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*J Immunol* 2004; 173:2353-2361; doi: 10.4049/jimmunol.173.4.2353

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*The Journal of Immunology* is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852
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Print ISSN: 0022-1767 Online ISSN: 1550-6606.


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The contribution of dendritic cells (DCs) to initiating T cell-mediated immune response in and T cell homing into the CNS has not yet been clarified. In this study we show by confocal microscopy and flow cytometry that cells expressing CD11c, CD205, and MHC class II molecules and containing fluorescently labeled, processed Ag accumulate at the site of intracerebral Ag injection. These cells follow a specific pattern upon migrating out of the brain. To track their pathway out of the CNS, we differentiated DCs from bone marrow of GFP-transgenic mice and injected them directly into brains of naive C57BL/6 mice. We demonstrate that DCs migrate from brain to cervical lymph nodes, a process that can be blocked by fixation or pertussis toxin treatment of the DCs. Injection of OVA-loaded DCs into brain initiates a SIINFEKL (a dominant OVA epitope)-specific T cell response in lymph nodes and spleen, as measured by specific tetramer and LFA-1 activation marker staining. Additionally, a fraction of activated SIINFEKL-specific T cells home to the CNS. Specific T cell homing to the CNS, however, cannot be induced by i.v. injection of OVA-loaded DCs alone. These data suggest that brain-emigrant DCs are sufficient to support activated T cells to home to the tissue of DC origination. Thus, initiation of immune reactivity against CNS Ags involves the migration of APCs from nervous tissue to peripheral lymphoid tissues, similarly to that in other organs.


Materials and Methods

Mice

C57BL/6 and CD11cDTRtg mice were purchased from The Jackson Laboratory (Bar Harbor, ME). The GFP-transgenic mouse strain on the C57BL/6 strain background was a gift from Dr. P. Marrack (National Jewish Medical and Research Center, Denver, CO; Ref. 15). The animals were housed according to the guidelines of the National Institutes of Health and University of Wisconsin-Madison Research Animals Resource Center.
**Abs and MHC class I tetramers**

Anti-LFA-1 (clone M71A), anti-CD4 (clone RM4-5), anti-CD8 (clone 53-67.1), anti-B7-1 (clone GL1), anti-I-A^d^ (clone AF6-120.1), anti-I-A^a^ (clone 34-5-3), and anti-HLA-DR (clone L243, isotype control) Abs and streptavidin-CyChrome and streptavidin-allophycocyan conjugate were purchased from BD Pharmingen (San Diego, CA). Streptavidin-Alexa568 conjugate was purchased from Molecular Probes (Eugene, OR). Anti-CD205, anti-CD11b, anti-CD11c, and anti-VE2 TCR (isotype control) Abs were purchased from the supernatant of clones NLDC-145, M170, N418, and B20.6, respectively (American Type Culture Collection, Manassas, VA), and were used in an FITC- (Sigma-Aldrich, St. Louis, MO), biotin (Sigma-Aldrich), or Cy5 fluorochrome- (Amersham, Piscataway, NJ) labeled format. Mouse CCR7-specific Ab raised in goats was purchased from Research Diagnostics (Flanders, NJ). Anti-goat IgG-Cy5 conjugate was obtained from Chemicon International (Temecula, CA), and anti-goat IgG FITC conjugate was purchased from The Jackson Laboratory. H-2K^b^-SIINFEKL tetramer staining was conducted for 30 min at --FITC conjugate was purchased from The Jackson Laboratory. H-2K^b^-SIINFEKL tetramer staining was conducted for 30 min at --FITC conjugate was purchased from The Jackson Laboratory.

**Dendritic cells (DCs)**

DCs were differentiated from mouse bone marrow as previously described (16). Briefly, bone marrow cell suspensions were cultured for 7 days in the presence of 20 ng/ml GM-CSF (Sigma-Aldrich) or titrated 10% supernatant from the supernatant of clones NLDC-145, M170, N418, and B20.6, respectively (American Type Culture Collection, Manassas, VA), and were used in an FITC- (Sigma-Aldrich, St. Louis, MO), biotin (Sigma-Aldrich), or Cy5 fluorochrome- (Amersham, Piscataway, NJ) labeled format. Mouse CCR7-specific Ab raised in goats was purchased from Research Diagnostics (Flanders, NJ). Anti-goat IgG-Cy5 conjugate was obtained from Chemicon International (Temecula, CA), and anti-goat IgG FITC conjugate was purchased from The Jackson Laboratory. H-2K^b^-SIINFEKL MHC class I tetramer was purchased from Beckman Coulter (Fullerton, CA).

