Mast cells in health and disease

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ABSTRACT

Although MCs (mast cells) were discovered over 100 years ago, for the majority of this time their function was linked almost exclusively to allergy and allergic disease with few other roles in health and disease. The engineering of MC-deficient mice and engraftment of these mice with MCs deficient in receptors or mediators has advanced our knowledge of the role of MCs in vivo. It is now known that MCs have very broad and varied roles in both physiology and disease which will be reviewed here with a focus on some of the most recent discoveries over the last year: MCs can aid in maintaining a healthy physiology by secreting mediators that promote wound healing and homeostasis as well as interacting with neurons. Major developments have been made in understanding MC function in defence against pathogens, in recognition of pathogens as well as direct effector functions. Probably the most quickly developing area of understanding is the involvement and contribution MCs make in the progression of a variety of diseases from some of the most common diseases to the more obscure.

INTRODUCTION

Paul Ehrlich first described MCs (mast cells) or ‘mastzel- len’ in 1878 based on their unique staining characteristics and their large granule content. Research into the role of MCs in health and disease has come a long way since Ehrlich’s initial speculations that these cells with their large granules were present to ‘nourish’ the surrounding tissue [1]. Today, MCs are known to play pivotal roles in maintaining a healthy physiology, in wound healing and angiogenesis and defence against a whole host of pathogens, participating in both innate and adaptive immunity. They also contribute in the inflammatory process, attracting different leucocyte subsets to the site of injury and in allergy and allergic diseases. The most compelling evidence of the importance of MCs in health and disease is their conservation in evolution and that there has never been a description of a human lacking MCs. One of the major advances in this field has been made by the development of MC-deficient (MC−/−) mice (reviewed in [2]). These themes will be discussed in the present review with a focus on recent developments in MC research in the last year.

Key words: asthma, atherosclerosis, autoimmune disease, host defence, mast cell activation, mast cell progenitor.

Abbreviations: BM, bone marrow; BMDC, BM-derived MC; CAPS, cryopyrin-associated periodic syndrome; CCR, CC chemokine receptor; CMp, common myeloid progenitor; CNS, central nervous system; CTMC, connective tissue mast cell; EAE, experimental autoimmune encephalomyelitis; ET-1, endothelin-1; FGF, fibroblast growth factor; GMp, granulocyte/macrophage progenitor; IFN, interferon; IL, interleukin; LT, leukotriene; MAdCAM, mucosal vascular addressin cell adhesion molecule; MC, mast cell; MCp, MC progenitor; MCγ, tryptase MC; MCβ, tryptase chymase MC; MMC, mucosal MC; MS, multiple sclerosis; MPL, NOD-like receptor; NLRP, leucine-rich repeat protein; PG, prostaglandin; SCF, stem cell factor; TGF, transforming growth factor; TLR, Toll-like receptor; TNF, tumour necrosis factor; T-reg, regulatory T-cell; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; WAT, white adipose tissue.

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MC BIOLOGY

Origins and development

Like other myeloid cells, MCs derive from the bone marrow [3]; however, the intricacies of their origin are only now being elucidated. MCs (MC progenitors) were first identified as a minor population of circulating c-kit+ committed MCs in mouse fetal blood [4]. Recent findings have shown that a MC is derived from a CMP (common myeloid progenitor), but not from a GMP (granulocyte/macrophage progenitor), which has been reported previously [5]. There is also evidence for a bipotent basophil/MCP population in the spleen [6], illustrating the complexities of MC ontogeny. Unlike other leukocytes, MCs are thought to be released from the bone marrow into the peripheral blood as committed MCs and undergo maturation under the control of local cytokines, once they are recruited into specific tissues [3,6–9]. Here, they develop and mature into granulated MCs, where they are found in specific locations.

