Invited Review

Insulitis and islet microvasculature in type 1 diabetes

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Summary. Type 1 diabetes is characterized by a mononuclear infiltration, commonly called «insulitis». The cells that constitute the insulitis are mainly monocytes that are recruited from extra-islet areas and arrive at the islet site via the vascular system. Infiltrating cells must then pass across the endothelia to gain access to the islet parenchyma.

The anatomy and physiology of the islet microvasculature shows that islet B cells are firstly perfused and influence both endocrine non-B islet cells and peri-insular exocrine cells.

The low dose streptozocin (LDS) treatment is able to induce, other than a monocyte/macrophage recruitment and activation, islet vascular alterations, mainly at the level of post-capillary venules encircling the islets of Langerhans and a concomitant fall in Superoxide dismutase (SOD) (the first cellular defence against free radicals) activity. These findings, together with the increase in vascular permeability and the morphological evidence of areas of oedema formation within the islets, have raised the interest in the «islet microvasculature» approach to this disease. Actually the reduction in B-cell perfusion and the concomitant attack by phagocytes with a fall in SOD activity should be considered as events that are linked to each other. On the other hand both macrophages and endothelia are able to produce free radicals and, in particular, nitric oxide. This confirms that the islet vascular system seems to be involved in early insulitis and B-cell lysis.

Key words: Insulitis, Monocytes, Macrophages, T-lymphocytes, Dendritic cells, Microvasculature, Type 1 diabetes, Ultrastructure

Introduction

Insulin-dependent (Type 1) diabetes mellitus occurs in humans, as in animal models, with an islet inflammation, commonly called «insulitis» (Like and Rossini, 1976). This islet infiltration was first discovered in 1965 by Gepts and De Mey in pancreatic sections belonging to a young recent-onset type 1 diabetic patient and the infiltrating element were depicted as being «mononuclear» cells.

The discovery of islet cell antibodies (Bottazzo et al., 1974; MacCuish et al., 1974) and of insulin autoantibodies (Palmer et al., 1983), together with the finding of an increased expression of HLA molecules in the infiltrated islets (Bottazzo et al., 1985), may be proofs in favor of the hypothesis that the process against islet B-cells is of autoimmune origin.

Numerous studies focused on the appearance of the first and/or the more relevant element invading the islets of Langerhans and many types of cells were, in turn, assumed to be the key element involved in initiating the inflammatory process: these included monocyte/macrophages (Walker et al., 1988), T-lymphocytes (Hayakawa et al., 1991) and dendritic cells (Voorbij et al., 1989). CD8+ T-cells were found to be predominant in man (Bottazzo et al., 1985; Sibley et al., 1985), but at a late phase of the disease. Recently, Hanninen et al. (1992) found an involvement of macrophages as well as antigen-specific CD8+ T-cells. With the exception of the non-obese-diabetic (NOD) mouse model, in which an initial predominance of CD4+ T-cells has been reported (Miyazaki et al., 1985; Signore et al., 1989), monocyte/macrophages have been found to be the first element invading the islets by several authors; in particular, Kolb-Bachofen et al. (1988) found activated «resident macrophages» within the islets in the earliest phase of the low-dose streptozocin (LDS)-induced diabetes model. This very initial phase has been termed «single cell insulitis» and resident macrophages were consequently involved in the selective attack against the islet B-cells.

Studies on this animal model of type 1 diabetes have ascertained that rather than «resident» macrophages (their number is extremely limited within the islets), «recruited» ones are mainly involved in islet B-cell phagocytosis (Papaccio et al., 1991a). Moreover, in
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Further studies, it has been shown that, after recruitment of monocytic phagocytes from blood takes place within the postcapillary venules encircling the islets, especially at their vascular pole (Fig. 1), these phagocytes marginate (Papaccio et al., 1993a) and later cross the vessel wall, penetrating the islet parenchyma, where they undergo morphofunctional transformation into tissue macrophages (Papaccio and Esposito, 1992). In fact, these cytotoxic effector cells acquire membrane protrusions (ruffled membranes) and primary and secondary lysosomes can be seen in their cytoplasm (Fig. 2). They then lyse the islet B-cell membranes and phagocytose islet B-cells. These events occur in a day by day sequence (Fig. 3) together with other biochemical and morphofunctional phenomena including the islet vascular bed alterations, extra-islet infiltration and a decrease of the islet's superoxide dismutase (SOD) levels, the first cellular defence against superoxide anions and oxygen free radicals.

