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Stress Hormone and Skin Disease

Jung Eun Kim and Hyun Jeong Park
Department of Dermatology, College of Medicine, The Catholic University of Korea, Korea

1. Introduction

Stress activates several neural pathways. The main stress response systems are the locus coeruleus, sympathetic-adrenal medullary system, and the hypothalamic – pituitary – adrenal (HPA) axis (Zhang et al., 2005). Stressors stimulate the paraventricular nuclei of the hypothalamus, where corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) are synthesized. CRH is a central component of the HPA axis and regulates the expression of pro-opiomelanocortin (POMC) and POMC-derived peptides (adrenocorticotropin (ACTH), α-melanocyte-stimulating hormone (α-MSH) and β-endorphin) from the anterior pituitary gland (Chrousos, 1998). CRH stimulates AVP secretion and AVP has synergistic effect with CRH, particularly under chronic stress. Pituitary ACTH stimulates adrenal cortisol and glucocorticoid production. Stress influences cellular and humoral immune responses by releasing glucocorticoid, catecholamine, and CRH and POMC peptide secretion as well as by altering cytokine profiles (Elenkov & Chrousos, 1999).

The skin is directly exposed to various environmental stresses. Skin should be able to defense immediately against these stressors and reestablish tissue homeostasis. Recent studies have identified the existence of a peripheral stress response system equivalent to the central HPA axis in the skin. CRH, urocortin, POMC-derived peptides, and their receptors are expressed in normal skin. Response to local CRH stimulation in melanoncytes and fibroblasts confirmed the presence of a fully functional local HPA axis (Slominski et al., 2007). Stress hormone of the HPA axis produced locally under stress enables the skin to regulate the local homeostasis.

CRH, the main coordinator of the stress response can be secreted by various skin cells including epidermal and hair follicle keratinocytes, sebocytes and mast cells (Kono et al., 2001). The peptide acts through CRH receptor (CRH-R), which belong to the calcitonin/vasoactive intestinal peptide (VIP)/growth hormone-releasing hormone subfamily of G protein-coupled receptors. These include CRH-R1 and CRH-R2, both being subdivided into CRH-R1α/1β and CRH-R2α/2β. CRH-R1 is the major receptor in the epidermis and dermis. CRH-R2 is the predominant type of receptor in adnexal structures (Chalmers et al., 1996; Pisarchik & Slominski, 2004; Slominski et al., 2001).

CRH has a pleiotropic effect in the skin depending on the cell type and experimental growth conditions. CRH stimulates diverse signaling pathways via CRH-R1 activation, which modulates proliferation, differentiation, apoptosis and pro- or anti-inflammatory activities of skin cells (Elenkov & Chrousos, 1999; O'Kane et al., 2006).

CRH activates various cells to release the pro-inflammatory cytokines. For example, CRH stimulates interleukin (IL)-6 release by keratinocytes (Zbytek et al., 2002) and IL-1β release by monocytes (Paez Pereda et al., 1995). Skin mast cells function as "sensors" of environmental and emotional stress (Theoharides et al., 2010). There have been a few

evidences that CRH-induced activation of mast cells may explain the phenomenon of stress-related exacerbation of cutaneous inflammatory diseases. Mast cells express CRH-R1 (Cao et al., 2005). CRH and urocortin activates skin mast cells and increases vascular permeability in humans, through activation of CRH-R1 (Theoharides et al., 1998). Stress-induced mast cell degranulation is mediated by CRH, neurotensin, and substance P (SP) in the rat skin (Singh et al., 1999). CRH and urocortin stimulated selective release of vascular endothelial growth factor (VEGF) and IL-6, respectively from mast cells through CRH-R1 activation without degranulation (Theoharides et al., 2010; Zhou et al., 2010). Moreover, human mast cells can produce CRH and urocortin (Kempuraj et al., 2004).

On the while, CRH has anti-inflammatory activity. In rat injury models, CRH attenuated vascular leakage and reduced edema through pituitary ACTH and CRH-R2 (Wei & Gao, 1991). The peptide diminishes NF-kB activation in epidermal melanocytes (Zbytek et al., 2006) and inhibits IL-18 expression through the mitogen-activated protein kinase (MAPK) signaling pathway in human HaCaT keratinocytes (Park et al., 2005). IL-18 is a key mediator of peripheral inflammation and host defense responses. On the while, ACTH stimulates human keratinocytes to secrete IL-18 through melanocortin receptor 1(MC1R), melanocortin receptor 2 (MC2R), p38 and ERK MAPK pathways. Since CRH inhibits IL-18 expression in HaCaT cells, IL-18 may play an important role on the negative feedback loop of CRH regulation (Park et al., 2007). This provides insights on the pathophysiology of stress-related skin diseases.

