総 説

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温度ストレスが免疫機能に与える影響

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CHANGES IN IMMUNE ACTIVITIIES BY THERMAL STRESS

— An Overview of Findings in the 1980's and 1990's —

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Abstract

The immune system, reacting to bacterial and viral infections, affects nervous and endocrine systems, and the nervous and endocrine systems, by responding to various stressors, then affect both humoral and cell-mediated immune response. Acute thermal stress increases the number of NK cells and T (CD8) cells, and reduce the number of T (CD4) cells. These changes are mainly mediated by β-actions of the sympathetic neurones. The secretion rate of salivary sIgA (sIgA), the predominant immunoglobulin in the mucosal immune system, is increased by acute cold stress probably via β-adrenoceptors. Properties of stressors and individual differences in the styles coping with stress influence the sIgA response to stress. Long-term exposure to thermal stress activates the hypothalamic-pituitary-adrenal axis, and suppresses immune activities. The phagocytotic activity of macrophages, the number and activity of NK cells, and the antibody production are inhibited by chronic thermal stress. The composition of T (CD4) cell subtypes is also influenced by chronic stress. The decrease in the ratio of Th1 cells to Th2 cells by chronic stress provides different patterns of cytokines released by these T cells and influence the immune activity. The dominance of Th1 or Th2 predicts the susceptibility of the hypothalamic-pituitary-adrenal axis to stressors in animal models. Heat shock proteins (HSPs) induced by heat exposure influence the expression of the T cell receptor (TCR) and the intracellular signalling in T cells. HSPs also block the transcription of TNF mRNA and decrease the production TNF by macrophages.

Key words: Stress, sIgA, Heat shock proteins, Systemic immune system, Mucus immune system

要 旨

温熱生理学の分野では、温度ストレスが免疫機能に与える影響についての報告が頻繁に現れるようになったのは、1980 年代初頭からであった。それから 20 年の間に、免疫系と自律神経系との相互作用、さらにこれらに内分泌系を加えた三つの調節系の相互関連についての知見が急速に増大した。この現象は、温熱生理学分野のみに留まらず、広範な研究分野で同時に進行し、その結果、人の健康や病態についてより総合的に理解することが可能となった。さらに、人の心理状態や行動様式が、免疫系と自律神経系、内分泌系の三つの調節系に及ぼす影響についても大幅に理解が進み、社会神経科学（Social Neuroscience）や心理神経免疫学（Psychoneuroimmunology）などの新分野が誕生することとなった。本稿では、これらの進展を準備した 1980 年代と 1990 年代の温度ストレス関連の研究成果について概説する。急性温度ストレスを扱った部分では、ストレス時の細胞性免疫を修飾する自律神経系の働き、自律神経系を介した粘膜免疫の修飾と人の行動様式との関連に力点を置いた。長期温度ストレスを扱った部分では、視床下部－脳下垂体－副腎髄質系とサイトカインやケモカインを介したストレス時の全身性免疫の反応に焦点を当てた。熱ショックタンパクを扱った部分では、熱ストレスによって産生された熱ショックタンパクが、細胞性免疫に与える影響について述べた。山梨県環境科学研究所環境生理学研究室は、1997 年に開設された。本稿で取り上げたような研究が充実期を迎え、将来への展望が開けてきた時期と重なっていた。このような時背景は、環境と健康をテーマに研究を遂行する上で大きな恩恵となった。

キーワード：ストレス、分泌型免疫グロブリン A、全身性免疫、粘膜免疫、熱ショックタンパク

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Introduction

The immune system, reacting to the infections by pathogens, affects nervous and endocrine systems, and the nervous and endocrine systems, by responding to various stressors, in turn affect the immune system (Fig. 1). Cytokines, such as interleukin 1 (IL-1) and tumor necrosis factor α (TNF-α), produced and released by macrophages and monocytes in response to the infection affect the hypothalamus and cause various physiological responses including fever (Fig. 2). Concomitantly, cytokines activate the release of corticotropin-releasing hormone (CRF) from the hypothalamus. CRF stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland and activates the sympathetic nervous system at the same time. Adrenocortical hormones released by ACTH suppress immune activity (Fig. 3). Glucocorticoids induce the apoptosis of T cells and B cells and therefore suppress their immune activities. Glucocorticoids also suppress the production of interleukin 2 (IL-2) by T cells and the production of immunoglobulins by B cells. Glucocorticoids act on the macrophages and inhibit their phagocytotic and chemotaxic activities as well as their production of cytokines such as IL-1 and TNF-α. The increased level of catecholamines as a result of the activation of the sympathetic neurones and adrenal medulla also suppresses T cell activities via β-adrenergic receptors.

