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Dendritic cells from the elderly display an intrinsic defect in the production of IL-10 in response to Lithium Chloride

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**A B S T R A C T**

Chronic, low grade inflammation is a characteristic of old age. Innate immune system cells such as dendritic cells (DCs) from the elderly display a pro-inflammatory phenotype associated with increased reactivity to self. Lithium is a well-established anti-inflammatory agent used in the treatment of bipolar disorders. It has also been reported to reduce inflammation in DCs. Here, we investigated whether Lithium is effective in reducing the inflammatory responses in DC from the elderly. The effect of Lithium Chloride (LiCl) was compared on the response of TLR4 agonist, LPS and TLR2 agonist, PAM3CSK4 stimulated aged and young DCs. LiCl enhanced the production of IL-10 in the young DCs. However, it did not affect TNF-α and IL-6 production. In contrast, in aged DCs, LiCl reduced the secretion of TNF-α and IL-6 in LPS stimulated DCs but did not increase IL-10. LiCl had no significant effect on PAM3CSK4 responses in aged and young DCs. LiCl treated DCs also displayed differences at the level of CD4 T cell priming and polarization. LPS-stimulated young DCs reduced IFN-γ secretion and biased the Th cell response towards Th2/Treg while LiCl treated aged DCs only reduced IFN-γ secretion but did not bias the responses towards Th2/Treg. In summary, our data suggests that LiCl reduces inflammation in aged and young DCs via different mechanisms. Furthermore, the effect of LiCl is different on LPS and PAM3CSK4 responses.

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1. Introduction

Advancing age is characterized by constitutive inflammation termed inflammaging (Boren and Gershwin, 2004). It is also the underlying cause of most age-associated diseases such as Alzheimer’s, hypertension, atherosclerosis, diabetes, cancer etc. (Chung et al., 2009; Dorshkind and Swain, 2009; McElhaney and Effros, 2009; Weiskopf et al., 2009). Excessive inflammatory cytokine production results in tissue damage and toxicity that are harmful to the host. Therefore, strong inducers of inflammatory cytokines also activate homeostatic mechanisms that serve to limit cell activation, cytokine production, and tissue damage (Murray and Smale, 2012). One key homeostatic mechanism is the induction of IL-10, a potent anti-inflammatory cytokine that mediates a feedback inhibition loop that limits pro-inflammatory cytokine production (Iyer and Cheng, 2012). IL-10 also inhibits multiple macrophage and DC effector functions and plays a critical role in limiting tissue injury during infections and in preventing autoimmunity by limiting the duration and intensity of immune and inflammatory reactions (Coombes et al., 2005; Iyer and Cheng, 2012). Evidence suggests that production of IL-10 from aged DCs becomes dysregulated with age (Ciaramella et al., 2011). This is particularly apparent in the innate immune system cells such as dendritic cells (DCs). DCs are the major antigen-presenting cells that bridge the innate and adaptive immune responses. DCs sense and respond to pathogens via the pathogen recognition receptors (PRRs) such as Toll-like receptors (TLRs). Activation of DCs results in the secretion of pro-inflammatory cytokines which play an important role in host-defense and are critical in directing the T cell proliferation and polarization (Agrawal et al., 2003, 2007a, 2007b, 2010; Manicassamy and Pulendran, 2009). We have previously reported that DCs from aged subjects display an increased propensity to secrete inflammatory cytokines after stimulation with TLRs (Agrawal et al., 2007a). In spite of this, there was no concomitant up-regulation in the production of IL-10 from aged DCs to prevent the over-production of inflammatory cytokines. Increased basal level of pro-inflammatory cytokine secretion has also been observed in DCs from the aged as compared to the young. These observations suggest that DCs from the aged are inefficient in inducing compensatory anti-inflammatory mechanisms. The age-associated changes profoundly affect DC functions including decreased response to pathogens and other foreign stimuli and increased responses to harmful self-antigens. Consequently, there is an urgent need to identify therapeutic options which can reduce the pro-inflammatory state of aged DCs and restore their functions.