Islet microvasculature: anatomy and physiology

The islet vascular system was first described as being a capillary glomerulus with a direct arterial blood supply (Wharton, 1932). Later, Fujita (1973) described an «insulo-acinar portal system» in which one or two afferent arterioles approach the islet, break into capillaries at the level of non-B-cells, form the glomerulus and leave the islet as numerous efferent capillaries passing into the exocrine pancreas (Fujita and Murakami, 1973). This pattern led to the thought that islet hormones could influence exocrine cells and their secretions (Fujita et al., 1976).

With regard to the endocrine cell population, islets were described as being «heterogeneous» both in their cell composition and in the B-cell response to glucose stimulation (Orci et al., 1976; Kolod et al., 1981). Moreover, Lifson et al. (1980) demonstrated that not all the blood to the pancreas goes through the islets. Therefore, a careful re-examination of the islet's microvascular organization was performed by Bonner-Weir and Orci (1982). These authors grouped the islets into three classes on the basis of their size (small, intermediate and large) and modified the previously described pattern as follows: an afferent arteriole enters the islet at a «gap» in the non-continuous mantle of A-, D- and PP-cells and goes directly to the B-cell core. As this vessel enters the islet, it branches into capillaries which cross first the B-cell core and then pass through the mantle of non-B-islet cells. The efferent capillaries coalesce around the islets into collecting venules. This pattern is typical of large and intermediate islets but not of the small ones in which efferent capillaries either coalesce at the periphery of the islet or pass through perisinusoidal exocrine tissue before forming venules. It has also been noted that in the islets of large and intermediate size, the «overlying collecting venule network» is closely apposed to the mantle. All these anatomical findings indicate that: i) a microportal circulation within the islets exists, but not all the efferent vessels are part of it; and ii) the efferent vessels reach the B-cell core first without perfusing the non-B islet tissue. The latter is of some importance and Samols et al. (1988), studying the islet blood flow, found that within the islet a «core to mantle circulation» exists so that the B-cell core is perfused before blood flows to the mantle; in terms of microcirculation it has been found that the order of perfusion is, in the rat (Samols et al., 1988) and in the dog (Stagner et al., 1988), the following: B,A,D. This order of microvascular circulation suggests several regulatory interactions and implications.

A «vascular order» in perfused human islet pancreas

Fig. 1. Light micrograph belonging to an LDS-treated mouse showing infiltrating mononuclear elements localized at a «pole» of the islet. x 250
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has also been studied by Stagner and Samols (1992) and these authors concluded that: a) the direction of blood flow is «core to mantle» and the majority of D-cells are further downstream than the majority of A cells; b) B-cells microvascularly suppress A-cells and possibly also D-cells; c) A-cells microvascularly stimulate D-cells; and d) D-cells are vascularly neutral within the islet.

A direct consequence of the above described vascular order is that the B-cell is the primary glucose sensor which may explain the dual elevation of glucagon and somatostatin secretion reported in type 1 diabetes (Samols et al., 1986). Furthermore, islet B-cells possess microvilli and canaliculi that allow the passage of interstitial fluids from an «arterial» capillary to a «venous» capillary (Bonner-Weir, 1989).

An additional portal system has been proposed in the rabbit pancreas by Lifson and Lassa (1981). They suggested that acinar venous blood supplies the capillaries of interlobular ducts (acinoductal portal system).

On the other hand, it is well known that both endocrine and exocrine cells derive from the ductular epithelium and an intimate relationship between ducts and islets and the endocrine and exocrine tissues has been hypothesized since periinsular halos were first observed by Jarotzky (1989). Periinsular halos consist of a rim ranging from 50 to 100 μm of exocrine tissue surrounding the islets; in this rim, acinar cells are bigger, with larger nuclei and nucleoli and with more numerous zymogen granules than those commonly found in the other acinar cells. These «halos» have been related to locally high insulin levels and disappear after alloxan treatment but are unusually prominent in streptozocin-treated rats (Hellman et al., 1961). The presence of periinsular halos strongly suggests that the periinsular effects of local high concentrations of islet hormones derived from the islet-acinar portal system are indeed local; this means that two populations of acinar cells may exist: 1) periinsular acinar cells, sensitive to high concentrations of islet hormones; and 2) teleinsular acinar cells, sensitive to systemic levels of islet hormones (Stagner and Samols, 1992).