On the other hand, stressors, if they are strong enough, affect the nervous and endocrine systems and suppress immune activity by the same mechanism involving CRF release and sympathetic activation. Antibody and cell-mediated responses of the immune system are both influenced by a variety of stressors. For example, the activity of the splenic killer T cells (NK cells), which attack target cells in a major histocompatibility complex-restricted manner (Herberman and Ortaldo 1981), is reduced in students undergoing an examination (Kiecolt-Glaser et al. 1984) or persons experiencing adverse life events (Locke et al. 1984). The reduction of NK cell activity is also observed in women who are pregnant (Gregory et al. 1985; Salméron et al. 1991) or who are suffering the death of their spouse (Irwin et al. 1988). In patients who have undergone general anaesthesia or traumas due to burn and surgery, NK cell activity is reduced as well (Blazar et al. 1986; Koenig et al. 1987; Tonnesen et al. 1984; Walton 1978).

The secretory immunoglobulin A (sIgA) is the predominant immunoglobulin in the mucosal immune system, acts protectively against respiratory and gastrointestinal infections. A number of studies have shown that salivary sIgA concentration and its secretion rate are reduced in individuals reporting relatively high levels of chronic stress and the absence of a positive attitude (Evans et al. 1996; Graham et al. 1988; McCleland et al. 1985). On the contrary, acute stress such as mental arithmetic has been reported to cause an increase in salivary sIgA during or shortly after exposure to the stressor (Bristow et al. 1997; Carroll et al. 1996; Willemsen et al. 1998;

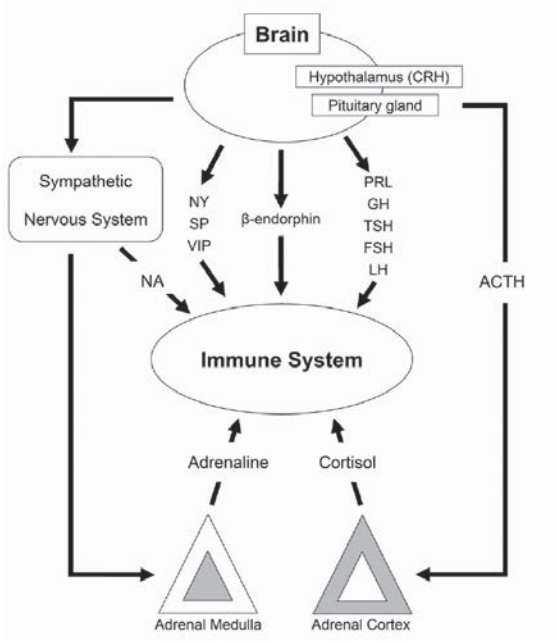

Fig. 1 Interactions between the brain and immune system via neuroendocrine systems. CRH: corticotropin releasing hormone, ACTH: adrenocoroticotropic hormone, NA: noradrenaline, NY: neuropeptide Y, SP: substance P, VIP: vasoactive intestinal peptide, PRL: prolactin, GH: growth hormone, TSH: thyroid stimulating hormone, FSH: follicle stimulating hormone, LH: luteinizing hormone