Lithium Chloride (LiCl) is one the major drugs used in humans for the treatment of bipolar disorders and neurodegenerative diseases (Montero-Lomeli et al., 2007; Zhang et al., 2011). It also exerts a broad range of effects on immune cells and is reported to inhibit inflammation and apoptosis. It is speculated that this may be one of the mechanisms of action of Lithium since inflammation and aberrant immune responses are often associated with psychiatric diseases (Knijff et al., 2007; Makoukji et al., 2012). LiCl treatment is reported to protect against...
TNF-α endotoxemia, experimental colitis, type II collagen-induced arthritis, zymosan and ovalbumin-induced asthma. LiCl also reduces inflammation in DCs via the induction of IL-10 (Cortes-Vieyra et al., 2012; Hofmann et al., 2010; Hu et al., 2006; Martin et al., 2005; Spinnler et al., 2010; Wang et al., 2011). Hence, LiCl is a potent anti-inflammatory agent with low toxicity and proven effectivity in humans.

In the present study we investigated the effect of LiCl on TLR induced inflammation in DCs from aged and young subjects.

2. Materials and methods

2.1. Blood donors

Blood was collected from healthy elderly (65–90 years of age) and young (20–35 years of age) volunteer donors. Elderly subjects were of middle-class socio-economic status and are living independently. An extensive medical history was obtained to exclude individuals with any major diseases. None of these volunteers had any significant medical illness. Young, healthy subjects, matched for the gender were drawn from students, staff, and blood donors at the University of California, Irvine. 15 young and 15 aged donors were used for the study. The Institutional Review Board of the University of California, Irvine, approved this study.

2.2. Dendritic cells, LiCl treatment and TLR activation

Monocyte-derived DCs were prepared essentially as described (Agrawal et al., 2007a). Briefly, purified monocytes from the aged and young were cultured with GMCSF and IL-4 (from PeproTech New Jersey, USA). DCs obtained were treated with LiCl (20 mM Sigma Aldrich) for 1 h. Initial experiments were performed at different concentrations of LiCl ranging from 10 to 40 mM and 20 mM was found to be the optimum. After 1 h DCs were stimulated with Escherichia coli LPS (100 ng/ml, Invivogen, San Diego, CA) and PAM3CSK4 (10 μg/ml, Invivogen). 24 h later the cells were harvested and stained for surface markers CD40, CD80, CD86, CD83 and HLADR using directly conjugated antibodies (BD Pharmingen, San Jose, CA). Analysis was performed using the Flow jo software (Treestar Inc, Ashland, OR).

Supernatants were assayed for IL-10, IL-12p70, IL-6, TNF-α, and CXCL-10 using specific ELISA (BD Bioscience, San Jose, CA).

2.3. DC-T cell co-culture

Stimulated DCs (1 × 10^5) were cultured with purified, naïve, CFSE labeled, allogeneic T cells (1 × 10^5) from young donors at a ratio of 1:10 for six days. Naïve CD4 and CD8 T cells were purified by negative selection using a magnetic bead based kit (Stemcell technologies). Proliferation of gated CD4 and CD8 T cells was assayed by measuring the dilution of CFSE dye using flow cytometry. IFN-γ, IL-5 and IL-10 in the supernatants were assayed by specific ELISAs.

2.4. Statistical analysis

Statistical analysis was done by using the Graph Pad Prism software. Non-parametric Mann–Whitney or Wilcoxon signed rank test was used to measure significance. Values of p < 0.05 were considered significant.

3. Results

3.1. LiCl differently regulates CD80 expression in DCs in response to TLR4 and TLR2 ligands

LiCl has been reported to inhibit TLR induced inflammatory cytokine production in DCs. Here we compared the capacity of LiCl to inhibit TLR induced inflammatory responses in DCs from aged and young subjects. To investigate this, immature DCs from 8 aged and 8 young subjects were treated with LiCl for 1 h and then stimulated with either LPS (TLR4 agonist) or a synthetic triacylated lipopeptide, PAM3CSK4 (PAM-TLR1/2 agonist). The two stimuli were chosen for the study because we have previously reported (Agrawal et al., 2003; Martin et al., 2005) that the pattern of cytokine secretion by DCs in response to the two ligands is widely different with LPS predominantly inducing inflammatory cytokines and PAM favoring the production anti-inflammatory cytokine, IL-10. Stimulation of DCs with both LPS and PAM led to the activation of DCs from aged and young subjects with a comparable level of upregulation of co-stimulatory markers, CD80, CD86 and CD40 (Fig. 1A, B, C & D). The presence of LiCl resulted in a significant (p < 0.05) but comparable downregulation of LPS and PAM induced CD86 and CD40 expressions in both aged and young DCs (Fig. 1A, B & C). The effect of LiCl on CD80 expression was also comparable between aged and young DCs (Fig. 1A & D). However, LiCl had a differential effect on CD80 expression between LPS and PAM-stimulated DCs. LiCl treatment resulted in the downregulation of CD80 expression in LPS-stimulated DCs while it led to the upregulation of CD80 in PAM-stimulated DCs (Fig. 1A&D). The effect was more apparent at the level of MFI (Fig. 1D). LiCl had no significant effect (p > 0.05) on HLADR expression in aged and young DCs (Fig. 1A & E). In summary, LiCl exhibited no significant difference in its effect on LPS and PAM induced expression of CD40, CD80, CD86 and HLADR in aged and young DCs. However, CD80 expression in response to LPS and PAM was differentially regulated by LiCl with inhibition in LPS and upregulation in PAM treated DCs.