Islet microvascular alterations in early type 1 diabetes

Several approaches have been taken in order to study the alterations of islet microvasculature in type 1 diabetes. Papaccio et al. (1990) have studied the effects of the LDS treatment on the islet capillaries and found a
significant decrease of the islet capillary area. Administration of streptozocin (STZ) has been shown to induce an increase in the permeability of the islet capillaries with consequent oedema formation (Sandler and Jansson, 1985; Beppu et al., 1987; Martin et al., 1989). The resulting state of hypoxia may worsen B-cell destruction. In a further study on this argument Papaccio and Chieffi Baccari (1992) have shown that the most dramatic decrease occurs on day 11 after the first STZ administration (Fig. 4). These authors have hypothesized that this reduction in the islet capillary area could allow recruited macrophages to enter the islet parenchyma and damage islet B-cells. The reduction in B-cell perfusion and the concomitant attack by phagocytes with a reduction of cellular defence against free radicals may be considered as events that are linked to each other.

De Paepe et al. (1992), using a technique based on high resolution protein-A-gold cytochemistry, found an increased vascular permeability in diabetic Bio Breeding (BB) rat islets. On the other hand, fenestrated endothelia of the islet capillaries have been described as being «restrictive» to exogenous and endogenous molecules (Hart and Pino, 1986).

Therefore, the islet vascular system seems to be involved in early insulitis and B-cell lysis in several animal models. The role of the vascular endothelium is also under examination and is now of great interest.

Post-capillary venules and activation of endothelial cells: the role of cytokines and adhesion molecules

It is commonly known that the infiltrate is organized about the post-capillary venules of the inflamed tissue. These venules become leaky, permitting extravasation of macromolecules (Papaccio et al., 1990; Papaccio and Chieffi Baccari, 1992). Moreover, the endothelial cells become hypertrophied, protruding into the lumen and their cytoplasm contains increased quantities of endoplasmic reticulum and Golgi apparatus, a sign of raised biosynthetic activity. Willms-Krestschmer et al. (1967) called this phenomenon «endothelial cell activation», implying a functional consequence to the altered morphology. This point of view has changed the opinion on the endothelium’s role in the inflammatory process, from passive to active, mainly in the case of the autoimmune type.

Analogously to the activation of macrophages, as described above, Pober (1988) defined endothelial activation as «quantitative changes in the level of expression of specific gene products (i.e. proteins) that, in turn, endow endothelia with new capacities that cumulatively allow endothelial cells to perform new functions».

Class II antigen expression by endothelial cells, as expressed by monocyte/macrophages (Papaccio et al., 1991a, 1993a) in the early type I inflammation process, or in other cases, is indeed an example of activation in the cell biological sense. With regard to this, Bretzel et al. (1990) found an increased expression of MHC antigens of class I and II in endothelia of diabetic rat pancreas. Actually, the findings of cells within the islets during early insulitis showing increased expression of MHC II molecules is of importance but difficult to interpret; in other words, it means that an autoimmune process is at work but nobody can say with security which cells are really expressing these antigens: monocyte/macrophages, endothelial cells, B-cells, singularly or all together. This problem has not been adequately stressed by authors, but it must also be clarified in the light of the recent observations of an increased expression of class II molecules in pancreatic

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* from the first STZ injection.

Fig. 3. Figure summarizing the events occurring in early LDS diabetes.

Fig. 4. Histogram showing the percentage of islet capillary areas in control and LDS-treated mice (from: Papaccio and Chieffi Baccari, Histochemistry 97, 371-374, 1992).
products of NOD- and LDS-treated mice (Papaccio et al., 1993b; Papaccio, unpublished observations).