**Results**

**CD205^- (DEC-205), CD11c^-, and MHC class II-expressing APCs accumulate in brain parenchyma at the site of intracerebral injection of Ag**

To study the accumulation of DCs in the CNS as a response to neuroantigen injection, we intracerebrally injected OVA or chemically modified DQ-OVA. In DQ-OVA, the protein OVA is conjugated with BodipyFL fluorochrome dye that self-quenches its fluorescence in the intact molecule and emits green and red fluorescence upon proteolytic cleavage. Previously we have shown that DQ-OVA injected into brain parenchyma is processed in situ by CD11b-expressing cells and is distributed along the external capsule 7 days after intracerebral injection (5). In this report we extend these studies, showing that CD205^- and CD11c^-expressing cells can be isolated from normal mouse brain and that the number of these cells significantly increases after intracerebral injection of OVA protein Ag (Fig. 1, A and B). Flow cytometric analysis of CD11c^-expressing cell populations from the brain revealed three subpopulations based on CD11c and CD205 expression, which also differed in MHC class II expression (Fig. 1A).

Collectively, these data indicate that cells expressing DC markers accumulate in the brain after intracerebral Ag delivery. It is not...
known whether some of these Ag-processing cells traffic to cervical LNs. The fluorescent protein could drain to cervical LNs (5) and be processed by LN APCs, making it difficult to distinguish between brain-derived and local LN APCs. To determine whether brain DCs are capable of migrating from CNS to peripheral LNs, we injected GFP-expressing, Ag-loaded DCs into the brain and tracked the migration of these cells.

DCs injected into brain parenchyma migrate to cervical LNs along the external capsule in brain

To address the migration of DCs from the brain, we differentiated DCs from bone marrow precursors of GFP transgenic mice. These cells were pulsed with Ag (OVA) and injected intracerebrally. We measured the phenotype of these DCs before injection and found high expression of GFP, CD205, and I-A<sup>b</sup>; moderate expression of CD11c molecules (Fig. 2A); and low expression of the CCR7 molecule (Fig. 2B). This phenotype resembles the characteristics of mature DCs described previously (16). OVA Ag-pulsed GFP-DCs also induced a robust T cell response in OT-1-transgenic mice, indicating the potent Ag-presenting properties of these cells before injection (data not shown).

To test the migratory abilities of GFP-DCs in the brain, we injected these cells directly into brain parenchyma and tracked their appearance in the CNS and peripheral lymphoid organs using GFP and CD205 expression as markers (Fig. 2, C and D). We show that GFP-DCs primarily migrated to cervical LNs, which is the draining site for CNS-derived Ags (2–4, 22). GFP-DCs could be detected in brain parenchyma both 3 days (data not shown) and