Stress or an abnormal response to stressors has been found to modify the course of skin disorders. A few studies revealed dysregulated central and peripheral HPA expression in some stress-exacerbating skin diseases. This review focuses on what is known about the distribution and function of stress hormone in the representative stress-exacerbating skin diseases such as atopic dermatitis (AD), psoriasis, and alopecia areata (AA). By summarizing the literature, this comprehensive review may help clinicians understand "stress hormone and skin disease" better.

2. Psoriasis

Psoriasis is a polygenic disease that is characterized by keratinocyte hyperproliferation, abnormal differentiation and chronic inflammation. Many psoriatic patients believe that there is a causal relationship between stressors and their disease outcome. Earlier retrospective studies have suggested that exacerbation of psoriasis occur a few weeks to months after a stressful event (Gupta et al., 1988). Recently, Verhoeven et al. have found a positive significant correlation between preceding daily stressors and Psoriasis Area and Severity Index and itch 4 weeks later through a prospective study (Verhoeven et al., 2011). It has been suggested that exacerbations of psoriasis after stress might be related to alteration of the HPA axis and the release of neuropeptides.

Earlier studies have found a blunted HPA axis function in psoriatic patients during exposure to the acute stressor (Arnetz et al., 1985; Richards et al., 2005). The hyporesponsiveness of HPA axis might result in exaggerated inflammatory responses due to the diminished suppressive effect of the low level of cortisol. This may explain why psoriatic patients are more vulnerable to the influence of stressors on their symptoms. Recent study revealed that peak levels of daily stressors were related to an increase in disease severity a month later, and the highest levels of daily stressors were also significantly associated with a lower cortisol level. Furthermore, patients with persistently high levels of stressors had lower mean cortisol levels (Evers et al., 2010).

However, two studies by Karanikas et al. and Buske-Kirschbaum et al. detected no alteration of the HPA axis function in psoriasis and suggested that the systemic HPA axis response could

be normal in a T helper type 1 (Th1)-dominant inflammatory condition (Karanikas et al., 2009; Buske-Kirschbaum et al., 2006).

After psychosocial stress, psoriasis patients showed increased number of activated T cell with a shift towards a Th1-derived cytokine profile and increased number of cutaneous lymphocyte-associated antigens-positive T cells and natural killer cells in the circulation, which was pathologically relevant in aggravation of psoriatic plaques (Buske-Kirschbaum et al., 2007; Schmid-Ott et al., 2009).

β-endorphin is one of the POMC-related peptides. The peptide is produced by the HPA axis but can be secreted by immune cells. Psoriatic patients with actively spreading plaque lesions showed increased levels of β-endorphin in sera. β-endorphin may be produced by inflammatory cells in psoriatic lesions rather than activation of HPA axis by chronic stress (Glinski et al., 1994). The presence of high levels of β-endorphin in psoriatic lesions might induce SP-mediated neurogenic inflammation and have an antinociceptive effect on peripheral sensory nerve function (Glinski et al., 1994). This may be responsible for the absence of itching in psoriatic lesions in the majority of psoriasis patients.

There have been some conflicting results of peripheral HPA axis expression in psoriatic lesions. Prior studies reported that CRH/CRH-R expression was increased in the affected epidermis (Kono et al., 2001; O'Kane et al., 2006). We previously reported increased expression of CRH in various clinical subtypes of psoriasis (Kim et al., 2007). CRH treatment on HaCat cell lines induced proliferation/differentiation (Zbytek & Slominski, 2005; Slominski et al., 2006). Aberrant CRH/CRH-R1 expression in active psoriatic lesions might result in disharmony in proliferation/differentiation.

Many researchers focus on the proinflammatory role of CRH. CRH may activate mast cells via a CRH-R-dependent mechanism, leading to the release of histamine with increased vascular permeability (Theoharides et al., 1998). The proinflammatory cytokine IL-1, 6, and tumor necrosis factor (TNF)-α secreted by mast cells are upregulated in psoriatic skin. They are recognized as potent stimulators of CRH and POMC production in human skin (Tsigos & Chrousos, 2002).