With regards to the secretory products, interleukin-1 (IL-1) is the predominant secretory product both of blood monocytes and endothelial cells. Cytokines modulate the expression of adhesion molecules on the endothelial cell surface, which, in turn, can account for the increased adhesion of leukocytes to cytokine-activated endothelium (Poher et al., 1986). Moreover, cytokines can alter endothelial morphology, along with membrane cytoskeletal and matrix organization (Stolpen et al., 1986).

Immune inflammation is assumed to be initiated by T-cell recognition of a foreign antigen in a tissue; when T-cells recognize the foreign antigen (presented by monocyte/macrophages, dendritic cells or by vascular endothelium), secreted lymphotoxins and interferon gamma combine to activate local venular endothelial cells. Increased expression on endothelial cells of class I and II MHC antigens grants increased ability to present foreign antigen to additional T-cells. As a consequence, endothelial cells can use the complex of antigen plus MHC to bind circulating lymphocytes and monocytes, which, once bound, preferentially extravasate and accumulate in the parenchyma. Increased Inter Cellular Adhesion Molecule 1 (ICAM-1) expression (also induced by cytokines) will promote the adhesion and extravasation. Morphological changes induced by cytokines will facilitate extravasation and binding of monocytes and may also underlie the vascular leakiness to macromolecules (Poher, 1988). The above-reported model of endothelial cell participation in «in vivo» immunity relates well with the findings of a recruitment of monocytes, of their margination and extravasation and of an intra-islet oedema formation in the LDS model (Papaccio et al., 1991a, 1993a) and also with the more recent observations of an increased expression of ICAM-1 molecules in post-capillary vessels encircling the islets of LDS-treated mice (Papaccio et al., unpublished observations) and with the results of Hanninen et al. (1992), who found in the human pancreas of a recent-onset insulin-dependent diabetes mellitus patient, an increased expression of ICAM-1 on vascular endothelium. Therefore, endothelial cell «activation» now seems to be an obligatory and necessary step of cell-mediated immunity.

Endothelial leukocyte adhesion molecule (ELAM-1) which serves to bind polymorphonuclear leukocytes, may also serve to distinguish the leaky activated venules of acute immunological inflammation from the nonleaky, chronically activated high endothelial venules (HEV) found in peripheral lymphoid tissue and elsewhere (Bevilacqua et al., 1987; Messadi et al., 1987). The latter is of great interest and importance in type 1 diabetes, due to the presence of a leakiness and a not yet proven presence of such HEVs. Moreover, is very hard to distinguish between normal and high endothelial venules (Freemont and Ford, 1985). These vessels (HEV) are specialized segments of postcapillary venules where lymphocytes leave the circulation to enter perivascular tissues; the term HEV derives from the morphology of their «cuboidal» or «columnar» endothelial cells lining the wall; as well as being taller than the resting endothelial cells, they possess cytoplasmic pyroninophilia and ribonuclease-labile metachromasia, one or more prominent nucleoli and a well-developed Golgi apparatus (Freemont and Jones, 1983). The post-capillary venular segment is indeed an object of future studies also in type 1 diabetes due to the occurrence of monocyte and leukocyte trafficking and macromolecular extravasation.

As proposed by Poher (1988) it is reliable that circulating cytokines, produced by monocyte/macrophages and/or by endothelial cells, cause a systemic activation of postcapillary venular endothelial cells, inducing the same morphological changes and consequent vascular leakiness found locally at sites of cell-mediated immune reactions. Interferon gamma (IFN-gamma), another secretory product, on its own causes increased expression of endothelial HLA-DP and accumulation of relatively few mononuclear cells; both «de novo» endothelial cell ELAM-1 expression and increased ICAM-1 expression were induced by Tumor Necrosis Factor (TNF), which also led to the accumulation of large numbers of polymorphonuclear and mononuclear cells (Monro et al., 1989). Therefore, during immune inflammation, locally-produced TNF and IFN-gamma, are important in mediating initial cellular accumulation through their action on endothelial cells (Chin and Hay, 1980). Moreover, an increased vascular permeability and extravascular fibrin deposition, other than endothelial cell hypertrophy occur (Wilms-Kretschmer, 1967). The former is under recent study in early onset of type 1 diabetes (De Paepe et al., 1992; Papaccio and Chieffi Baccari, 1993).