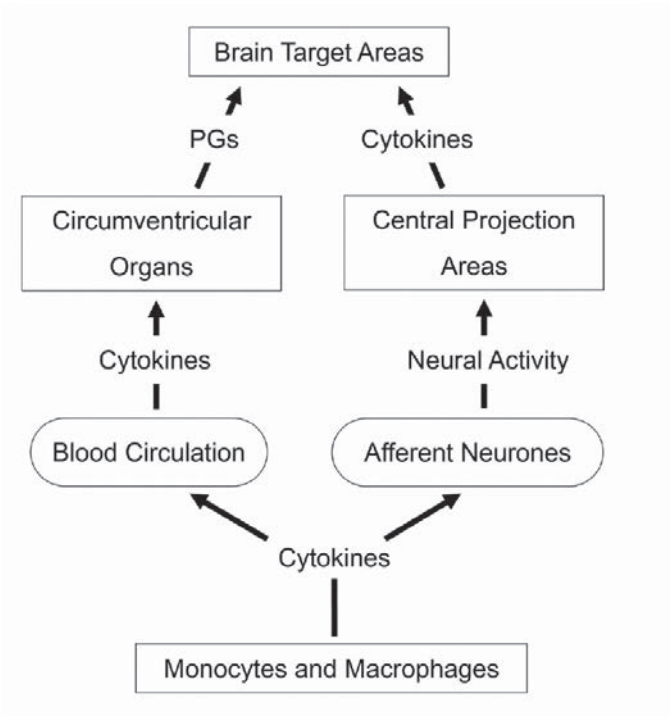

Fig. 2 Interactions between the brain and immune system via cytokines. Cytokines in the brain are synthesized and released by resident macrophages and microglial cells. PGs: prostaglandins

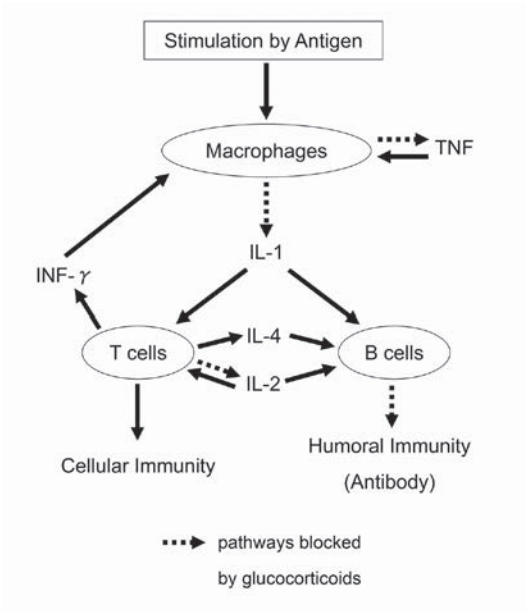

Fig. 3 Glucocorticoids and the cytokine network.

Table 1 Major HSP members and related peptides. Based on Motomura et al. (2001).

Table1 Major HSP members and related peptides

Hsp70(DnaK/BiP)	ATP dependent stabilization of hydrophobic regions extended polypeptide segment
Hsp40/DnaJ	
Hsp20/GrpE	
Hsp60(GroEL/Chaperonin/TCP1)	ATP-dependent facilitation of folding to the native state
Cpn10(GroES)	
Hsp100/104(ClpB/ClpA/ClpX)	ATP-dependent disaggregation and unfolding for degradation
ClpP	
Trigger factor	cotranslation folding catalyst, binding on ribosome
Hsp90	Conformational maturation of steroid hormone receptors and signal transducing kinases. Very weak activity of ATP dependent stabilization
Hsp47	collagen-binding stress protein
FtsH	membrane-bound ATP-dependent metalloprotease involved in degradation of the heat-shock transcription factor sigma 32

Zeier et al. 1996). Long-term reduction of sIgA is considered to reflect the activity of the hypothalamic-pituitary-adrenal axis, i.e. increases in CRF, ACTH and glucocorticoid release, whereas short-term increase in sIgA is supposed to be a result of an increase in catecholamines from the sympathetic nerve terminals and adrenal medulla (Willemsen et al. 1998). Alternatively, reduced sIgA associated with chronic stress may be explained by the downregulation of receptors as a result of repeated exposure to short-term challenge (McCleland et al. 1985). Whatever the case, these findings clearly show that the nervous and endcrine systems affect both antibody- and cell-mediated immune response when challenged by various physical and psychological stressors.

Besides the hypothalamic-pituitary-adrenal axis and the sympathetic nervous activities, heat shock proteins (HSPs) also modulate immune activities. As molecular chaperones (Craig 1993), HSPs binding to polypeptides play essential roles in folding and transportation of polypeptides in almost all cells (Table 1). HSPs, expressed at moderately higher levels by heat stress, protect cells by removing denatured proteins and restoring normal ones. Experiments in vitro have shown that HSPs affect the expression of T cell receptors (TCR) and presentation of antigens (Liossis and Tsokos 1997; Nambiar et al. 2000; Nossner et al. 1996). In this article, the relationship between immune activity and stress is discussed with special reference to thermal stress.