In contrast, Tagen et al. and Zhou et al. found increased serum CRH and decreased lesional skin CRH/CRH-R1 gene expression and suggested that downregulated CRH/CRH-R1 expression in psoriatic lesion may be the result of negative feedback of systemic CRH elevation (Tagen et al., 2007; Zhou et al., 2009). CRH could downregulate pro-inflammatory cytokine IL-18 as we previously reported (Park et al., 2005). In this view, CRH might have protective function from developing the psoriatic lesions.

Altered CRH/CRH-R expression was observed not only in the psoriatic skin but also in the psoriatic arthritis. Upregulation of CRH-R1α mRNA and peptide in the endothelial cells and mast cells of inflamed synovium was observed in patients with psoriatic arthritis. CRH potentially play a role through angiogenesis or inflammatory effects in psoriatic arthritis (McEvoy et al., 2001).

SP, one of the stress neuropeptides, is suggested to have a role of neurogenic inflammation in the pathogenesis of psoriasis. Expression of SP and its receptor correlated with the severity of depression and was associated with low level of cortisol, which indicates chronic stress (Remröd C et al., 2007; Amatya et al., 2011). SP also play a critical role in stress-induced mast cell degranulation in mice (Kawana et al., 2006).

In conclusion, exposure to real life- and experimental stressors showed altered HPA axis in psoriatic patients. Dysregulated HPA activity might result in changes of immune responses and peripheral CRH levels. CRH-induced mast cell activation plays an important role in

stress-induced psoriasis exacerbation. Inflammatory mediators released from psoriatic lesions not only interact with peripheral HPA axis, but also may influence central HPA axis. The stress-dependent mechanism of CRH and POMC-related peptides with the symptom of psoriasis should be studied further.

3. Atopic dermatitis

AD is a chronic, inflammatory, allergic skin disease, provoked by the imbalance of Th1/ T helper type 2 (Th2) immune responses. Epidemiological and experimental studies suggest that psychological stress triggers the symptom of AD. This phenomenon has been explained by the finding that activation of the HPA axis by stress aggravates the symptoms, mainly by inducing a shift toward Th2 cell phenotype.

After stress, blunted HPA axis responsiveness and increased reactivity of the sympathetic adrenomedullary system in atopic patients was demonstrated (Buske-Kirschbaum et al., 2010). Interestingly, neonates with a parental atopic history and elevated cord IgE were found to show significantly increased responsiveness of the HPA axis to the heel prick stress, which may be due to maternal stress hormonal effect or which may increase the vulnerability to develop AD in later life (Buske-Kirschbaum et al., 2004). Adolescents with AD had an attenuated cortisol response to laboratory stress (Wamboldt et al., 2003). However, Afsar et al. identified that children with AD do not have different basal cortisol levels nor more anxiety compared with normal children (Afsar et al., 2010).

Dendritic cells (DCs) promote allergic immune responses by inducing Th2 cell differentiation. Recently, Lee et al. detected CRH-R1α, 1β, 2α mRNA and CRH-R1, CRH-R2 protein in mononuclear cell-derived dendritic cells in AD patients. IL-18 is a potent inducer of Th1 responses. CRH significantly decreased the expression of IL-18 in DCs of AD patients. Stress-induced CRH may enhance Th2 immune responses by acting directly on DCs via CRH-R and aggravate the clinical manifestations in AD (Lee et al., 2009).

Increased levels of β-endorphin in the sera had been considered as a biological marker for severe AD (Lee et al., 2006; Glinski et al., 1994, 1995). The increased neuropeptide has been suggested to be produced from lesional inflammatory cells rather than activation of central HPA axis by chronic stress. Stress-related pruritus may be associated with a systemic pruritic effect of β-endorphin (Glinski et al., 1995).

Altered POMC-related gene expression also influences the development of postinflammatory hyperpigmentation. Increased plasma α-MSH levels and MC1R and MC3R expression in the skin and intestine, respectively was associated with pigmentation of AD in an NC/Nga mouse model. The changes were completely blocked by pretreating with MC1R antagonist or MC3R antagonist (Hiramoto et al., 2010).

There have been several attempts to reveal how various stressors could affect central and peripheral HPA axis in AD animal models.

Amano et al. demonstrated that psychological stress by itself could develop AD-like skin lesions along with concomitant increase of serum immunoglobulin E in NC/Nga mice. The lesions were not induced by treatment with CRH antagonist (Amano et al., 2008).

