune system (immunocompromised), an increased production (upregulation) of CD200 is not observed. Thus, in female mice, a competent immune system appears to promote the expression of CD200 on the surface of breast cancer cells. CD200 can bind to its receptor on the host’s immune cells within the tumour microenvironment and potentially inhibit an immune system response against the tumour. Thus, cancer cells can hijack the body’s own immune system to protect themselves from being eradicated by the host’s immune system.

Overexpression of CD200 is associated with increased production of transforming growth factor β, an important molecule in the regulation of immunity that blocks activation of various immune cells. In mice, CD200 also stimulates regulatory T cell development, which prevent an inflammatory immune response and may protect breast tumour cells from the host’s anti-tumour inflammation and result in more tumour growth and metastasis (Gorczynski & Clark et al., 2011).

Investigating the source of CD200 in the female mouse: CD200 regulates tumour growth, but it is not clear whether CD200 is produced by tumour cells, or whether tumour cells cause immune system cells to produce it. This is important to understand, because our goal is to target CD200 molecule to regulate breast cancer. Since CD200R is an immune

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26 Immunocompromised (immunodeficient) means that the immune response is reduced or absent

27 Inflammation is a protective tissue response to injury, involving the recruitment of immune cells
inhibitory receptor, blocking the CD200-CD200R interaction can remove the “brakes” on the immune response and allow for activation of immune cells to eradicate cancer cells. In order to better understand the relationship between CD200 production, the immune system and tumour cells, we genetically modified female mice and the EMT6 cancer cells we inject into them, obtaining various levels of CD200 and its cell surface receptor, CD200R. This allows us to investigate whether the necessary immunosuppressive effect of CD200 expression to promote cancer metastasis comes from host’s immune cells or breast tumour cells.

While increased inflammation due to blocked CD200-CD200R interaction can reduce the progression of some tumours, it may facilitate the growth and metastasis of other cancers that can use the host’s inflammatory response for their benefit. EMT6 breast cancer cells appear to be susceptible to inflammation, while other types of mouse breast cancer cell line, such as 4T1, seems to flourish under inflammatory conditions. Since in humans inflammatory breast cancer is a rare and aggressive type of the disease that progresses rapidly (Makower & Sparano, 2013), we reasoned that comparing EMT6 and 4T1 mouse breast cancer models might be a robust comparison that would help clarify the biology of breast cancers that thrive under inflammatory conditions.

In addition to our experiments involving mice, we are currently investigating CD200 expression in humans. Specifically, we are assessing the levels of soluble CD200 (sCD200) in the plasma of breast cancer patients, correlating our findings with tumour characteristics and disease stage. We hypothesize that sCD200 levels in the serum of cancer patients may help define subsets of both female and male cancer patients with different prognoses and responses to treatment.

CD200 & sex: Little is known about how the effect of CD200 - CD200R interaction differs depending on sex. One recent study reported that CD200 receptor signaling deficiency in females significantly affects the clearance of viral infection (Karnam et al., 2012). It would be interesting to see if that were also the case in males. This finding raises important issues about widely used mouse models, and may require a reinterpretation of previous research. Since many cancer treatments targeting immune inhibitory interactions have been investigated in mice without consideration of their sex, re-visiting such studies using sex/gender inclusive framework will be important for successful therapeutics.

CD200 is not only important in cancer biology but also in development. It is expressed by trophoblasts (cells that provide nutrients to the embryo) and by cells in the maternal uterine lining. Blocking CD200 in pregnant mice increases spontaneous abortions. If a soluble form of CD200 is injected, spontaneous abortions are drastically reduced
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(Gorczynski et al., 2002). Thus, CD200 may play an important role in increasing a mother’s immunological tolerance—or reducing immune response—to the fetus during pregnancy. A Phase I clinical trial assessed its possible application to treat recurrent pregnancy loss in humans (Clark, 2008). The effect of CD200 on pregnancy outcome further supports the need to consider female sex when developing anti-CD200 therapies for cancer, because such treatments may have adverse effects on pregnant women with cancer. It would also be interesting to investigate whether blocking CD200 affects menopausal women in a different way since estrogen levels differ between pre-menopause and menopause. By allowing the answer to still open questions such as these, our work demonstrates that, previous CD200 studies can be improved by using female as well as male mice in the future.

Sex and reproductive phase differences are extremely important in scientific research, clinical trials, and vaccine studies (Klein & Jedlicka & Pekosz, 2010; Kim, 2010); biological differences associated with sex can have major effects on the immune response. CD200 blocking antibodies are currently being used in clinical trials in women for cancer treatment, as well as to block increased inflammation and immune-mediated pathology during infections.

CONCLUSIONS

Although breast cancer mortality rates have declined over the last several decades, 62 Canadian women are diagnosed with breast cancer every day (Canadian Cancer Society, 2012). Many aspects of anti-tumour immune responses have already been clarified, resulting in the development of novel cancer immunotherapies (Lesterhuis et al., 2011). However, the success of these therapies depends, in part, on the sex of the patient corresponding to the sex of the animal model. Genetics, steroid sex hormones, and gender influence the development, maturation, activation, and death of immune cells (Verthelyi, 2001) (Table 1). By clarifying the physiology of the interaction between sex/gender and immune function, it may be possible to learn more about the development of cancer and possible new directions for treatment. We believe that experiments involving mice that take sex into account can help clarify possible sex-based differences in responses to cancer immunotherapy before translating treatments to human patients.

We hypothesize that targeting the interaction of CD200-CD200R interaction and the environment that promotes this interaction may lead to promising new therapeutic options for strengthening women’s and men’s own anti-tumour responses in breast cancer. However, these effects should be studied in both female and male mice before therapeutic application to either sex. As we continue our research on
cancer immunotherapies, it will be important not only to increasingly involve females in both the experimental models and the clinical trials, but perhaps most importantly so when testing immunotherapies, since there are well-established sex differences in immune responses. The increasing consideration of sex/gender in biomedical research, drawing from insights and interactions with social science approaches to sex/gender and health research, facilitates exciting new dialogues between social and basic sciences, which help frame health research to target effective cancer treatments for both men and women.

REFERENCES

Canadian Cancer Society (2012). Breast Cancer Statistics at a Glance. Abstract 2465 entitled “First-in-Human Phase I Dose Escalation Study of a Humanized Anti-CD200 Antibody (Samalizumab) in Patients with Advanced Stage B Cell Chronic Lymphocytic Leukemia (B-CLL) or Multiple Myeloma (MM),” presented in a poster session at the 52nd American Society of Hematology (ASH) Annual Meeting and Exposition, December 5, 2010, at 6:00 p.m. by Dr. Daruka Mahadevan.


Meier, A, Chang J.J., Chan, E.S., Pollard, R.B., Sidhu, H.K., Kulkarni, S., Wen, T.F., Lindsay, R.J., Orellana, L., Mildvan, D., Bazner, S.,