FIGURE 1. Dendritic-like cells are present in the naive brain and accumulate in higher numbers in response to Ag injection. A, Expression of CD11c and CD205 in leukocyte suspensions prepared from brain of naive C57BL/6 mice (left column, upper plot) and from OVA-injected C57BL/6 mice 7 days postinjection (right column, upper plot), gated on the forward scatter<sub>high</sub>/side scatter<sub>medium</sub> population. The lower graph shows the relative expression of I-A<sup>b</sup> on the surface of the indicated cell populations. One representative experiment is shown of three performed with similar results. The numbers in the red boxes indicate the average percentage of CD11c<sup>+</sup>/CD205<sup>+</sup> cells from the total mononuclear cell population prepared from brain ± SEM. n = 5 in both groups. B, Absolute numbers of CD11c<sup>+</sup>/CD205<sup>+</sup> cells in the brain of differently treated C57BL/6 mice 7 days postinjection (upper graph). The mice were either naive (—) or injected with 30 μl of PBS intracerebrally (PBS) or 60 μg of OVA in 30 μl of PBS solution intracerebrally (OVA). The lower graph shows the absolute number of I-A<sup>b(high)</sup> and I-A<sup>b(low)</sup> populations from the CD11c<sup>+</sup>/CD205<sup>+</sup> population in naive mice and in mice injected with 60 μg of OVA in 30 μl of PBS solution intracerebrally 7 days postinjection. Error bars represent the SEM. n = 5 in all groups. C, CCR7 expression on the surface of the CD11c<sup>+</sup>/CD205<sup>+</sup> population in naive C57BL/6 mice. Black line, anti-goat-IgG-FITC secondary Ab control; solid red area, goat anti-mouse CCR7 Ab plus anti-goat-IgG-FITC. D and E, DCs appear in the brain upon OVA injection and take up and process OVA. Naive C57BL/6 mice were intracerebrally injected with 60 μg of DQ-OVA. On day 7 after injection, free-floating sections were prepared from brain tissue, and immunohistochemistry was performed. The sections were stained with anti-CD205 or its isotype control (rat IgG2a, κ; D) and anti-MHC class II or its isotype control (mouse IgG2a, κ; E). The white triangles and arrows indicate CD205-expressing (D) or MHC class II-expressing (E) cells that ingested DQ-OVA. The insets show high magnification of the cells indicated with the white arrows. Scale bars = 50 μm. Scale bars in insets = 5 μm.
7 days (Fig. 2C, upper row) after injection. Intact GFP\(^+\) cells appeared at lower frequency in cervical LNs (Fig. 2C, lower row), indicating that intact injected GFP-DCs can reach cervical LNs. The trafficking of injected GFP-DCs was also indicated by the dose-dependent increase in the absolute numbers of these cells in cervical LNs 7 days after injection (Fig. 2E). Phenotypically, the GFP-DCs appeared intact in the brain and cervical LNs using confocal microscopy at high magnification (Fig. 2D). Intact GFP-expressing cells should show uniform cytoplasmic GFP fluorescence, whereas ingestion of the apoptotic injected cells would present a punctate fluorescence due to cellular granularity. GFP\(^+\) cells with uniform cytoplasmic fluorescence could only be found in the injected hemisphere (Fig. 2, C and D, upper rows), and no cell with either uniform or punctate fluorescence could be found in the uninjected hemisphere (not shown). Together, these results indicate that intact DCs can migrate out of the brain to cervical LNs.

To further eliminate the possibility that injected GFP-DCs leak Ag and GFP protein that is picked up and carried to cervical LNs by a brain-resident APC, we tested the effect of pertussis toxin (PTX) on the migratory capability of injected GFP-DCs in the brain. PTX is a G protein inhibitor that blocks chemokine receptor signaling and prevents DC migration from the skin and monocyte migration into uninflamed tissues (7, 23, 24). We injected intact, paraformaldehyde-fixed, or PTX-treated, OVA-loaded GFP-DCs into the brain and followed their migration in the CNS. Fig. 3A shows the orientation of the injection site and the external capsule in the pictures shown in Fig. 3B and D. Intact GFP-expressing cells were present at the injection site in the brain and exhibited a migration pattern similar to the drainage pattern of injected DQ-OVA described previously (5) (Fig. 3B, right panel). Fixation or PTX treatment blocked the migration of GFP-DCs from brain detected by confocal microscopy (Fig. 3B, center and
and reduced the absolute number of GFP$^+$ cells in cervical LNs as measured by flow cytometry (Fig. 3C). Approximately 0.5–1% of injected GFP-DCs were found in cervical LNs at this time point, which corresponds to data published recently (25) quantifying the amount of injected DCs migrating out of the skin.

To address the concern that injected DCs may differ from endogenous brain DCs, we used a mouse strain in which only CD11c-expressing cells are labeled with GFP (26). In the CD11cDTRtg mouse strain, the CD11c promoter drives the expression of a chimeric transgene consisting of the human diphtheria toxin receptor and GFP separated by an internal ribosome entry site (26). This results in the expression of diphtheria toxin receptor and GFP only in CD11c-positive cells, enabling selective depletion and identification of these cells. We intracerebrally injected OVA into CD11cDTRtg mice and examined their brains 7 days postinjection. In response to the injection, endogenous GFP- and CD11c-expressing cells accumulated in brain parenchyma in the injected hemisphere, which were also CD205$^+$ (Fig. 3, D and E). The majority of these cells were distributed along the external capsule, which corresponds to our previous results (5) and the data shown in Fig. 3B. Together, these data show that CD11c$^+$ cells accumulate in the brain upon exogenous Ag injection and, regardless of whether they are endogenous or exogenous cells, migrate along the same pathway in the brain.