Acute thermal stress and immune activities

It is consistently reported that laboratory stressors, such as stroop test and mental arithmetic, cause an increase in the number of circulating NK cells and T suppressor/cytotoxic (CD8) lymphocytes, a decrease in the ratio of T cell subsets (CD4/CD8) and the proliferation of T cells to mitogens (Bachen et al. 1992; Herbert et al. 1994; Sieber et al. 1992; Zakowski et al. 1992).

Levels of environmental temperature and the rate of temperature changes constitute potent stressors and affect immune activity. Acute cold exposure, at 5 ˚C for 20 min, reduces the number of helper T cells (CD4) in male students (Henning et al. 1993). Also, acute cold exposure of young men at 4 ˚C for 30 min suppresses the proliferative response of lymphocytes to a mitogen, phytohemagglutinin, at 3-4 h after exposure (Jurankova et al. 1995). In heat stroke, the number of T helper (CD4) lymphocytes is decreased and the number of circulating NK cells and T suppressor/cytotoxic (CD8) lymphocytes is increased (Hammami et al. 1998).

Microinjection of CRH into the lateral ventricle of the rat increases the sympathetic nervous activity and decreases the splenic NK cell activity and T cell proliferation (Irwin et al. 1992). The increase in splenic sympathetic nervous activity by stress causes a suppression of the splenic NK cell activity in rats (Shimizu et al. 1996). Adrenalectomy blocks the stress-induced suppression of T cell proliferation in the peripheral blood but not in the spleen, and intravenous injection of β-adrenergic antagonist blocks T cell proliferation in the spleen but not in the peripheral blood *vice versa* (Cunnick et al. 1990). Transection of the splenic sympathetic nerves enhances an antigen production by the spleen in mice (Williams et al. 1981). Therefore, immune activities of the spleen are tonically inhibited by the splenic sympathetic neurones through their β-actions. In humans, a nonselective adrenoceptor antagonist, labetalol, blocks the cellular immune responses to mental stress, i.e. an increase in peripheral NK cell number, a decrease in the ratio of T cell

subsets (CD4/CD8), and a reduced T cell proliferation (Bachen et al. 1995). The increase in peripheral NK cell number in response to acute mental stress is inhibited by oral administration of β-adrenoceptor antagonist, propranolol (Benschop et al. 1994).

Among acute stresses, passive stress such as a cold pressor test decreases the secretion rate of sIgA, and active stress such as mental arithmetic increases the rate of sIgA secretion in males but not in females (Willemsen et al. 2002). In addition to properties of stressors, coping styles with stress also affect the secretion of sIgA. Coping styles with stress are grossly divided into two groups, i.e. emotion-focused type and problem-focused type, according to Lazarus (1993). We have recently observed that videotaped public speech, as a laboratory stressor, decreases the rate of sIgA secretion in female students with emotion-focused type but not in those with problem-focused type (Wada et al. 2005). On the other hand, speech stress causes an increase in variation of interbeat intervals (CVPP) in female students with problem-focused type. It is, therefore, hypothesized that anticipatory styles in coping with stress cause different responses in the mucosal immune system and autonomic nerves innervating the heart. Our observation coincides with the fact that preejection period (PEP) of the heart, employed as an index for β-adrenergic activity (Cacioppo 1994), reveals a negative correlation with the secretion rate of sIgA during mental arithmetic (Williams et al.1981). At the same time, this result provides a possibility that the secretion rate of sIgA is inhibited by the sympathetic nervous activity via β-adrenoceptors. On the other hand, α-blockade by phentramine has been reported to enhance the cold stress-induced increase in serum IgA in mice (Carr et al. 1992).

The mechanism underlying sIgA responses to stress is not well clarified, but following three processes are at least involved. The first process is a facilitation of the translocation that enables the salivary gland to release more sIgA, the second is a stimulation of active transport of sIgA across the membrane from its store site in either glandular connective tissue (Brandtzaeg 1971) or salivary epithelial cells (Snider 1991), and the third is an increase in IgA release by plasma B cells. Released IgA is formed into secretory sIgA (sIgA) and transported into the saliva.