The mechanisms controlling MCP recruitment are essential to determining where MCs are found, but the mediators involved in recruitment to different tissues are often being newly defined. Certain integrins, chemokines and lipid mediators have been implicated in these mechanisms using a combination of limiting dilution assays and in vitro chemotaxis assays. Mouse BM (bone marrow)-derived MCs respond chemotactically to LTB4 (leukotriene B4), acting through the high-affinity BLT1 receptor, but this receptor is lost during cell dilution assays and in these mechanisms using a combination of limiting chemokines and lipid mediators have been implicated in recruitment with IL-4 increased the level of chymase in their granules [18]. Human MCs can also be distinguished by these two waves of mediator release. Initially, histamine become soluble immediately, but others may remain associated with insoluble particles and be released slowly and for a prolonged time. These particles can be altered by IL-10 [20], and treatment of human MCs

Phenotype and location

Despite MCs all deriving from a common lineage and having a granulated morphology, they are extremely heterogeneous and ‘plastic’ in phenotype and function [16]. Their heterogeneity is starting to be defined and is most probably shaped by the specific microenvironment around the MCs and the mediators or pathogens that they encounter. Rodent MCs can be broadly divided into two phenotypes, CTMCs (connective tissue MCs) and MMCs (mucosal MCs), which differ based on localization, mediator content and responses to different stimulations. Mouse MCs have been characterized based on their heterogeneous expression of proteases, including the chymases (mMCP-1, -2, -4, -5 and -9), tryptases (mMCP-6, -7, -11 and mTMT, a transmembrane tryptase) and mMCP-6 (carboxypeptidase) [17]. CTMCs contain chymases and tryptases, bound to heparin and the MMCs contain just chymases, bound to chondroitin sulphate [18]. Human MCs can also be distinguished by these two types of protease, with MC-T (tryptase) or MC-T (tryptase chymase) MCs; however, they are less tissue-specific [19]. Protease expression can also be altered with different stimulation. For example, in mouse, MC protease content can be altered by IL-10 [20], and treatment of human MCs with IL-4 increased the level of chymase in their granules [21]. These results emphasize the plasticity shown within the MCs, how redundant the two-MC-type classification may be and how much more there is to understand about the way in which MCs respond to their environment.

MCs are found at the interface between the host and the external environment near blood vessels, lymphatic vessels, nerve fibres and a range of immune cells, including dendritic cells [22]. This strategic positioning allows them to act as sentinels of invading microbes, but also to respond rapidly to any change in environment by communicating with different cells involved both in physiological and immunological responses.

MC responses

The plethora of mediators and the speed at which some of these mediators are released from MCs makes the control of MC activation key to their function. There are two waves of mediator release. Initially, insoluble granules (and their associated mediators) are exocytosed within seconds in a process known as degranulation. Some associated mediators such as histamine become soluble immediately, but others remain in an insoluble particulate form maintained by interactions between negatively charged carbohydrates (heparin) and positively charged proteases. Granule proteins such as TNF (tumour necrosis factor) can remain associated with insoluble particles and be released slowly and for a prolonged time. These particles can...
Mast cells in health and disease

Figure 1  MC development and recruitment

MCp derived from a CMp in the bone marrow. Also, GMPs may migrate to the spleen, where the bipotent BMCPs (basophil/MCps) probably differentiate into committed basophil progenitors and MCps, which are then released into the circulation. The basophil progenitors likely differentiate into basophils in the circulation. In the naive mouse, committed MCps home to the intestine, a process dependent on their expression of α4β7 and CXCR2 and by the expression of VCAM-1, MAdCAM-1 and CXCR2 on the endothelium. Resident intestinal MCps and MCs down-regulate α4 integrin and up-regulate αE integrin. In airway inflammation, MCps are recruited to the lung in greater numbers than in homing conditions, a process dependent on their α4β1 and α4β7 expression and on VCAM-1, CXCR2 and CCR2 expression by the stroma. CLP, common lymphoid precursor; MPP, multipotential progenitor, Ba, basophil.

The second wave of de novo synthesized mediators, including cytokines and chemokines, occurs hours after initial activation and have been reviewed previously, with TNF, IL-4, IL-5, IL-6 and IL-13 being well-characterized examples. MC-derived chemokines and cytokines activate local cells and promote cell recruitment to sites of inflammation (reviewed in [28]).

MC activation

IgE-dependent activation

The best studied mechanism of MC activation is through the high-affinity IgE receptor FceRI. These receptors on the surface of MCs can bind to both IgE as well as IgG and become sensitized to antigens that the host has previously contacted. Cross-linking of IgE or IgG on the surface of MCs by specific antigens leads to activation and the subsequent degranulation and de novo synthesis of mediators [29].

