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Chapter 3

Sex and Sex Hormones in Tissue Homeostasis

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Abstract

Women are not small men. Sex-specific differences do not only affect the classical target organs of sexual differentiation and reproduction, but have been found to involve most, if not all the organs and tissues in the body. One of the consequences of this dimorphism is that diseases manifest in a sex- and gender-specific way. Key to maintenance of a healthy state is functioning tissue able to cope with insults. Regulated death of damaged cells and replacement with new cells by proliferation is a prerequisite for maintaining tissue function taking place at different pace in the different organs. The intent of this chapter is to review current evidence for sex-specific differences in tissue homeostasis focusing on the variability of hormone exposure characteristic for the female reproductive life stages.

Keywords: tissue maintenance, sex differences, proliferation, cell death, kidney, menstrual cycle

1. Introduction

Living systems are continuously challenged by potentially toxic internal and external processes. The normal metabolic function of the cells produces a plethora of potentially damaging oxidative metabolites inducing damage in DNA, proteins, and lipids. In addition, living cells are exposed to a variety of external factors, which may be internalized as building blocks and/or energy sources. These vital processes put the organism at risk to be harmed. Coping strategies are necessary to avoid damage. There are several lines of cellular defenses induced via cell stress pathways, including compartmentalization processes, enzymatic modification, externalization, degradation, and repair [1, 2].

Ultimately, these processes may not be sufficient to prevent major cellular damage. Therefore, every cell is in addition equipped with internal cell death programs, which can be activated in order to prevent a damaged cell to cause harm to the organism [3]. Cell losses are inevitable

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and take place continuously in our bodies even without a specific trigger. The rate of cell death may be significantly enhanced at times of increased challenges. Cellular losses are necessary in order to prevent detrimental effects like neoplastic transformation [4]. Thus, programmed cell death needs to be carefully balanced, and this ability is a key determinant for the health and survival of the organism.

Cells lost by cell death need to be replaced in order to maintain cell numbers and ultimately tissue function. Controlled regeneration is, thus, required to cope for cell losses due to toxic challenges derived from internal and external sources, be they derived from normal metabolic processes or damaging environmental stimuli. Cell losses and proliferation need to be carefully balanced in order to guarantee proper function. Thus, the process of tissue homeostasis, that is, the capability to send damaged cells into cell death programs, to replace the cells by proliferation, and to regulate the exact balance of these events are crucial processes for preserving a healthy state. Any distortion of the balance between cell death and cell proliferation—be it by overwhelming damaging events beyond the host's range of tolerance and/or primarily ineffective or maladaptive homeostatic mechanisms by the host—is prone to induce malfunctioning of the organs in the body ultimately causing disease and potentially death.

2. Sex and sex hormones in tissue homeostasis

2.1. Origin of sex differences

During development, sex differences originate from genetic and hormonal influences. Master regulators for male sex differentiation, like SRY, are encoded by DNA of the Y chromosome governing the embryonic development of the male phenotype in mammals. Female or male gonadal development gives rise to a sex-specific hormonal environment [5]. Sex hormones induce organizational effects during the life span causing persistent sex-specific changes within the tissues, for example, by epigenetic modifications [6, 7]. Activational effects further introduce sex differences in tissue structure and function depending on the pattern of exposure to gonadal hormones. All the organs in the body are affected throughout life [8]. In this respect, sex differences are based on the different chromosomal equipment that qualifies every cell in the body as male or female. These basic differences are further shaped by sex hormones depending on previous or current, transient or persistent exposure [9]. This hypothesis was phrased by Arnold [10] as follows: "XX and XY cells are different prior to the secretion of gonadal hormones, and gonadal hormones affect XX and XY cells unequally."

Sex hormones act through receptors widely expressed throughout the cells of the body. The classical estrogen (ERα, ERβ), androgen (AR) and progesterone (PR) receptors belong to the nuclear receptor protein family acting through the nucleus as transcription factor or co-factor. In addition to their nuclear actions, they were found to be localized to the cell membrane and mitochondria inducing fast, non-genomic intracellular signaling pathways, for example, by the interaction with growth factor or cytokine receptors. Estrogen-binding cell membrane-localized receptors of the seven transmembrane receptor family were also characterized, for example, G-protein coupled estrogen receptor, GPR30/GPER-1 [11–13].