Long-term exposure to thermal stress

Chronic stress generally activates the hypothalamic-pituitary-adrenal axis, and suppresses immune activities (Fig. 3). The defence of the lung against bacteria relies on the phagocytotic activity of alveolar macrophages (Goldstein et al. 1977). The survival rates of *Staphylococcus aureus* and *Proteus mirabilis* in the mouse lung 4 h after inhalation are increased by heat exposure at 35.5 ˚C for 7 days and 14 days (Yamamoto et al. 1999b). This result shows that the phagocytotic activity of alveolar macrophages becomes less efficient when exposed to chronic heat.

Long-term cold exposure at 4 ℃ and heat exposure at 35both decrease the number and activity of splenic NK cells in mice from day 1 to day 16 of exposure accompanying elevated levels of serum cortisol (Won and Lin 1995).

The primary immune response of mice to inactivated Sendai virus (HVJ), which is characterized by an increase in immunoglobulin G (IgG) production with its plateau on 13 days after the challenge of the antigen, is suppressed by heat exposure at 35.5 ℃ for 4 – 12 days (Yamamoto et al. 1999a). In animals exposed to heat, a decrease in tissue weight is obvious in the thymus and spleen as well as a general decrease in body weight. The serum concentration of corticosterones increases consistently, reaches its maximum on day 1 of heat exposure, and decreases gradually.

Cold exposure of calves at –5 ˚C enhances the delayed-type hypersensitivity (DTH) response of the skin by 42% in the first week of exposure, but reduces DTH response in the second week by 14% (Kelly et al. 1982). Heat exposure of calves at 35decreases DTH response by 42% without causing any increase during whole course of exposure. These results indicate that the number or the activity of T helper (CD4) lymphocytes is decreased by thermal stress lasting over 2 weeks.

Heat exposure of mice to 35 ℃ influences the composition of T cell subtypes (Asaki and Iriki 1998). Within T helper (CD4) lymphocytes, Th0, Th1, and Th2 cells can be distinguished (Jacobs and Schmidt 1999). They are identified by their patterns of cytokine-release. Th0 cells secrete anti-inflammatory interleukin 4 (IL-4) and proinflammatory interleukin 2 (IL-2) and interferon γ (IFN-γ). Th1 cells are proinflammatory cells which release IL-2, IFN-γ, and tumor necrosis factor α and β (TNF-α and TNF-β). Th1 cells are essential for DTH response. Th2 cells produce IL-4, IL-5, IL-6, and IL-10. These cytokines released from Th2 cells play indispensable roles in the differentiation and proliferation of B cells. The number of Th1 cells decreases at the third week of exposure, while the number of Th2 cells increases shortly after the onset of heat exposure and remains at high levels during the exposure. The decrease in Th1 cells from the third week predicts a decrease in DTH response observed in calves.

Cytokines such as IL-2 and IFN-γ, released from Th1 cells support cell-mediated immune responses. In contrast, Th2-type cytokines, IL-4 and IL-5, enhance the humoral immune responses. In animal model, a possibility is proposed that the dominance of Th1 or Th2 predicts the susceptibility of the hypothalamic–pituitary-adrenal axis to stressors. Balb/c mice are Th2-dominant animals, and C57bl/6 are Th1-dominant (Heinzel et al. 1991; Scott et al. 1989). In comparison with these two strains, the stress-induced increase in glucocorticoids is greater in Balb/c mice (Shanks et al. 1994).

A similar association between the immune reactions and the hypothalamic-pituitary-adrenal axis has also been observed in rats (Kavelaars et al. 1997). It is likely that a high reactivity of the hypothalamic-pituitary-adrenal axis is associated with a high capacity to generate Th2-type responses and low reactivity of the hypothalamic-pituitary-adrenal axis with a high capacity to generate Th1-type responses. Long-term exposure to heat affects immune activities by modulating the ratio of Th1 cells to Th2 cells.