Orita et al. demonstrated that AD-like lesions in NC/Nga mice was exacerbated by strong exercise but ameliorated by mild exercise. Plasma a-MSH, transforming growth factor- β (TGF- β) and lesional SP expression correlated with exacerbation of the symptom. Plasma levels of β-endorphin increased by the mild exercise. Exercise-induced stress differently affects the symptom of AD and stimulates POMC-related hormone depending on the

strength of exercise (Orita et al., 2011). β-endorphin has been known to strengthen natural immunity and proper exercise might be helpful to control the symptom of AD by stimulating the HPA axis and inducing balanced Th1/Th2 immunity.
AD is also exacerbated by stress through mast cell activation (Katsarou-Katsari et al., 1999) Mast cells in the presence of stem cell factor (SCF) and IL-4, produce mostly Th2 predominant cytokines (Bischoff et al., 2001) and release neuropeptide such as SP and nerve growth factor (NGF) (Theoharides et al., 2010; Xiang & Nilsson, 2000).
Computer-induced stress or video games-induced stress enhanced allergen specific immune responses with elevated levels of plasma SP, VIP and NGF, with concomitant increase of Th2 cytokines, in patients with AD (Kimata, 2003).
There have been little studies about local stress hormone expression in AD lesions. Recently, Oh et al. reported that CRH and SP expression was not different between AD lesions and normal, whereas NGF and neuropeptide Y (NPY) expression was significantly higher in the epidermis of affected skin of four AD patients, although the result was not quantitated (Oh et al., 2010). Increased expression of NGF in AD lesions was supported by Dou et al. (Dou et al., 2006). NGF and NPY have been known to be related with anxiety. Anxiety score positively correlated with pruritus in AD patients (Oh et al., 2010). Stress aggravates pruritus by lowering the itching threshold (Gieler et al., 2003; Paus et al., 2006). For the mechanism, increased contacts of nerve and mast cells have been suggested. The neuropeptides NGF and NPY might have a role to activate intraepidermal mast cells in AD lesion and contributes to stress-induced pruritus (Oh et al., 2010).
Blunted HPA axis responses to stressors are shown in AD patients. In general, stress negatively impact the severity of AD by down-regulating cellular immunity and enhancing humoral immunity. CRH, and POMC-related peptide hormones, as well as neuropeptide SP, NGF, and NPY modulate immunological and inflammatory response under stress.

4. Alopecia areata

The hair follicle (HF) is a unique mini organ that has immune-privilege (IP) during the anagen phase. Several factors are involved in the maintenance of HF-IP. Those include absence of MHC class I molecules expression, and upregulation of immunosuppressant such as Insulin-like growth factor-1, TGF- β1, ACTH, α-MSH and cortisol (Ito, 2010). The hair follicles have their own local equivalent of the HPA axis, termed the brain-hair follicle axis (BHA) (Arck et al., 2003). There have been few evidences that BHA hormones modulate the hair cycle (Maurer et al., 1997; Slominski et al., 1998).

4.1 Normal hair follicle HPA axis

In normal human hair follicle, CRH/CRH-R2 is expressed in the outer root sheath (ORS) and hair bulb (Arck et al., 2003). CRH-R2 plays an important role in modulating hair cycle and is detectable in the cells-derived from HF keratinocytes and dermal papilla fibroblasts. In murine HF, the highest intensity of CRH occur during anagen IV/VI, and the lowest levels are found during catagen and telogen (Roloff et al., 1998)
CRH induce POMC mRNA and peptide in human HFs in vitro. Moreover, CRH stimulates cortisol secretion by organ-cultured human HFs that also possess feedback systems (Ito et al., 2005)
ACTH is solely expressed in ORS of anagen HFs and its concentration significantly increases during anagen and stimulates intrafollicular cortisol production (Ito et al., 2005). α-MSH is

detected in ORS and hair matrix during anagen (Paus et al., 1999). The POMC peptide and cortisol production contribute to the anagen-dependent immune-suppression.

4.1.1 Stress hormone and hair follicle mast cells

Perifollicular mast cells play an important role in human hair cycling. Degranulation of mast cells abruptly increase just before the onset of catagen. Inhibition of mast cell degranulation can delay catagen development in the murine hair cycle (Ito et al., 2010). It was recently reported that CRH induces differentiation of human HF precursors into mast cells (Ito et al., 2010). CRH-induced mast cell degranulation is mediated by SCF stimulation in human HFs (Kumamoto et al., 2003).