Under normal conditions the endothelial cells provide the major barrier to permeability. Four kinds of alterations during phlogosis lead to increased permeability (Poher and Cotran, 1990): these included endothelial cell contraction, endothelial cytoskeletal and junctional reorganization, endothelial cell injury with retraction, lysis and denudation and endothelial denudation without lysis. Endothelial cell contraction takes place in minutes and leads to extravasation of fluids and plasma proteins but not of cells (the leakiness then worsens haemostasis).

**Vasodilation and vasoconstriction**

Poher (1988) affirms that the vascular leak syndrome is an example of endothelial cell activation causing a «dysfunction» without evidence of vascular injury (at an early time).

We share this opinion other than for the reasons and proofs reported by the author also because of two findings up to now believed to be of only secondary importance in type 1 diabetes: 1) the finding of an
inflammation not limited to the islets of Langerhans, but involving many organs and tissues, including the exocrine pancreas, thyroid, salivary glands and Harderian glands (Asamoto et al., 1984; Miyagawa et al., 1986; Sugihara et al., 1989; Goiliot et al., 1991), with the main finding of post-capillary venules engulfed with mononuclear cells; and 2) the alterations in the islet capillary bed together with the areas of oedema within the islet parenchyma, phenomena occurring in succession and not surely secondary to vascular injury, but, at least at the onset of the disease, secondary to a «dysfunction» of unknown origin (Papaccio and Chieffi Baccari, 1992, 1993).

A point of major controversy is the occurrence of «vasodilation» or «vasoconstriction» together with the increased vascular permeability. It is not a rule that vessel dilation must be the first step; in some systems a vasodilation may be preceded by transient vasoconstriction. The latter event could happen in LDS diabetes (Papaccio and Chieffi Baccari, 1992).

As a consequence of local vasodilation, there is increased blood flow and delivery of mononuclear cells to the tissue site (Pober and Cotran, 1990). Vasodilation results from relaxation of vascular smooth muscle cells. Most vasodilators are known to act indirectly, stimulating endothelial cells to release mediators, including prostacyclins and endothelial-derived relaxing factor (EDRF) (Brenner et al., 1989). Nitric oxide, a relatively newly discovered free radical (see below), is the principal component of EDRF (Breidt and Snyder, 1990).

Free radicals (oxygen radicals and nitric oxide) and scavengers (superoxide dismutase): a new model of pathogenesis and therapeutic intervention in type 1 diabetes

Grankvist et al. (1981) and Asayama et al. (1986) found that islet cells have a very low level of superoxide dismutase, the first cellular defence against free radical activity. Moreover, Gandy and coworkers (1982) experimented with the benefits of an administration of exogenous SOD in diabetes. Later a free radical scavenger, namely citioline, was found to possess a protective action against LDS diabetes (Papaccio et al., 1986; Papaccio, 1991). Moreover, it has been found that SOD levels in LDS diabetes dramatically decrease from day 5 through to day 12 from the start of STZ administration (Papaccio et al., 1991b) and that this decrease happens at the same time as the activation of macrophages and phagocytes of the islet B-cells (Papaccio and Esposito, 1992). Furthermore, in the BB Wistar rat model the islet SOD levels are significantly lower with respect to Wistar rat controls of the same age (Pisanti et al., 1988). These results were interpreted as a prerenes factor that favours the development of the diabetic syndrome.

Those studies on the relationships between free radicals and islet B-cell damage were confirmed by other authors (Mendola et al., 1989; Sumoski et al., 1989).

More recently a new free radical, namely nitric oxide, has been claimed by authors as responsible for B-cell damage in type 1 diabetes. Nitric oxide is enzymatically released from arginine by NO synthase; at least two isoforms of this enzyme exist: one is calcium/calmodulin-dependent and is constitutively expressed by the endothelium and neurons, it delivers small amounts of NO for short periods and exerts a smooth muscle relaxation effect with consequent vasodilation; the other isoform is calcium/calmodulin-independent, is inducible and large amounts of NO are delivered for longer periods of time. These high levels of NO are able to impair the mitochondrial function and determine DNA damage (Kolb and Kolb-Bachofen, 1992a; Fehsel et al., 1993).