Non-IgE-dependent activation

MCs can also be activated through a variety of non-IgE-dependent mechanisms including proteases, cytokines, complement, adenosine, TLRs (Toll-like
MCs are present in many tissues of the body not only as sentinel cells to detect and respond to pathogens/antigens or to communicate with the adaptive immune system, but also to maintain physiological homoeostasis.

**Homoeostasis**

MCs are important in the homoeostasis of organs that undergo continuous growth and remodelling such as hair follicles and bones. MC−/− mice have normal hair growth; however, hair follicle cycling is severely impaired [47]. MC-derived histamine, TNF and substance P are implicated in regulating growth and regression of hair follicles between periods of hair growth and rest [48]. MCs also contribute to bone remodelling. In MC−/− mice, femurs are lighter, thinner and more fragile [49]. It has been speculated that MC IL-1, TGF-β, IL-6 and histamine could influence osteoclast recruitment and development. Recently, MCs were found to produce OPN (osteopontin), a secreted glycoprotein that controls bone metabolism and also has a role in immune responses [50]. They can also maintain homoeostasis by degrading toxins such as the endogenous peptide ET-1 (endothelin-1) and snake venom. ET-1 is a potent vasoconstrictor derived from several cell types, which is known to mediate the toxic effects of sepsis. MCs are directly activated by ET-1 to release proteases that degrade this peptide, thus limiting toxicity and promoting survival in mice during acute bacterial peritonitis [51].

**Wound healing**

MCs produce many different growth factors including NGF (nerve growth factor), PDGF (platelet-derived growth factor), VEGF (vascular endothelial growth factor), FGF2 (fibroblast growth factor 2), histamine and tryptase, which are involved in proliferation of epithelial cells and fibroblasts [52]. They are known to be involved in wound healing from the initial inflammatory response followed by re-epithelialization and re-vascularization of the damaged tissue and finally in deposition of collagen and re-modelling of the matrix [53].

**Nervous system**

MCs localize near nerve endings in many different tissues, including the lungs, skin, intestinal mucosa and CNS (central nervous system). MCs and neurons can communicate through the mediators they release, e.g. histamine, serotonin and tryptase, released from MCs, can influence neuronal activity, and neurons can release CGRP (calcitonin gene-related peptide), substance P and ET-1, which activate MCs [18]. In certain situations of wound healing and stress response, MCs and neurons work co-operatively. For example, in the gut, MCs and neurons maintain homoeostasis by regulating ion transport, secretory activity of mucous epithelial cells, vascular permeability and intestinal motility (reviewed in [54]). MC–neuron interaction may also lead to immunosuppression, illustrated by the observation that MCs migrate to lymph nodes...
Role of MCs and their mediators in health and disease: some recent developments

Upon UV irradiation, prevention of which abrogates the induction of immunosuppression [55]. MC products IL-10, TNF-α, histamine, PGE_2 (prostaglandin E_2), serotonin, PAF (platelet-activating factor) and IL-4 have all been implicated in the subsequent immunosuppression [56]. Recently, vitamin D₃ has been reported to reduce skin pathology at sites of chronic UVB irradiation, by inducing IL-10 production from cutaneous MCs via engagement of the VDR (vitamin D receptor) [57] (Figure 2).

**Role of MCs in immunity and host defence**

The strategic position of MCs near the surface of the airways, gut and skin allows them to act against invading microbes including bacteria, parasites, fungi and viruses. They express receptors on their cell surface that are able to ‘sense’ pathogens, and their secreted products contribute to protective immunity and pathogen clearance or containment (reviewed in [22,58] and recent advances are summarized in Figure 2).

**Parasites**
Parasitic infections are often associated with high levels of IgE (parasite-specific or non-specific), increased MC numbers and redistribution and evidence of MC activation, which all point strongly to MC involvement in host response to parasite infection [59]. Research into the control and clearance of parasites by MCs has described roles in the recruitment of key immune cells, the regulation of gut permeability and parasite expulsion, containment, chronic inflammation and nematode fecundity [60–63]. What is not fully clear and requires further investigation is whether or not MCs confer a benefit to the host during parasite infection, and current evidence suggests that the outcome depends on the type of infection/parasite.