4.1.2 Stress and substance P

Neuropeptides, SP, are expressed in the hair follicles and also affect the hair growth cycle (Maurer et al., 1997; Zhou et al., 2006). SP facilitates catagen development by promotion of mast cell degranulation and also induces a loss of IP markers in HFs (Arck et al., 2001; Peters et al., 2007).

4.2 Alopecia areata and hair follicle HPA axis

AA is a hair cycling disorder, which is characterized by early catagen development. The condition is initiated by the collapse of the anagen-specific IP. Anagen HFs are attacked by inflammatory cells and move prematurely into catagen.

Many patients often experience development or recurrence of AA after trauma or stressful events. It was hypothesized that the chronic inflammatory state of AA might modify the HPA axis and subsequent stress responses or abnormal expression of HPA axis-related hormone itself might implicate the development of AA (Ito et al., 2010).

4.2.1 Central HPA axis in Alopecia areata

AA mice have a significantly blunted systemic HPA response to acute physiological stress and a defective adaptation to repeated psychological stress. Increased expression of hypothalamic AVP following stress exposure increased pituitary POMC under both basal and stress conditions. AVP has been known to potentiate the effects of CRH under chronic stressed conditions. An increased AVP appears to be critical for maintaining pituitary responsiveness to repeated stress (Zhang et al., 2009).

4.2.2 Peripheral HPA axis in Alopecia areata

In our previous study, the epidermis and pilosebaceous units of AA lesion showed intense expression of CRH, ACTH and α-MSH peptides (Kim et al., 2006). Enhanced CRH/CRH-R2 expression in human AA lesion was obtained by others (Katsarou-Katsari et al., 2001) but CRH was not detected in some studies (Zhang et al., 2009).

Upreguated CRH/CRH-R2 and ACTH peptide and insufficient glucocorticoid and higher glucocorticoid receptor levels in affected skin of human AA have been reported. Recently, Guo et al. revealed increased MC2R mRNA and decreased MC2R protein expression in AA lesions. They hypothesized that these reciprocal changes indicated a defect of post-transcriptional control of MC2R gene expression. Stressors activate CRH/CRH-R system, then increase ACTH, which upregulates MC2R mRNA expression. However, due to decreased MC2R protein, ACTH cannot produce sufficient amount of cortisol (Guo et al., 2010, 2011).

Hyper-active BHA axis was observed in not only in the HFs but also in the lymph nodes of AA mice. Increased POMC mRNA levels with decreased Nr3c1 levels in HFs and lymph nodes were detected. Nr3c1 is a mineralocorticoid receptor and is activated by cortisol. Thus, the findings suggest that there may be a negative feedback mechanism in BHA axis of AA mice (Zhang et al., 2009). Stress hormone release from the skin may modulate AA-associated inflammation. Plasma ACTH levels and lesional ACTH receptor expression were positively correlated to TNF-α expression in AA mouse skin (Zhang et al., 2009).

4.2.3 Stress-induced perifollicular neurogenic inflammation

Early catagen development is characteristic of AA. SP and its receptor, NGF, and mast cells play key roles in stress-induced perifollicular neurogenic inflammation. SP plays an important role in catagen development. It causes MHC-class I based IP to collapse (Peters et al., 2007). The number of SP-immunoreactive nerve fibers increase during early stage of AA, and decrease during advanced stage. SP and SP-degrading enzymes are highly expressed in the skin of AA-affected humans (Toyoda et al., 2001) and in the C3H/HeJ mouse model (Siebenhaar et al., 2007). AA onset may require stress-induced SP expression in the skin (Peters et al., 2006, 2007). Exposure to stress increase expression of SP (Arck et al., 2001, 2003). Sound stress upregulated SP protein expression and activated mast cells with premature catagen development in CBA/J mice, and neurokinin1 receptor antagonist normalized most stress-induced alterations (Maurer et al., 1997)

AA patients have highly active central and peripheral HPA tone. HPA activity has positive correlation with Th1 cytokine activity in AA mice. There may be interactions between systemic HPA hormones, expression levels of cutaneous HPA hormone receptors, and proinflammatory cytokine production in AA skin.

5. Skin tumors

We previously investigated CRH and POMC-related hormone expression in benign and malignant skin tumors. CRH, ACTH and α-MSH expression of skin cancer was increased compared with normal and precancerous skin lesions, consistent with prior results (Kim et al., 2006; Slominski et al., 2004). Immunoreactivity of CRH expression increased in line with malignant tendency (Kim et al., 2006).

