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Review Article

Clinical biomedical research of indoleamine 2,3-dioxygenase: update on current available reports from Southeast Asia

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Abstract: Indoleamine 2,3-dioxygenase is an important enzyme in human, which plays roles in the rate-limiting first step in tryptophan catabolism. Indoleamine 2,3-dioxygenase is currently studied by research groups worldwide. Association between Indoleamine 2,3-dioxygenase and medial disorders in clinical medicine is proposed and is an interesting topic in clinical biochemical reasearch. Here, the author briefly reviews and discusses on the available important scientific reports on Indoleamine 2,3-dioxygenase from tropical Southeast Asia.

Keywords: Indoleamine 2,3-dioxygenase, Indochina, analysis

Introduction

Indoleamine 2,3-dioxygenase is an important enzyme which has its physiological function of the first step in tryptophan catabolism. At present, Indoleamine 2,3-dioxygenase research is a topic widely studied in clinical biomedicine. Indoleamine 2,3-dioxygenase is an inducible antioxidant enzyme [1]. In 1963, Hayaishi et al. firstly discovered this enzyme from their study in animal organ [1]. Indoleamine 2,3-dioxygenase has many specific substrates, which are Indoleamine derivatives. Regarding biochemical process, the enzyme plays role in catalyzing the oxidative cleavage of the indole ring of many important biomolecules including tryptamine, serotonin, tryptophan and melatonin [1].

Indoleamine 2,3-dioxygenase's action is also strongly related to the biological process of interferon (IFN)-gamma and tryptophan metabolism [2, 3]. Hence, Indoleamine 2,3-dioxygenase plays important role in the inflammation response process [2]. Clinical relationship between the enzyme and several medial disorders are observed. Due to its biological process relating to interferon, the enzyme is overexpressed in response to interferon gamma in a variety of different cancers. An immunosuppression through breakdown of tryptophan in the tumor microenvironment and lymph nodes results from the physiological action of this enzyme. Inhibition of this enzyme can decrease growth of tumor. In addition, the immune-mediated mechanism of this enzyme is the focus in researching in chemotherapy and cancer vaccine development. Hence, this enzyme is currently widely studied in clinical oncology [2, 3]. Additionally, due to its role in the immune system, its pathophysiological associations with other inflammatory medical disorders are also studied in biomedicine.

After the successful discovery of inhibitors of this enzyme, many researches on therapeutic purposes are currently performed. For example, Indoleamine 2,3-dioxygenase inhibitor is a new therapeutic alternative cancer therapy [4]. Some new patents on this enzyme are registered and currently used for new drug development [4]. Many scientific reports on Indoleamine 2,3-dioxygenaseare published from many countries worldwide. Most reports are from developed Western countries. Regarding developing areas of the world, there are few publica-

tions. Here, the authors briefly review and discuss on available reports on Indoleamine 2,3-dioxygenase from Indochina countries (Myanmar, Lao, Vietnam, Cambodia and Thailand), a developing area in tropical Asia.

Indoleamine 2,3-dioxygenase research in Southeast Asia

In Southeast Asia, there are some interesting publications on Indoleamine 2,3-dioxygenase. Examples of important publications are hereby summarized.

Research in clinical dentistry

The clinical relationship between Indoleamine 2,3-dioxygenase and dental problem is mentioned in the literature. Dental science research on this enzyme is the first scope of study in Southeast Asia. In Thailand, an Indochina country, there are many researches from clinical dentistry study groups. The first publication in Thailand was on human gingival fibroblast (HGF) by Mahanonda et al. in 2007 [5]. Mahanonda et al. studied on the clinical association between HGF and the enzyme and concluded that HGFs were related to both innate immune response and periodontal inflammation [5]. Mahanonda et al. also further mentioned that IL-17 and IFN-gamma had an important physiological role in periodontal disorder by immune modulation process via stimulation of HGFs [6]. In another report, Nisapakultorn et al. further studied the role of the enzyme in chronic periodontitis [7]. Nisapakultorn et al. concluded that the activation of HGFs by inflammatory cytokines and bacterial products was associated with the increased enzymatic expression in periodontitis lesions [7].