With the use of MC⁻/- mice and MC protease-deficient mice, MCs were shown to contribute to host defence against many different infections including those caused by *Strongyloides venezuelensis* [64], *Trichinella spiralis* [61] and *Leishmania major* [62]. However, in some nematode infections, there is a mixed picture of protective and pathological, functions depending on the type of infection and the genetic background of the mice, as highlighted by responses to *Nippostrongylus brasiliensis* [58]. A recent study has shown that MC-deficient MC⁻/- mice have significantly higher nematode fecundity than MC-reconstituted MC⁻/- mice or wild-type mice [63].

It is becoming clear that MCs and basophils have overlapping and possibly complimentary roles in defence against parasite infection as highlighted by recent results showing basophils to be central in the defence to re-infection by different parasites, whereas in primary infections, MCs appear to be more important [65,66].

**Bacteria**
MCs have been described as initiating both innate and adaptive immune responses to bacterial infection using MC⁻/- mice. MCs can be activated by bacteria via TLRs and by other mediators to kill bacteria directly [67], recruit neutrophils [68] and degrade potentially toxic
endogenous mediators such as ET-1 [51] and neurotensin [69].

In the peritoneum, the critical protective function of MCs is apparent in a model of acute septic peritonitis [68], in particular, through their ability to recruit neutrophils. Recently, this work was confirmed in moderate peritonitis caused by caecal ligation, but in experimentally severe conditions, MCs were no longer protective, with MC-TNF contributing to pathology [70]. MC−/− mice infected via the airways with Mycoplasma pneumoniae have higher bacterial burdens, worse lung pathology and lose more weight than wild-type mice [71], while in Klebsiella pneumoniae infection, MC−/− mice have lower survival rates compared with wild-type littermates [72]. A recent study shows that human lung MCs directly respond to the pneumococcal virulence factor, pneumolysin, by releasing mediators including cathelicidin [73]. Activated MCs are also crucial for the induction of protective innate immune responses to Pseudomonas aeruginosa skin infections. In these models, the common mode of action, whether in the lungs, skin or peritoneum, is through the recruitment of neutrophils by MC TNF. MC TNF can be stored preformed in granules, and therefore, a ready supply can be released immediately upon meeting pathogen [74].

Viral

Much less is known about the contribution MCs make in controlling and containing viral infections. MCs can recognize and respond to virus and viral products through TLRs and release cytokines in response [75]. They can also promote recruitment of CD8 T-cells during viral challenge [76] and production of type-I interferon [75]; mechanisms which contribute to clearance of intracellular viral infection. MC numbers increase in the lungs after respiratory viral infection [77]; however, interaction between MC and virus does not always favour the host. HIV can infect MCP via CXCR4 co-receptor, which is down-regulated after maturation of MCs leaving a reservoir of latent virus within the host [78]. This reservoir can be stimulated to replicate after exposure to TLR2, 4 or 9 ligands [79]. In addition, IgE–FcεRI interactions may influence HIV co-receptor expression on MCs and their susceptibility to infection with HIV [80]. In a mouse model of viral myocarditis where MC−/− mice were administered encephalomyocarditis virus intraperitoneally, survival rates were significantly increased in the absence of MCs compared with wild-type controls, suggesting that inhibition of MC function may be beneficial to disease outcome in this instance [81].

MCs in disease pathology

Allergy and asthma

Allergies occur when components of the immune system, in particular MCs, respond inappropriately to innocuous antigens. The importance of MCs in allergic reactions is emphasized by the increased numbers seen in the affected tissues [82]. Patients with asthma have increased MC numbers in the airway smooth muscle, mucus glands and epithelium [83,84]. In mouse models of antigen-induced Th2-mediated pulmonary inflammation, there is a marked increase in airway MCs, although the lungs of normal laboratory-bred mice have few MCs [85]. MCs are thought to be the major initiator of the symptoms associated when a sensitized individual ‘encounters’ antigen. The extent of these allergic symptoms is highlighted in anaphylaxis, where, after exposure to very small amounts of antigen, an individual can have an excessive reaction within seconds, which can sometimes be fatal [29].