Ultimately, differences between the sexes derive from chromosomal and hormonal sex differences, which are further influenced by environmental factors. Thus, differences originating from the biological sex are further shaped by gender, which refers to the perceptions of male or female identity and depends on sex-based social structures [8].

2.2. Influence of sex and sex hormones on cellular proliferation

Tissue homeostasis is guaranteed, when cells lost in physiological tissue turnover or under stress conditions are replaced by proliferation. Organs with high demanding functions have increased regeneration potential and continually renew their cell populations. This is the case for intestine, skin, and blood, for example. Liver, bone, and blood even have the capacity to fully recover to the original size after loss of tissue [14]. Other organs have lower regeneration potential, like the heart, brain, and kidney [15–17]. Many organs contain stem cell niches hosting adult tissue stem cells that are precursor cells maintained in a relatively undifferentiated state ready to replace lost cells by proliferation followed by differentiation [18, 19].

Sex hormones have classically been implicated in regulation of proliferation of cells of reproductive organs and cancer of reproductive tissue [20–24]. Besides these effects, sex hormones were also found to have pronounced effects on the proliferation of different stem cell populations. Cell proliferation of embryonic stem (ES) cells was found to be enhanced by female gonadal hormones [25]. ES cells are derived from the inner cell mass of the embryoid body. They can self-renew in vitro and are pluripotent, that is, they can differentiate into all the cell types of the body [26]. Estrogen appears to act via nuclear and cell surface signaling pathways involving Erk1/2 activation, cyclin-dependent kinases and proto-oncogenes like c-myc, c-fos, c-jun, and pRB in ES cells. In addition, store-operated calcium channels were found to play a role in estrogen-mediated cell proliferation through the transcription factor NF-AT [27].

Differentiation of ES cells into dopaminergic neurons was also shown to be affected by estrogen. ERβ promoted differentiation by crosstalk signaling with insulin like growth factor-1 [28]. Motor neuron differentiation from ES cells was found to be enhanced by 17-β estradiol and progesterone through nuclear ERα and progesterone receptor [29]. Dopaminergic precursors derived from ES cells were found to increase proliferation upon treatment with progesterone in vitro [30].

Induced pluripotent stem (iPS) cells are similar to ES cells with regard to their ability to differentiate into all cell types, providing a promising tool for in vitro research and regenerative medicine. They are derived from adult mature cells by reprogramming through the introduction of specific transcription factors [31]. Similar to ES cells, sex hormones were shown to affect iPS cells. Neuronal cells derived by differentiation of iPS cells showed increased dendritic branching by treatment with 17-β estradiol [32]. Functional integration of dopaminergic neuronal cells from iPS cells into neuronal circuits was found to be enhanced by estradiol [33]. Testosterone was described to enhance differentiation of iPS cells into insulin-producing cells [34].

Sex differences were also described for tissue stem cells in vivo. Adult stem cells are believed to provide a local pool of self-renewing, multipotent cells pivotal in tissue homeostasis and

recovery upon damage [35]. Stem cells in many stem cell niches appear to have a higher ability to self-renew, have an increased regeneration potential, and in some cases, show higher proliferative activity in women [36, 37]. Intrinsic sexual dimorphism was described for neural stem cells that hold much promise for potential brain damage repair therapy in the future. Proliferation of neural stem cell was, for example, shown to depend on hormone changes in the adult mouse due to the estrous cycle, pregnancy, reproductive status, and age. Phases of high estrogen exposure like pro-estrus were found to be associated with increased hippocampal adult neurogenesis indicating a role of estrogens [38]. Differential expression of sex steroid receptors and androgen metabolizing enzymes may result in differential outcomes in neural stem cell transplantation [39]. Neural stem cell proliferation was found to be dependent on nuclear ERs, while oligodendroglial differentiation was stimulated by cell membrane-associated ERs [40]. Other researcher also proposed that actions of sex steroids on the brain might be correlated with reduced brain damage. Intact females were found to be less susceptible upon injury than ovariectomized females and males [41]. Similarly, muscle-derived stem cells derived from female mice and transplanted into dystrophic mutant mice showed a better potential to regenerate skeletal muscle than stem cells from males [42].