**Ag-specific T cell response to Ag-loaded DCs in brain**

The potential relevance of Ag-loaded DC migration from the brain to the periphery was assessed by measuring the activation of naive, Ag-specific CD8$^+$ T cells using MHC class I tetramers presenting the immunodominant SIINFEKL peptide from OVA. OVA-specific CD8$^+$ LFA-1$^{high}$ cells accumulated in a dose-dependent manner in the spleen in mice injected with OVA-loaded GFP-DCs 7 days after injection (Fig. 4A), but not 3 days postinjection (data not shown). In cervical LNs, between 1 and 2% of the total CD8$^+$
Brain-derived DCs induce preferential homing of Ag-specific T cells into brain

To determine the role of Ag-loaded DCs in inducing T cell homing into the CNS, we analyzed the frequency and absolute number of Ag-specific T cells in the CNS after Ag-loaded GFP-DC injection into brain. The injection of increasing numbers of OVA-pulsed, live GFP-DCs led to a dose-dependent increase in both the percentage and the absolute number of Ag-specific, activated CD8\(^+\) T cells in brain (Fig. 5, A and B). The preferential homing of Ag-specific T cells into brain was dependent on live GFP-DCs capable of migrating out of brain tissue (Fig. 5, C and D). There was a significant decrease in the absolute number of Ag-specific T cells when fixed or PTX-treated GFP-DCs were injected into brain (Fig. 5D). Activated CD4\(^+\) cells also accumulated in brain in response to DC injection, and the ratio of CD4\(^+\) to CD8\(^+\) T cells did not differ significantly from the 2:1 ratio detected in peripheral lymphoid organs (data not shown). Together, these data suggest that brain-emigrating GFP-DCs are necessary and sufficient to induce the accumulation of activated Ag-specific T cells in the brain.

Peyer’s patch-derived DCs preferentially induce the accumulation of activated T cells in Peyer’s patches (27). To test whether GFP-DCs need to derive from the brain to promote accumulation of T cells in the brain, we compared the effect of intracerebral and i.v. injection of OVA-loaded GFP-DCs. To exclude the possibility that accumulation of specific T cells in brain is an artifact of intracerebral injection, the animals receiving i.v. GFP-DCs were injected with medium (RPMI 1640 without serum). Intravenously injected GFP-DCs failed to induce accumulation of Ag-specific T cells in brain, leading to an ~10-fold decrease in absolute T cell number in the CNS (Fig. 5E). Thus, preferential homing of Ag-specific T cells into the CNS is induced by brain-derived GFP-DC migration to the periphery.

Discussion

Previous studies of DC appearance in the CNS have raised two main questions. Can these cells function in the CNS as in other organs and can these cells migrate from CNS tissue to peripheral lymphoid organs and participate in initiation of immunity against CNS Ags? Our data show that DCs accumulate in the CNS as a response to intracerebrally injected Ag and can migrate out of the CNS and induce systemic immune responses in the secondary lymphoid organs. One consequence of this migration is that Ag-specific T cells home to the brain. Thus, brain DCs behave similarly to skin-originated (7, 28) and Peyer’s patch-originated (27) DCs in that they migrate from Ag injection sites to LNs and induce a...
second wave of Ag presentation necessary for induction of immunity against tissue-localized Ag (7). Our data indicate that despite the dampened immune response at this immunologically privileged site, when an immune response is initiated, it follows the pattern previously described for Ags derived from other organs. This conclusion is based on the observation that intracerebrally injected, Ag-loaded GFP-expressing DCs accumulate in cervical LNs and induce the appearance of Ag-specific (H-2K\(^b\)-SIINFEKL
tetramer”), activated CD8+ T cells in brain. Reverse transmigration of DCs through the endothelial cell monolayer has been demonstrated (29); however, reverse migration of DCs through the BBB has not been proven. These data correspond to previous results showing that intrathecally injected DCs migrate to cervical LNs, and CNS-derived Ags can be found in DCs in cervical LNs of monkeys with EAE (30, 31). T cell activation results from a primary response to Ag-presenting DCs and not from the cross-presentation of Ags by endogenous APCs. Thus, brain-originated DCs are important in the initiation of immunity against brain Ags.