CRH is known to have endothelial cell chemotaxis and angiogenesis through CRH-R (Arbiser et al., 1999). CRH can enhance cell migration ability by ERK1/2 pathway in murine melanoma cell line (Yang et al., 2007). Yang et al. reported that CRH-POMC axis can also control metalloproteinase expression (Yang et al., 2002). CRH can stimulate tumor growth in vivo (Arbiser et al., 1999).

CRH may play a role in tumorigenesis in certain types of skin cancer by promoting angiogenesis and migration. Psychosocial stress might be related to the development and progression of tumors. However, whether the elevated expression of CRH-POMC is a cause or a result in carcinogenesis needs further studies.

6. Acne and seborrhea

CRH/CRH-R2 system is normaly expressed in human sebaceous gland (Kono et al., 2001) and regulate sebaceous lipid synthesis (Zouboulis et al., 2002).

Acne is an inflammatory disorder of the pilosebaceous unit. Increased CRH and CRH-binding protein immunoreactivity was observed in the sebaceous gland cells of acne lesions (Ganceviciene et al., 2009). *Propionibacterium acnes* increased the CRH expression in the epidermis (Isard et al., 2009). CRH-activating pathways which affect keratinocyte differentiation, lipogenic activity and inflammatory processes lead to the development of formation of the microcomedo and inflammatory acne lesions (Ganceviciene et al., 2009). This might be the reason why stress exacerbates the symptom of acne and seborrhea.

7. Urticaria and contact dermatitis

Stress-induced CRH expression increases the disease severity of type IV delayed hypersensitivity and chronic contact dermatitis through CRH-R1-expressing mast cell activation (Dhabhar & McEwen, 1999; Kaneko et al., 2003). Enhanced vascular permeability and vasodilation by CRH is expected to involve the pathomechanism of aggravation of urticaria or contact dermatitis after stress (Theoharides et al., 1998; Crompton et al., 2003). Furthermore, urticarial lesions from patients with chronic urticaria have shown increased expression of CRH-R1 and histidine decarboxylase, which is a mast cell-related gene and regulates the production of histamine (Papadopoulou et al., 2005). CRH/CRH-R and mast cells seems to participate in the pathogenesis of chronic urticaria under the stress.

8. Conclusion

Skin has its own equivalent of the central HPA axis and responses to various stressors. HFs also possess unique form of the HPA axis dependent on hair cycle. Aberrant CRH-POMC expression was observed in stress-exacerbating inflammatory skin disorders and malignant skin tumors. Stress hormone showed unique expression patterns in each disease, and some inconsistent expression results have been reported in an identical disease.

Skin HPA axis modulates inflammatory mediators in response to various stressors. Peripheral HPA axis in the skin may interact with central HPA axis with a feedback loop of inflammatory responses.

We summarized the role of HPA-related hormone in stress-related skin diseases. Impact of stress and stress hormone on the disease development, course, response to treatment, and stress management should be studied further.

9. Acknowledgment

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (2011-0001390) and Basic research program through the NRF funded by the Ministry of Education, Science and Technology (2010-0002431). We thank Dr. Eujin Cho for English editing.

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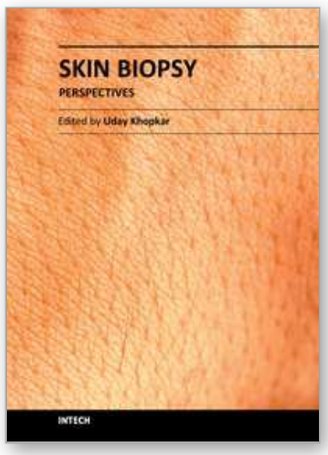

Skin Biopsy - Perspectives

Edited by Dr. Uday Khopkar

ISBN 978-953-307-290-6
Hard cover, 336 pages
Publisher InTech
Published online 02, November, 2011
Published in print edition November, 2011

Skin Biopsy - Perspectives is a comprehensive compilation of articles that relate to the technique and applications of skin biopsy in diagnosing skin diseases. While there have been numerous treatises to date on the interpretation or description of skin biopsy findings in various skin diseases, books dedicated entirely to perfecting the technique of skin biopsy have been few and far between. This book is an attempt to bridge this gap. Though the emphasis of this book is on use of this technique in skin diseases in humans, a few articles on skin biopsy in animals have been included to acquaint the reader to the interrelationship of various scientific disciplines. All aspects of the procedure of skin biopsy have been adequately dealt with so as to improve biopsy outcomes for patients, which is the ultimate goal of this work.

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University Campus STeP Ri
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Phone: +385 (51) 770 447
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