3.2. Differential regulation of cytokine secretion in aged and young DCs by LiCl

LiCl exerts its anti-inflammatory effect by promoting the secretion of IL-10 from DCs. Therefore, we determined the secretion of cytokines by aged (n = 15) and young (n = 15) DCs in response to LPS and PAM in the presence or absence of LiCl. LPS and PAM induced comparable levels of IL-10 in aged and young DCs (Fig. 2A). However, IL-10 production in the presence of LiCl was severely impaired in aged DCs (Fig. 2A, left). This was in contrast to young DCs where the addition of LiCl resulted in a two fold enhancement in IL-10 secretion (Fig. 2A, right; p = 0.003). Induction of IL-10 by LiCl has been reported to inhibit the production of IL-12 and thereby IFN-γ. Therefore, we determined the level of IL-12 and the IFN-γ inducing chemokine, CXCL-10 in aged and young DCs following LPS and PAM induced stimulation in the presence and absence of LiCl. The effect of LiCl was comparable on IL-12p70 and CXCL-10 production in aged and young DCs (Fig. 2B). Though aged DCs displayed reduced IL-12 production in response to LPS as compared to young DCs, the difference was not significant (p > 0.05). Treatment with LiCl resulted in approximately 90% inhibition in the production of IL-12p70 from both aged and young DCs (Fig. 2B). Secretion of IL-12p70 by both aged and young DCs in response to PAM was substantially decreased as compared to LPS. This is in agreement with our previous studies (Agrawal et al., 2003). However, in contrast to LPS, LiCl had virtually no effect on IL-12 production in response to PAM in both aged and young DCs. Similar results were observed for CXCL-10 whereby, LPS-stimulation resulted in enhanced levels of CXCL-10 production as compared to PAM and presence of LiCl led to a significant decrease in CXCL-10 production in both aged and young DCs (Fig. 2C). Stimulation with PAM resulted in low levels of CXCL-10 production which were not affected by the treatment with LiCl in both aged and young DCs.

LiCl also exerted differential effects on pro-inflammatory cytokine secretion in aged and young DCs. Stimulation with both LPS and PAM resulted in increased IL-6 and TNF-α production from aged DCs as compared to young DCs (Figs. 2D, 2E). The addition of LiCl resulted in a differential effect on the production of these cytokines in aged and young DCs. Stimulation of aged DCs in the presence of LiCl resulted in an approximately 20–24% decrease in IL-6 production in response to both LPS and PAM (Fig. 2D, left). The decrease was even greater for
TNF-α where a 28–35% decrease was observed in aged DCs (Fig. 2E, left). Young DCs on the other hand displayed an approximately 5% decrease in IL-6 production when stimulated with LPS or PAM in the presence of LiCl (Fig. 2D, right). In contrast to aged DCs, the presence of LiCl resulted in enhanced secretion of TNF-α from young DCs in response to LPS while LiCl had no effect on TNF-α production in response to PAM (Fig. 2E, right).

Taken together these data suggest that the action of LiCl as an anti-inflammatory agent differs between aged and young DCs. LiCl reduces the production of LPS and PAM induced inflammatory cytokines, IL-6 and TNF-α in DCs from aged subjects while LiCl enhances LPS and PAM induced IL-10 in young DCs.