The initial rapid release of mediators such as histamine, PGD2 and LTC4 can all contribute to features of asthma, including bronchoconstriction, mucus secretion and mucosal oedema. MCs also have a role in the later consequences of allergen exposure including leucocyte migration, local accumulation and activation of T-cells, dendritic cells, neutrophils, eosinophils and monocytes [86]. MCs also synthesize and secrete a large number of pro-inflammatory cytokines (including IL-4, IL-5 and IL-13), which regulate both IgE synthesis and the development of eosinophilic inflammation, and several profibrogenic cytokines, including TGF-β and FGF2 [87]. Indeed, in a mouse model of chronic allergic inflammation, MCs were found to be critical for development of several features of tissue remodelling, including increased numbers of mucus-producing goblet cells in the airway epithelium and increased lung collagen deposition, changes accompanied by a MC-dependent exacerbation of airway hyper-reactivity to methacholine [88]. MC products may also inhibit the pathology of allergic inflammation as shown in mMCP-4−/− mice that exhibit substantially more airway inflammation and AHR (airway hyper-responsiveness) in response to methacholine [89]. Co-ligation of allergin-1 (an immunoglobulin-like receptor) and FcεRI suppressed IgE-mediated degranulation of BMMCs, and allergin-1−/− mice develop enhanced passive systemic and cutaneous anaphylaxis [90] (Figure 2). This work suggests a new mechanism of regulation of MCs, and it would be interesting to assess its suppressive effects in a mouse model of allergic airway disease.

The IL-33 receptor ST2 (T1/ST2) is expressed on several immune cells including Th2 cells, basophils, eosinophils, NK (natural killer) cells and MCs [91–94]. Systemic administration of the IL-33 enhances IgE-mediated anaphylactic shock in an MC-dependent manner [95], and MCs have been shown to produce IL-33 after IgE/antigen activation [96]. These findings suggest that the IL-33/ST2 pathway in MCs may be important for the regulation of IgE-dependent inflammation.
Chronic inflammation and autoimmune disease

The correlation seen in MC hyperplasia and increased MC products at sites of tissue injury in chronic inflammatory and autoimmune diseases, although circumstantial, suggests MCs contribute to these diseases. Much work has been published on the role of MCs in chronic inflammatory and autoimmune disease. A few examples where MCs are shown to contribute to inflammation and disease are described below and summarized (Figure 2).

Autoimmune disease

EAE (experimental autoimmune encephalomyelitis) is the rodent model of MS (multiple sclerosis) and shares many features with MS [97]. MCs have been observed in human MS plaques [98]. In the brain and spinal cord of EAE mice, increased MCs and MC activation products have been observed compared with wild-type. In addition, MC−/− mice have delayed onset and decreased severity of EAE compared with wild-type littermate controls. Initially, Th1 cells were thought to derive disease pathogenesis, but more recent results suggest Th17 cells and IL-23 are also key [99]. Engraftment of MC−/− mice with wild-type MCs restores disease severity, but not MCs in the CNS, suggesting MCs exert their pathogenic effects in the periphery. A population of resident MCs in the meninges and spinal cord were found to regulate basal CNS barrier function, facilitating initial T-cell CNS entry. Specifically, MC-derived TNF recruited neutrophils to the CNS, which, together with T-cells, led to the blood–brain barrier breach and myelin damage [100]. However, a different group observed that, although BMMC can be recruited to the CNS during EAE, disease developed normally in the absence of either MCs or BMMC reconstitution, contradicting previous results and suggesting that, although MCs do accumulate in the brain and CNS during EAE, they are dispensable for development of disease [101]. The differences between these results have yet to be clearly explained.

K/BxN mice spontaneously develop disease resembling RA (rheumatoid arthritis). MC−/− mice are resistant to arthritis, whereas engraftment of these animals with wild-type MCs restores susceptibility [102]. MCs contribute to initiation of autoantibody-mediated arthritis by production and release of IL-1 [103]. IL-33 is also a key mediator in the development of mouse models of rheumatoid arthritis. rIL-33 treatment exacerbated both CIA (collagen-induced arthritis) and AIA (autoantibody-induced arthritis) in ST2−/− mice (IL-33 receptor) engrafted with wild-type MCs, but not ST2−/− MCs, through MC degranulation and pro-inflammatory cytokine production [104,105].