Hematopoietic stem cells were found to be more abundant and proliferative in female mice in comparison to males dependent on estrogen exposure [43]. 17-β estradiol was found to improve hematopoietic differentiation from human iPS cells and from human umbilical cord blood through ERα signaling suggesting a universal function for estrogen in hematopoietic stem cell differentiation [44, 45].

Estrogens have beneficial effects on bone regeneration [46]. Osteoblasts are stimulated by estrogen to proliferate with distinct roles for ERα and ERβ [47]. In vitro, proliferation of bone marrow mesenchymal stromal cells was found to be enhanced by estrogen [48]. Estrogens enhanced the proliferation and migration of bone marrow-derived endothelial progenitor cells to ischemic regions of the heart facilitating repair and regeneration [49]. Androgens were also described to stimulate the proliferation and angiogenesis/vascular repair capability of circulating endothelial progenitor cells in males, not females [50].

2.3. Sex differences in cell survival

When progenitor cells involved in tissue regeneration enter a cell senescence state, tissue homeostasis may be compromised. The cells are able to permanently halt the cell cycle and persist in a quiescent, but still functional state [51]. This is a possible fate of cells damaged beyond repair. The three major types of senescence are replicative senescence, oncogene-induced senescence, and DNA damage-induced DNA damage. The DNA damage response pathway appears to be eventually involved in the execution of the program independent of the primary stimulus [52]. Furthermore, senescent cells are able to influence their neighboring cells by secretion of a range of activating signals referred to as senescence-associated secretory phenotype. The signals may favor a pro-inflammatory or—alternatively—an immunosuppressive/pro-fibrotic state. Both phases appear to be important for successful tissue repair and the timing of the shift in the secretome might be crucial [53]. The etiology and progression of

many cancerous or age-related diseases have been shown to be influenced by the secretome of senescence cells [54–56].

Alternatively, cells may activate a cell death program as a means to ensure physiological tissue renewal or in response to overwhelming damage. The most common are type I cell death programs or apoptosis, type II or autophagy, type III or necrosis, and mitotic catastrophe [57, 58]. The cell death modalities are characterized by different morphological criteria and are executed by specific intracellular signaling cascades. Specific catabolic enzymes are typically associated with specific forms of cell death, for example, caspases with apoptosis. The pathways are interdependent. The intensity of the damage signal is often decisive for the type of cell death program that is executed or the switch from one modality to the other. In addition, autophagy is not primarily regarded as a cell death mechanism. Autophagy describes a process involving the break-down and recycling of specific subcellular organelles. This process may provide a cell survival strategy by reducing damaged organelles and/or shifting internal resources in order to optimize cell survival. Only if the damaging process exceeds the cellular defenses, cells die in the process [59, 60].

Regarding the role of sex in cell fate decisions, several reports have highlighted distinct sex-dependent differences. Sex hormones have been shown to influence the propensity of cells to undergo apoptosis. In general, lower concentrations of estrogen were found to be protective, while higher concentrations were found to promote apoptosis. Androgens were found to enhance, but also to suppress apoptosis depending on the cellular context [61, 62]. For example, estrogen and testosterone were described to reduce apoptosis in skeletal muscle cells [63]. Both hormones also appear to prevent apoptosis in neuronal cells adding to their neuroprotective function [64, 65]. An anti-apoptotic action of testosterone was also described in pancreatic β cells from male rats, but not from female rats [66]. Estrogen and estrogenic compounds, however, appeared to enhance apoptosis in pancreatic β cells in elderly mice, while it reduced apoptosis in young animals [67]. Regarding vascular endothelial cells, several studies have shown that estrogens protect from apoptotic cell death [68, 69], while apoptosis increased in coronary artery endothelia from postmenopausal women [70]. Testosterone was found to induce apoptosis in endothelial cells [71–73]. Treatment with testosterone also induced apoptosis or senescence in human dermal papilla cells, a process implied in inherited male alopecia [74, 75]. In addition, androgens were found to promote apoptosis in renal and intestinal cell lines and bone marrow-derived macrophages [76–78].