3.3. Effect of LiCl on CD4 T and CD8 T cell proliferation by LPS and PAM stimulated aged and young DCs

Next, we determined whether the LiCl induced changes in DC cytokine secretion affected the proliferation of T cells. As shown in Fig. 3A, culture of CD4 T cells with unstimulated aged DCs resulted in significantly higher proliferation (p = 0.03; n = 8) compared to unstimulated young DCs. This is in keeping with our previous results (Agrawal et al., 2009) since aged DCs display an increased basal level of activation compared to young DCs. LPS-stimulated aged DCs had no significant effect on the proliferation of CD4 T cells (Fig. 3A, left, p > 0.05) and were not changed significantly on the addition of LiCl. In contrast, LPS-stimulated young DCs...
Fig. 2. Differential regulation of cytokine secretion in aged and young DCs by LiCl. Bar graphs depict the levels of cytokine and chemokines secreted by LPS and PAM stimulated LiCl± aged and young DCs. Left panel — Aged DC; Right panel — Young DC. A. IL-10; B. IL-12p70; C. CXCL-10; D. IL-6; E. TNF-α. Data is mean ± S.E. of 15 aged and 15 young subjects.
led to significant enhancement (about 10% above basal level) in CD4 T cell proliferation (Fig. 3A, right, p = 0.04, n = 8). The addition of LiCl resulted in reduction in proliferation in the young but was not significant (p = 0.06).

PAM-stimulated aged and young DCs led to a slight but insignificant (p > 0.05) increase in proliferation of CD4 T cells which was not significantly impacted by the addition of LiCl. The coculture of CD8 T cells with unstimulated aged DCs led to slightly higher proliferation than the coculture with young DCs (approximately 5%) but was not significant (Fig. 3B, p > 0.05). The addition of LPS, PAM or LiCl had no significant effect on the proliferation of CD8 T cells both in aged and young subjects (Fig. 3B). In summary, these results suggest that LiCl had a slight but insignificant suppressive effect on CD4 T cell proliferation in young but not in aged subjects.

3.4. Effect of LiCl on CD4 T cell cytokine induction by LPS and PAM-stimulated aged and young DCs

Though LiCl had no significant effect on proliferation, it may affect the T cell cytokine secretion since cytokines secreted by DCs dictate the polarization of T helper cell responses towards Th1/Th2/Treg/Th17. Therefore, we determined the effect of LiCl on CD4 T helper cell differentiation by aged (n = 8) and young (n = 8) DCs. Purified, naïve CD4 T cells from young subjects (to exclude any T cell defect) were cultured with aged and young DCs stimulated with LPS or PAM in the presence or absence of LiCl. Cytokine secretion by T cells was assayed by ELISA. As evident from Fig. 4A, LPS-stimulated DCs from both the aged and young induced significantly higher (p < 0.05) levels of IFN-γ in T cells as compared to PAM-stimulated DCs. However, IFN-γ secretion by T cells in response to LPS was significantly impaired (p < 0.05) in aged DCs as compared to young DCs. Nevertheless, the addition of LiCl resulted in significant abrogation (p < 0.05) of IFN-γ secretion induced by LPS-stimulated DCs. The reduction was significantly greater (p < 0.05) in young DCs as compared to aged DCs. LiCl had no effect on IFN-γ secretion by T cells after culture with PAM-stimulated DCs in both aged and young subjects.

IL-5 secretion by T cells was comparable in the LPS and PAM-stimulated aged and young DCs though IL-5 induction by PAM stimulated DCs was significantly higher (p < 0.05) than LPS stimulated DCs (Fig. 4B). The presence of LiCl led to a significant (p = 0.012) enhancement in IL-5 secretion from LPS stimulated young DCs as compared to aged DCs (p = 0.31). LiCl had no significant effect on IL-5 secretion by T cells after culture with PAM-stimulated aged and young DCs. IL-10 secretion by T cells displayed a pattern similar to IL-5 with PAM inducing significantly (p < 0.05) higher levels of IL-10 compared to LPS (Fig. 4C). The presence of LiCl led to a significant enhancement of IL-10 production by both LPS (p = 0.015) and PAM (p = 0.04) stimulated young DCs (Fig. 4C, right). This enhancement was impaired in aged DCs. There was slightly enhanced IL-10 and IL-5 production in LPS stimulated aged DC and T coculture, but was not significant (p = 0.6).

In summary, LiCl abrogated LPS induced IFN-γ secretion and enhanced IL-5 and IL-10 secretions in young DCs while in aged subjects, LiCl inhibited IFN-γ production in response to LPS but did not enhance IL-5 and IL-10 production. LiCl has virtually no effect on PAM induced IFN-γ, IL-5 and IL-10 secretion in the aged subjects while in the young it enhanced the IL-10 secretion.