Research in respiratory medicine

There are some interesting reports on Indoleamine 2,3-dioxygenase in chest medicine from Thailand. Most scientific reports are on asthma. The first publication in Thailand is by Maneechotesuwan et al. in 2008 [8]. Maneechotesuwan et al. found an increased sputum indoleamine-2,3-dioxygenase enzyme activity in asthmatic airways after inhaled corticosteroids use [8]. Maneechotesuwan et al. noted that increased interleukin (IL)-10 secreting from macrophages was corresponding pathobiological process [8]. Maneechotesuwan et al. also further reported another interesting observation on the enzyme suppression by Der p 1 dendritic cells from house dust mite-sensitive patients with asthma [9]. Maneechotesuwan et al. noted that this pathoiological process was relating to IL-4 [9]. Recently, Maneechotesuwan et al. also reported that antilipemic drugs, statins, could enhance the anti-inflammatory effects of inhaled corticosteroids in patients with asthma [11]. Maneechotesuwan et al. proposed that the increased induction of indoleamine 2,3-dioxygenasedue to medication was the underlying pharmacological process [11]. Maneechotesuwan et al. concluded for enhancing the effects of corticosteroids on the regulatory T cells and Th17 cells equilibrium [11]. Apart from asthma, Maneechotesuwan et al. also studied the chronic obstructive pulmonary disease (COPD). Maneechotesuwan et al. found that there was a decreasing of enzymatic activity and IL-10/IL-17A ratio in patients with COPD [12]. Maneechotesuwan et al. noted that this observation was relating to IL-10 and IL-17A alteration and concluded that the alteration finally resulted in chronic airway neutrophilic inflammation [12].

Research in psychiatry

Basically, the enzyme is related to tryptophan, which is an important amino acid. Tryptophan is a widely studied amino acid in clinical psychiatry. In Indochina, there are many reports on a clinical psychiatry aspect of the enzymes from Thailand. Those Thai clinical studies are usually on depression [13-16]. Many publications are from a famous local medical center, namely Maes Clinic located at Bangkok [13-17]. Maes et al. concluded that somatization was related to tryptophan catabolite (TRYCAT) pathway [17]. Maes et al. noted for lower kynurenine aminotransferase activity and increased Indoleamine 2,3-dioxygenasein somatization [17].

Research in tropical medicine

As a tropical country, tropical disease is very common in Indochina. There is an interesting publication on relationship between Indoleamine 2,3-dioxygenase and tropical bacterial infection from Thailand. Prachason et al. studied scrub typhus and indoleamine 2,3-dioxygenase [18]. Prachason et al. found that the activation of the enzymatic process was a

defensive mechanism against infection [18]. Prachason et al. concluded that downstream of IFN-gamma inhibited intracellular *Orientiat-sutsugamushi* pathological expansion by interfering tryptophan metabolism [18]. There is another interesting report from Vientnam on association between indoleamine 2,3-dioxygenase and dengue, a tropical mosquito borne infection [19]. Tuyen et al. found a pronounced gamma-IFN immune response and tryptophan degradation induced by the enzyme in dengue [19]. Tuyen et al. noted that this might be an important pathological process of severe dengue [19]. A recent collaborative study between Australian researchers and research group in Vietnam additionally showed that there was an increased kynurenine to tryptophan ratio due to activation of Indoleamine 2,3-dioxygenasein dengue patients and ration returned to normal after dengue recovery [20].