NO has been recently identified as the most potent islet-toxic compound released by monocyte/macrophages (Kronke et al., 1991). Bergmann et al. (1992) found that IL-1, a macrophage product, causes islet cell lysis via the induction of NO secretion. Moreover, suppression of NO synthesis from L-arginine «in vivo» has been found to attenuate immune-mediated diabetes in the LDS model (Lukie et al., 1991) and administration of a nitric oxide synthase inhibitor has been reported to be able to suppress LDS-induced diabetes in mice (Kolb et al., 1991); this last study is rather contradictory and insufficiently demonstrative due to the small number of animals used, the short period of observation and the persistence of «macrophage insulitis» which, contrarily to what the authors stress, is of negative forecast for diabetes development. Moreover, the drug used exerts several side effects such as hypertension.

Oxygen-free radicals (superoxide and hydroxyl radicals) are liberated within the islets either directly by infiltrating macrophages or indirectly by cytokines secreted by them or by lymphocytes that induce the formation of oxygen-free radicals within the B-cell mitochondria. Islets are very sensitive to oxygen radicals due to the very low concentrations of SOD, as reported above.

Mandrup-Poulsen et al. (1990) has proposed a model of autoimmune destruction of the islet B-cells in which the presence of macrophages and helper T-cells and the secretion of cytokines is needed. More recently, Corbett and McDaniel (1992) proposed a new model of cytokine-mediated B-cell injury in which IL-1 is produced by activated macrophages infiltrating the islets and interacting with its receptors on the B-cell (Eizirik et al., 1991) inducing the expression of nitric oxide synthase. Macrophages, moreover, directly produce nitric oxide and cause further damage to the B-cells.

Several hypothesis of intervention are now being studied with the aim of inhibiting NO generation. A problem in using inhibitors of nitric oxide synthase is identifying a drug capable of selectively inhibiting only the «inducible» isoform of this enzyme. This would
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avoid the hypertensive side effect, a consequence of the inhibition of the constitutive isofrom. Aminoguanidine seems to be a selective drug for the inducible isofrom and is under examination as a therapeutic agent (Corbett and McDaniel, 1992).

Questions also still remain to be answered with regards to the paradox of the «protective» (Jacob et al., 1990) and «cytotoxic» (Bendtzen et al., 1986; Mandrup-Poulsen et al., 1986, 1990) role of cytokines.

Another point of great importance is the possible involvement of lipid peroxidation phenomena in islet B-cell damage by cytokines. Rabinovitch et al. (1992) reported that an end product of lipoperoxidation (namely malondialdehyde MDA), in rat islets incubated with cytokines, significantly increases and this is accompanied by islet necrosis. Moreover, an inhibitor of lipid peroxidation (namely U78518E, produced by the Upjohn Co., Kalamazoo, Michigan, USA) significantly decreases the cytokine-induced increase in islet MDA and protects islet B-cells from destruction. These findings led to test the effectiveness of this product «in vivo» in the LDS model. The drug resulted highly toxic for mice and poorly protective for pancreatic B-cells (Papaccio et al., unpublished observations).

Conclusions

The islet of Langerhans has been charmingly defined «a remarkably sophisticated microorgan» (Samols and Stagner, 1991).

The future goals of research in this area are strictly linked to the clarification of the role of the islet vascular system. Therefore, endothelium may also be a potential target for therapeutic intervention in type 1 diabetes. We think that the ability to maintain a normal vascular bed together with the ability to increase SOD levels or counteract increases in free radicals are the next challenge. This hypothesis is supported by the observation that, in absence of endothelial cells or macrophages in culture, cytokines are not able to induce detectable amounts of NO or B-cell lysis (Kolb and Kolb-Bachofen, 1992b).

Furthermore, the filling of postcapillary venules with mononuclear cells is not only limited to islet vessels, but involves the whole pancreas in NOD and LDS-treated mice. Moreover, this «vasculitis», together with interstitial inflammation processes, has been found in other organs such as salivary, lacrimal and Harderian glands, as reported above. This may suggest that a systemic process occurs unless a possible relationship between these glands and the autoimmune inflammation occurring in type 1 diabetes is discovered. Finally, research must clearly explain why a complete destruction of the islet B cells (real target element) takes place, but only a partial damage, and often a complete recovery, of the other organs seems to occur.

References


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