Overall, sex hormones appear to influence cell fate decisions depending on the cell context. Hormone independent sex differences are also apparent shaping the cellular response [79]. Thus, female and male cells appear to rely on different coping strategies in response to stressors. For example, vascular smooth muscle cells isolated from aorta of male rats appear to be more inclined to undergo apoptosis in response to UV irradiation, while female cells are more prone to execute the cell senescence program [62, 80]. Female cells showed characteristics of autophagy, which is presumed to help female cells to repair the UV-induced intracellular damages ultimately providing a survival strategy [81]. In addition, female cells were found to better adhere to the growth support, thus avoiding apoptotic cell death initiation by cell detachment, a process called anoikis-resistance. Differences in the intracellular organization

of the actin cytoskeleton and increased phosphorylation of focal adhesion kinase were attributed to this higher propensity of female cells to adhere [81]. Apparently, female cells are better equipped to prevent cell death. While autophagic processes were found to protect neuronal cells from cell death due to starving in female rats, male cells were not able to benefit and died more often from autophagic cell death [82]. Organ-specific sex differences were found in constitutive autophagy, a process implicated in physiological tissue turnover. While autophagic marker proteins were increased in the male versus female heart and liver, no such differences were observed in the kidneys [83]. Osteoblasts showed reduced autophagy in aging female mice, while the rate remained constant in males over the life span. This was correlated with higher oxidative stress in female cells, thus potentially enhancing bone loss and playing a role in the pathophysiology of osteoporosis in women [84]. Estrogens alter the redox balance and counteract bone loss [46]. Stem cells involved in generation of osteoblast, namely bone marrow derived mesenchymal stem cells, were found to be influenced by estrogens not only inducing increased proliferation, but also reducing senescence and apoptosis [85].

In general, increased antioxidative cellular defenses were implicated to provide females with better strategies to cope with oxidative stress and prevent cellular losses [62]. Differences in basal redox state and responses to oxidative imbalance were demonstrated between female and male cells [86]. For example, female cells were shown to produce less hydrogen peroxide and superoxide anion. Anti-oxidative enzymes, such as superoxide dismutase (SOD) and catalase, showed higher basic activity in female versus male cells [87]. Thioredoxin reductases and manganese SOD were increased by estrogen in cardiomyocytes [88, 89]. In vascular smooth muscle cells and circulating monocytes, estrogen was found to stimulate manganese and extracellular SOD expression [90]. Estrogen was, furthermore, shown to modulate the expression of other key molecular defense enzymes differently in XX and XY cells, for example, poly-ADP ribose polymerase (PARP), a DNA damage repair enzyme, or RLIP76, a cell-protective transporter protein [86].

PARP was also found to play a major role in sex differences in stroke. Experiments in mice have shown that ischemic neuronal cell death is dependent on intact neuronal nitric oxide synthase (nNOS)/PARP signaling, while in females a protection is provided by estrogen paradoxically also requiring an intact nNOS/PAPR axis [91]. While male neuronal cells appear to die via a PARP-mediated caspase independent pathway, ischemic cell death pathways appear to be dependent on activation of caspase-dependent cell death pathways in females [9, 92]. Such sex-specific differences may be relevant for the sex-specific difference in stroke prevalence [93, 94].

PARP signaling was also implied in sex differences in cell fate decisions in kidney cells. In a mouse model of immune-mediated nephritis, PARP signaling induced necrosis in male cells and inhibition of PARP shifted the pro-inflammatory necrotic cell death to an anti-inflammatory apoptotic pathway. In female cells, by contrast, cell death was independent of PARP and female cells preferentially underwent apoptosis. Estrogen acted in a pro-survival manner in female cells only. In addition to the kidney cells, bone marrow-derived hematopoietic cells showed similar sex differences [95].