The CNS is an immunologically privileged organ (1); however, immune responses against both pathogens and self-Ags in autoimmune demyelinating diseases point toward the presence of antigenic surveillance and inducible immune responses in this tissue. There must also be a delicate balance between induction of protective immune responses and that of autoimmune responses due to the sensitivity of irreplaceable neurons. A series of recent studies showed that DCs play an important role in the regulation of the T cell-mediated immune response against CNS-derived Ags, similarly to other tissues (32); in various diseases they accumulate in the CNS; and DCs prepared from the brain are able to induce specific T cell activation (33) or tolerance (14) in vitro.

A recent report showed that in an inflammatory skin model to achieve full activation of T cells against a skin Ag, the presentation of the Ag happens in two waves: direct drainage within a short time and DC-mediated transport thereafter. The latter type of Ag presentation accomplished by DCs emigrating from the skin is necessary to induce full T cell activation (7). However, it is not known whether presentation by only the tissue-emigrant DCs is necessary and sufficient to mediate full T cell activation. This is a fundamental question in the initiation of primary immune responses as well as for the reactivation of Ag-experienced T cells in LNs. Earlier studies from our laboratory showed that T cell accumulation in the brain peaks 7 days after intracerebral OVA injection, although direct drainage of OVA occurs within hours after Ag delivery (5). This suggests a requirement for APC migration to mediate Ag presentation at later time points. Importantly, the present study proves that brain-emigrant DC-mediated Ag presentation is necessary and sufficient to induce infiltration of the LFA-1high T cell population into the brain.

DCs are present under steady state conditions in the absence of inflammation in the choroid plexus and meninges. Their number increases, and they also become detectable in brain parenchyma when inflammation is induced by pathogens or autoimmune attack (4, 11, 12, 33). More studies are needed to address whether cells with a DC phenotype that accumulate around the Ag injection site in brain are recruited from systemic sources or derived from CNS-resident cells. Mononuclear cells, probably of microglial origin, that can be isolated from brain parenchyma and cultured in the presence of GM-CSF obtain a DC-like phenotype and are able to efficiently prime naïve T cells (9, 11). It is not known whether DCs present in the CNS under these conditions are able to migrate to draining LNs and function the same way as in other tissues. To our knowledge, there are no data on the ability of microglia to migrate out of the brain and present Ags to naïve T cells. GM-CSF, which we used in this study to differentiate DC from bone marrow, is a major differentiation factor of DCs in brain and other organs (9, 34) and is produced in brain (35). In the absence of GM-CSF production, EAE fails to develop (36), indicating the importance of DCs in the initiation of CNS immunity.

The primary site for the interaction of DCs and T cells is the secondary lymphoid organs (37). There is limited information on how CNS DCs migrate out to LNs. Cserr and Knopf (3) demonstrated in rats that CNS Ags drain to cervical LNs via cerebrospinal fluid circulation, mostly through the cribriform plate, although the exact mechanism and types of cells transporting the Ags are not known. In this study we show a possible route of drainage to the periphery via the migration of injected DCs along the external capsule and analyze the specificity of CNS-infiltrating T cell populations. Interestingly, injected neural stem cells as well as stem cells in adult brain migrate along the external capsule in the brain (38); however, the reason for this migration pattern is currently unknown. It is possible, however, that this correlation is coincidental and not the cause of LN homing. Intracerebrally injected Ag is also distributed in this pattern, and the Ag is presented in cervical LNs (5). Our study shows that one of the possible cell types able to take up, process, and present brain Ags is the DC. Our results correspond to a previous study showing that intrathecally injected in vitro differentiated DCs accumulate in cervical LNs and induce the disproportionate recruitment of CD8+ vs CD4+ cells to the CNS (31). However, we did not find differences in the ratio of CD8+ vs CD4+ populations of T cells between the target organ and secondary lymphoid tissues (data not shown). We addressed Ag-specific CD8+ T cell accumulation because MHC class I tetramers were readily available to us. We will also examine this process for CD4+ T cells using moth cytochrome c/I-Ek tetramers that we have recently generated. Our preliminary data using this model indicate that the accumulation of Ag-specific, activated CD4+ and CD8+ T cells is regulated by similar mechanisms (our unpublished observations). Our previously published studies using a different model show that CD4+ T cells accumulate in brain in response to intraventricular Ag delivery (39).