Heat shock proteins and immune activities

Almost all organisms synthesize a set of proteins called heat shock proteins (HSPs) in response to an increase in temperature (Lindquist 1986). HSPs are also expressed constitutively at normal temperatures, and synthesized by a variety of nonlethal transient stresses, including hyperthermia, oxygen radicals, heavy metals, ethanol and amino acid analogues. Exercise also induces an expression of HSPs in leucocytes (Shastry et al. 2002) and skeletal muscle (Thompson et al. 2002), and increases serum HSPs in humans (Febbraio et al. 2002). For this reason, HSPs are also termed stress proteins. In general, HSPs protect cells from stresses by inhibiting the aggregation of denatured proteins and refolding nature ones (Table 1). Heat tolerance of cells depends on the production of HSPs (Polla and Kantengwa 1991; Ribeiro et al. 1995).

HSPs influence the intracellular signalling of T cells and production of cytokines. In human T lymphocytes exposed to 42 ˚C for 8-24 hr, the production of inositol trisphosphate (IP_3) and subsequent increase in intracellular calcium concentration mediated by T cell receptor with CD3 antigen (TCR/CD3) are downregulated (Liossis and Tsokos 1997). A decrease in TCR ζ chain expression is thought to be a cause for the downregulation of TCR/CD3-mediated production of IP_3 and increase in intracellular free calcium (Nambiar et al. 2000). An overexpression of HSP 70 causes a deceleration of TCR/CD3-mediated response (Liossis et al. 1997). These studies lead a possibility that HSPs production due to heat stress modulates the signal transduction in T cells and therefore immune activities.

Tumor necrosis factor α (TNF-α) incites the production of interleukins (ILs), chemokines and nitric oxide (NO), and activates the inflammatory cascade. Studies in vitro show that HSPs block the transcription of TNF mRNA and decrease TNF production (Ensor et al. 1994; Fouqueray et al. 1992; Snyder et al. 1992). TNF-α potently stimulates macrophages to produce IL-1, and IL-1 reveals a broad effect on immune functions, e.g. proliferation of T and B cells and chemotaxis of neutrophils. Therefore, HSPs may influence the immune activities after heat stress by modulating the cytokine network. A possibility is also proposed that HSPs inhibit the inducible NO synthase and NO production (Hauser et al. 1996; Won et al. 1995; Wong and Wispé 1997).

The action of HSPs to inhibit the aggregation of mutant proteins may be useful for the protection and therapeutic treatment of protein folding diseases, e.g. spinocerebellar ataxia 1 (Cummings et al. 1998) and spinal and bulbar muscular atrophy (Kobayashi et al. 2000). The roles of molecular chaperones expressed in malignant cells are also emphasized in the etiology and therapy of cancer (Soti and Csermely 1998). Moderate overexpression of molecular chaperones expands life span in the fruit fly and nematodes (Lithgow et al. 1995; Smith 1958; Tatar et al. 1997). The accumulation of damaged proteins by oxidative stress is thought to be a major factor of senescence (Jazwinski 1996; Sohal and Weindruch 1996). Therefore, it is hypothesized that the elimination of damaged proteins by molecular chaperones delays senescence and increases life span.

Remarks

In this article, influences of thermal stress on immune activities and immuno-modulatory activities of the autonomic and endocrine systems are briefly reviewed on the basis of findings mainly attained between the 1980's and 1990's. Citing heat stress researches, interrelationships among the immune, autonomic, and endocrine systems are also emphasized. In these two decades, researchers have clearly noticed the fact that the immune, autonomic, and endocrine systems work in a synergetic manner for self-defense. It was generally accepted that the cooperation of these three systems results from the integrative function of the brain. Therefore, to know how the cooperation works and in what situation it does not work properly was expected for complete understandings of health and disease. It was obvious that the brain function managing the cooperation of these three systems contains mental aspects in it. Researchers, giving a great attention to mental aspects, founded new fields, such as social neuroscience (Cacioppo 1994) and psychoneuroimmunology (Schedolwski and Tewes 1999). Knowledge obtained between the 1980's and 1990's greatly contributed to advance interdisciplinary studies concerning physical and mental health.

Yamanashi Institute of Environmental Sciences (YIES) was founded in 1997. Studies exploring the relationship between the environment and health in the department of physiology of YIES were set up on the basis of scientific achievement in these two decades. Studies of the department brought us a great deal of new and important findings in 15 years after the foundation. Hereby, we remind that we greatly owe to the works of researchers and their efforts in these decades.

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