Research in oncology

As earlier noted, the enzyme inhibitor is the new focus in oncotherapy [4]. However, there are few publications on this aspect. An example is the report by Phacharapiyangkul et al. [21]. Phacharapiyangkul et al. found that extracts of *Astragalus membranaceus* could enhance chemosensitivity and reduce tumor Indoleamine 2,3-dioxygenase expression [21]. In another report, Issaranggun Na Ayuthaya et al. found that interleukin (IL)-12 upregulated the expression of interferon gamma in a dose-dependent manner and IL-12 also induced the expression of Indoleamine 2,3-dioxygenase [22]. Since there are many infectious diseases in Southeast Asia, the oncogenic infection is also a research focus in this area. An association between Indoleamine 2,3-dioxygenase and the oncogenic virus infection is also reported. Sunthamala et al. studied on immune responses against human papillomavirus (HPV) and found that HPV16 E2 protein promotes innate immunity by modulating immunosuppressive status [23]. Due to this pathological process, there is an impaired Indoleamine 2,3-dioxygenase transcription [23].

In general, clinical oncology is an important scope for clinical biomedical research on Indoleamine 2,3-dioxygenase [24-27]. Nevertheless, overall numbers of researchers in clinical oncology aspect are few in Southeast Asia. This might reflect that the enzyme inhibitor use is still extremely limited in Indochina.

Research in clinical cardiology

The role of Indoleamine 2,3-dioxygenase in heart disease is an interesting issue. A Thai study by Wongpraparut et al. showed possible role of Indoleamine 2,3-dioxygenase as a cardiac marker [28]. Wongpraparut et al. concluded that immunometabolic response mediated via Indoleamine 2,3-dioxygenase function was enhanced in patients with coronary artery disease [28].

Research in obstetrics

There are some studies on clinical interrelationship between Indoleamine 2,3-dioxygenase and obstetric problem. Roomruangwong et al. reported that body image dissatisfaction in pregnant women was associated with altered Indoleamine 2,3-dioxygenase level [29].

Research in clinical immunology

As earlier noted, the enzyme inhibitor has its role via many immune related mechanisms. There is a report from Vietnam on the association between the enzyme and autoimmune disease [30]. The role of aryl hydrocarbon receptor (AHR) is proposed by Nguyenet et al. [30].

Perspective

At present, there are limited scientific publications from tropical Southeast Asia on indoleamine 2,3-dioxygenase. This might imply the necessity for local scientists to have update knowledge on this specific area. When a new enzymatic inhibitor becomes widely used in clinical medicine, there will be an increased recognition by local medical scientists in this developing areas and there might be a number of researches who followed known knowledge from the developed area of the world, the Western hemisphere. This is an example of progress of clinical biochemistry research activity in a less developed area of the world that usually lacks of pioneer novel publications but repeatedly follow known knowledge and technologies.

Conclusions

There are few scientific reports on Indoleamine 2,3-dioxygenase from Indochina. Most scientific publications are published by famous research groups. The scientific publications are on many specific diseases, including asthma, den-

tal disorders, and depression. However, the numbers of publications are very few comparing to other areas of the world. Additionally, there is no report on clinical oncology. The lack of study on indoleamine 2,3-dioxygenase inhibitor in clinical oncology in Indochina implies little implementation of the new cancer therapy alternative in this area.

Compared to researches from the developed area of the world, the reports from Southeast Asia usually lack originality and novelty. While there are hundreds of reports from the Western countries, less than fifty publications on the enzyme are currently available from Indochina. Additionally, various aspects of reseaches are available in Western reports, but few scopes of publications are available from Indochina reports. Reports on important diseases such as cancers are also limited which might due to limited knowledge and technologies in this less developed area of the world. Less investigation on biochemistry research activity is reflected. However, there are also some collaborative researches on tropical diseases that remain novel and will be further references for academic society.

Further research on this specific field is required. Moreover, scientific publications of on indoleamine 2,3-dioxygenase are from only Vietnam and Thailand, implying a need to promote scientific research activity in this region.

Disclosure of conflict of interest

None.

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