Mitochondria play a crucial role in apoptotic cell death programs. Estrogens were described to modulate the propensity for mitochondrial initiation of apoptosis [61, 96]. Estrogen-mediated

modulation of mitochondrial function is achieved by hormone effects on the expression of mitochondrial and nuclear genome-encoded mitochondrial proteins [97–101]. Since mitochondria are central in the cellular defense against oxidative stress, mitochondria are especially sensitive to accumulate damage over time. Malfunctioning mitochondria accumulate during aging, a process regarded as a major contributor to the onset of many age-related diseases [102, 103]. Sex differences were observed in this process. Delayed malfunctioning of mitochondria during the aging process might provide females with better strategies to cope with cellular stressors. Maternal transmission of mitochondria appears to provide a more favorable environment in female offspring [104]. Xist, an RNA-coding gene involved in X chromosome inactivation in female cells, appears to be pivotal for mitochondrial maintenance [105]. Mitochondrial biogenesis and degradation by mitophagy are dependent on the transcription factors p53 and FOXO [106, 107]. Sex-specific differences in the activity of these nuclear factors were reported. Males were shown to exhibit relatively greater FOXO activity. Females, on the other hand, had higher p53 activity resulting in sex-specific differences in the ability to maintain healthy mitochondrial functionality during aging [105].

2.4. Potential consequences of sex-specific differences in tissue homeostasis

The abovementioned paragraphs have described examples of sex-specific differences regarding processes involved in tissue maintenance, like the control of cell proliferation and cell death. Such effects may ultimately result in differences in the ability of female and male tissues to cope with stressors affecting the ability to repair and restore function or develop disease. Many diseases show different incidence and prevalence rates in men and women derived from sex and gender specific pathophysiological mechanisms. Sex and gender differences have been studied intensively in the neural system, the cardiovascular system, and the development of cancer, among others [108–110].

Mechanisms underlying differences in kidney diseases between men and women are less well known, despite renal diseases with a high morbidity and mortality risk being a challenging problem for patients, clinicians and society [111, 112]. International registries show that fewer women than men develop kidney failure [113–116]. The underlying causes, however, are widely unknown. The presumed female protective effects appear to be most pronounced in women of reproductive age [117–120]. This finding suggests that female sex hormones might play a key role. Estrogen was proposed to be renoprotective via modulating renal perfusion and effects on the vasculature. Furthermore, a role of estrogen was proposed in the control of the local renal renin-angiotensin system [121–123]. On the other hand, estrogen was implicated in the control of mesangial and tubular cell proliferation and linked to neoplastic transformation of the kidney in hamster kidneys. Low estrogen concentrations were shown to induce proliferation in glomerular mesangial cell, while high concentrations suppressed it [124]. Primary proximal tubular cell explants and subcultured dissociated proximal tubular cells were shown to proliferate, when treated with estrogen at physiologic concentrations [125]. This finding was confirmed in primary rabbit proximal tubular cells, which showed increased proliferation upon estrogen treatment [126].

We have previously shown that renal tubular cell-specific proteins appear at higher rates in the urine of healthy women at specific hormonal transition phases of the natural ovulating