CAPS (cryopyrin-associated periodic syndrome) consists of a spectrum of disorders, including urticarial rash, which can be effectively suppressed by anti-IL-1 antibody treatment. MCs are the main producers of IL-1β in the skin of CAPS patients. Unlike normal MCs, MCs from CAPS patients constitutively produce IL-1β via NLRP3, which leads to neutrophil migration and vascular leakage (the hallmarks of urticarial rash) [106].

Heart disease

Increased numbers of MCs are observed at sites of plaque erosion, rupture and haemorrhage in human atherosclerotic plaques, suggesting a role in the pathogenesis of thin cap fibroatheroma or vulnerable plaques [107]. An indirect role is suggested by studies showing that MCs promote lipid accumulation and subsequent foam cell development as they mediate degradation of atheroprotective HDL (high-density lipoprotein) and impair cholesterol efflux [108]. The release of cytokines by MCs can alter vascular permeability affecting uptake of lipids and indirectly inflammatory cells. In addition, MC chymase and tryptase can activate matrix metalloproteases released by activated macrophages, which promote plaque instability and rupture [109]. MC−/− mice (KitW−/−/W+sh) × ldlr−/− mice identified the requirement for MCs in plaque development and inflammatory cell infiltration via MC IL-6 and IFN-γ (interferon-γ)-mediated protease production from endothelial and smooth muscle cells [110].

A similar mechanism of MC action has been described in obesity and diabetes. MC numbers are increased in obese WAT (white adipose tissue) in human and mouse compared with lean WAT. Using reconstitution of MC−/− mice and MC-stabilizing agents, MC derived IL-6 and IFN-γ were found to be key mediators in mouse adipose tissue cysteine protease cathepsin expression, apoptosis and angiogenesis, leading to diet-induced obesity and glucose intolerance [111].

Cancer

There is evidence for MCs both in promoting, but also in protecting against, tumour growth. The accumulation of MCs at the periphery of tumours has been observed in both rodent models and in a diverse array of tumours in humans. Enhanced MC accumulation in tumours is associated with poor prognosis in a variety of tumours, indicating a biological role for MCs in tumour progression [112]; however, the opposite was observed in some breast cancers [113]. MC−/− mice exhibit a reduced rate of tumour angiogenesis [114]; however, this has not been studied in depth for all tumours.

It is generally thought that MCs promote early angiogenesis events in tumour development through the mediators they are stimulated to release, including VEGF, IL-8, angiopoietin-1, FGF2, heparin and proteases after which the tumour cells take control of growth in a MC-independent manner [115,116].

MCs can be recruited to tumours by tumour-derived factors; for example, SCF mediates MC tumour infiltration and activation leading to both
pro-inflammatory mediator release, tissue remodelling and immunosuppression [117]. The role of MCs in tissue remodelling, although beneficial in circumstances discussed above, promotes tumour growth in the tumour environment. This is highlighted by the suggested use of MCs as prognostic markers for prostate cancer. Intratumoral MCs were shown to negatively regulate angiogenesis and tumour growth, whereas peritumoral MCs stimulated expansion of human prostate cancers [118] (Figure 2).

Transplantation

MCs have been shown to mediate T-reg-dependent peripheral allograft tolerance in both skin and cardiac transplants [119]. Degranulation of MCs causes the release of MC intermediaries and migration of both T-reg and MCs from the graft with a decrease in T-reg-suppressive cytokines such as IL-10, TGF-β and GZB (granzyme B) leading to allograft rejection[120].

CONCLUDING REMARKS

The present review gives an overview of the roles of MCs in physiology, defence against pathogens and in different diseases. Some of the mechanisms observed in the ‘beneficial’ roles of MCs in maintaining physiology, such as in UVB-induced immunosuppression, are the cause of the ‘pathogenic’ roles seen in different disease settings, for example, in different cancers. Interestingly, the roles of MCs in different diseases are still being discovered and open up the potential for developing new therapies for these common disorders. A key step in treating some of these diseases will be to understand the similarities and differences of how MC functions are regulated in both health and disease. As the understanding for a role of MCs in a wide variety of diseases grows, understanding the similarities and differences of MC functions in different contexts will be essential. With this knowledge, development of MC-directed therapies may provide novel treatments for various disorders through regulation of MC activation, promotion of their immunomodulatory capacities or interference with mechanisms governing the population of tissues by MCs.

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