The injection of unloaded cells and cells fixed with 1% paraformaldehyde or treated with PTX demonstrated the specificity of the response as well as a requirement for migration of DCs to cervical LNs. Ag leaking out of fixed DCs is apparently insufficient to induce an immune response in a naive mouse. Our previous studies demonstrate that injection of OVA Ag into the brain induces immune responses in the periphery and T cell recruitment into the brain (5). The results of this study indicate that the cell type responsible for the induction of this T cell response is the DC. The timing and nature of the immune response in the present study argue that the presentation of Ag in cervical LNs is necessary for the recruitment and activation of specific CD8+ T cells. DCs injected s.c. into mice accumulate in draining LNs and persist for time periods >7 days (40). Furthermore, DCs migrating out of the CNS induce T cell infiltration to the CNS (Figs. 4 and 5), showing that brain-emigrant DCs induce the accumulation of activated T cells in the CNS. Intravenous DC immunization together with intracerebral RPMI 1640 injection did not induce T cell infiltration to the CNS. This might indicate that the brain environment, the experimental injury induced by intracerebral injection, or both change the properties of DCs. Our results are in accordance with the recently described phenomenon that DCs induce the infiltration of T cells to the organ from which they originated (27). The lack of SIINFEKL-specific T cell activation in animals injected with fixed or PTX-treated DCs suggests that presentation of Ag by tissue-emigrating DCs is necessary, because possible cross-presentation of OVA due to local Ag processing or passive draining of OVA out of the brain failed to induce detectable SIINFEKL-specific T cell activation.

It is possible that DCs can migrate from brain to periphery through the bloodstream at the injury site induced by the injection. This represents one possible mechanism for our results. Indeed, DC migration from traumatic brain via the blood circulation to the periphery has very high relevance for brain Ag-induced immune responses after brain trauma. We are currently developing an in
vivo brain traumatic injury model to explore this possibility. However, our data, presented in Fig. 3, indicate that an additional, new pathway can guide DC migration from brain to periphery. This pathway is along the external capsule in the brain. To understand the possible importance of guided DC migration from brain along the external capsule is the focus of a major effort in our laboratory. We believe that this migration pathway is important because we demonstrate that DCs need to originate from brain to induce preferential specific T cell accumulation in brain. Additionally, Fig. 5E demonstrates that OVA-pulsed DC injection i.v. together with RPMI 1640 medium injection into brain is not sufficient to induce preferential T cell accumulation in brain. These results do not exclude the direct route of DC exiting to blood, but show that the injury alone is not sufficient to induce T cell recruitment to the site of the injury.

In summary, Ag-loaded DCs injected into brain parenchyma are able to migrate to cervical LNs, transport Ags out of the CNS, induce a primary immune response in the periphery, and instruct Ag-specific T cells to home to the brain. It is not known whether DCs are local resident cells in the CNS or whether they infiltrate from the periphery into inflamed CNS. In either case, they are capable of migrating to secondary lymphoid tissues from the brain, which has not been proven previously. This process has significant implications for understanding the mechanism of presentation of CNS-derived Ags in immunity against foreign and self-Ags in the CNS. Immune responses are initiated in the immunoprivileged environment of the brain, much like in other organs of the body. This indicates that presentation of Ags by emigrant DCs is necessary and sufficient for peripheral Ag-specific T cell activation and consequent induction of preferential homing of these cells into the CNS.

Acknowledgments

We thank Dr. Laura Hogan, Dominic Co, and Emily Reinke for critical reading of the manuscript, and Sinarack and Khen Macvillay, Shin-IK Kim, and Tashi Kinoshita for excellent technical assistance.

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