menstrual cycle. Urinary samples from healthy probands showed increased rates of urinary excretion of the marker proteins Fructose-1,6-bisphosphatase and Glutathione-S-transferase α, when estrogen levels decreased after a preceding height associated with ovulation and luteal phase [127]. Both enzymes are specifically found in proximal tubular cells, the most populous cell type in the kidney. When proximal tubular cells are damaged, intracellular enzymes are released into the urine, making them clinical markers for kidney injury. In contrast to ovulating women, male probands and postmenopausal women showed consistently low levels of these renal marker proteins over time. Other urinary proteins, for example, albumin, α1-microglobulin, and immunglobulin G, which are markers for functional changes of the glomerular filter and/or tubular protein resorption, showed constant urinary excretion suggesting that the observed increases of proximal tubular marker protein release in ovulating women are not accompanied by major functional distress of the kidneys [127]. This pattern of urinary marker proteins excretion suggests that cyclical changes of female hormones might affect kidney cell health. Tubular enzymes are released into the urine, if proximal tubular cells are sloughed off and/or their plasma membranes become leaky. This could be due to tubular cells being transiently more prone to damage in situ resulting in plasma membrane leakage or to the cells being removed from the tubular epithelium and released into the urinary space, for example, by apoptosis. Both processes lead to increased cell losses. Tissue homeostasis would be maintained, if increased cell removal was accompanied by increased cell proliferation. This could be the case during the high estrogen exposure phases preceding the observed tubular enzyme releases into the urine. The finding that tubular cells are able to proliferate upon estrogen treatment [126] is in line with this hypothesis. Such a periodic interplay between cell proliferation and cell loss brought about by the specific changes in the pattern of sex hormone exposure might result in an increased rate of tissue renewal. If this was the case, then women in their reproductive years would possess an efficient means to easily get rid of potentially injured, dysfunctional or simply older proximal tubular cells by replacing them with fresh new cells. Such a transiently increased repair capacity might provide an efficient means to cyclically renew renal tubular tissue leading to a higher resistance to damage. It is, however, also possible that during the short phases of increased tubular cell death, the kidneys might be especially sensitive to damage. With regard to the potential beneficial action of treatment of renal proximal tubular cells with a proliferation-inducing growth factor, we have previously demonstrated that epidermal growth factor (EGF) treatment was able to accelerate tissue repair after treatment with interferon α (IFNα) in vitro. However, if EGF was present before or during IFNα treatment, epithelial barrier destabilization was intensified [128, 129]. Therefore, the overall effect might be different in other cycle contexts or under hormone therapy, if the vulnerable phases might not be restricted to short periods.

3. Conclusion

In conclusion, it appears that males and females are equipped with stress coping strategies that may differ between the sexes. Sex differences have been demonstrated in the cellular

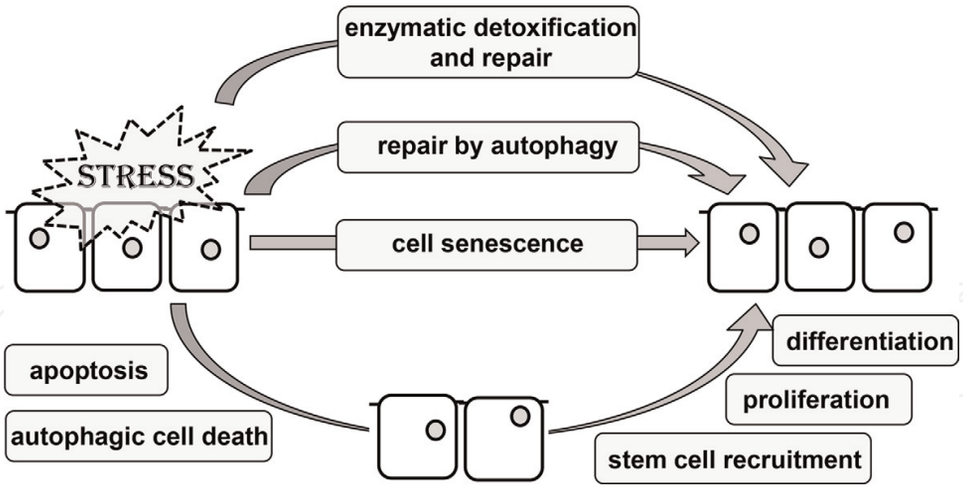


Figure 1. Sex and sex hormone-induced differences in tissue homeostasis. The figure shows strategies involved in tissue maintenance following cellular stress. Sex differences and sex hormone-dependent effects have been shown in these processes in different organs and tissues.

expression levels and activity of detoxifying and repair enzymes, in the propensity to use autophagic processes for repair, in senescence or cell death programs and in the ability to replace cells by proliferation (**Figure 1**). These effects are apparent in isolated cells and are further shaped by exposure to sex hormones. Sex hormone levels cyclically changing in dependence of the female reproductive hormone cycle might enhance physiological tissue regeneration and provide greater damage repair potential. Overall, female tissues appear to be more resistant to cellular stress than their male counterparts.

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Conflict of interest

The authors confirm that there are no conflicts of interest.

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