3.5. Effect of LiCl on CD8 T cell cytokine induction by LPS and PAM-stimulated aged and young DCs

Next, we determined the effect of LiCl on CD8 T cell cytokine secretion. In comparison to CD4, LiCl had no significant effect on IFN-γ and IL-10
secretions by CD8 T co-cultured with both aged and young DCs (Fig. 5A, B; n = 8). IL-5 was not detected in the culture (data not shown). There was a trend towards decreased IFN-γ and increased IL-10 secretion from CD8 T cells after culture with LPS plus LiCl-stimulated young DCs but the difference was not significant (p > 0.05). LiCl had no significant effect (p > 0.05) on induction of T cell cytokine secretion by PAM-stimulated aged and young DCs. Therefore, LiCl treated DCs have no significant effect on cytokine secretion by CD8 T cells.

4. Discussion

The functions of DCs in aging are dysregulated resulting in impaired immune responses to infections. The capacity of DCs to maintain tolerance to self is also compromised with advancing age. Furthermore, DCs from aged subjects display a chronic inflammatory phenotype in the absence of infection suggesting a deficiency in the regulatory mechanisms which dampen inflammation. Interleukin-10 is a potent anti-inflammatory cytokine which inhibits the synthesis of the pro-inflammatory cytokines and chemokines (Moore et al., 2001; Saraiva and O’Garra, 2010). The exogenous administration of IL-10 and the endogenous upregulation of IL-10 using gene therapy and IL-10 upregulatory agents protected mice in an animal model of LPS-induced sepsis (Braat et al., 2006). Our previous results (Agrawal et al., 2007a) as well as observations from other laboratories (Ciaramella et al., 2011) suggest that DCs from aged subjects display a deficiency in producing IL-10 in response to inflammation. Here we investigated whether LiCl, which is used for the therapy of neurodegenerative diseases and has been reported to upregulate IL-10 production in DCs, can reduce inflammatory responses in DCs from aged subjects (Brown et al., 2011; Cortes-Vieyra et al., 2012; Martin et al., 2005). Hence, in the present study we compared the effect of LiCl on the functions of aged and young DCs after stimulation with 2 different TLR agonists, LPS and PAM. Our results suggest that LiCl exerts a differential effect on TLR2 and TLR4 responses in DCs. Furthermore, the responses of aged and young DCs to LiCl are also differentially modulated.

Lithium is reported to substantially impact DC functions. Primarily it suppresses the activation of DCs. LiCl has been reported to downregulate the expression of co-stimulatory molecules in LPS-stimulated DCs. It also suppresses the production of pro-inflammatory cytokines from LPS-stimulated monocytes and DCs (Liu et al., 2011; Martin et al., 2005). Suppression was mainly due to increased production of the anti-

Fig. 4. Effect of LiCl on CD4 T cell cytokine induction by LPS and PAM stimulated aged and young DCs. Bar graphs depict the level of cytokines secreted by CD4 T cells after 6 days of co-culture with LPS and PAM stimulated LiCl± aged and young DCs. Left panel — Aged DC; Right panel — Young DC. A. IFN-γ; B. IL-5; C. IL-10. Data is mean ± S.E. of 8 aged and 8 young subjects.
inflammatory cytokine, IL-10 by LiCl treated DCs. Our own observations are similar to these reports. The effect of LiCl on the expression of activation molecules on aged and young DCs was comparable (Fig. 1). LiCl pre-treatment led to a significant decrease in the expression of CD40 and CD86 in both LPS and PAM stimulated aged and young DCs. Interestingly, the expression of CD80 was upregulated by LiCl treatment in PAM stimulated aged and young DCs while it was downregulated in LPS-stimulated DCs. Almost all previous studies have utilized LPS-stimulated DCs to determine the effect of LiCl on DCs. There is a scarcity of information about the effect of LiCl on the stimulation of DCs with other TLR ligands such as PAM. The stimulation of DCs by PAM exclusively utilizes the MyD88 pathway of cytokine induction and is significantly less pro-inflammatory as compared to the stimulation of DCs with LPS which utilizes 3 different adaptor proteins, MyD88, TIRAP (Toll-interleukin 1 receptor (TIR) domain containing adaptor protein) and TRIF (Toll-like receptor adaptor molecule 2) and induces high levels of pro-inflammatory cytokines in DCs (Kawai and Akira, 2010). Therefore, LiCl may differentially modulate the response of LPS and PAM stimulated DCs.

In concurrence with previous reports, LiCl enhanced the production of IL-10 from LPS and PAM stimulated young DCs (Brown et al., 2011; Martin et al., 2005). In contrast, in aged DCs, LiCl did not influence the production of IL-10 but inhibited the production of TNF-α and IL-6 in LPS and PAM stimulated aged DCs. Thus it seems that the mechanism of action of LiCl in reducing inflammatory responses differs between aged and young DCs. LiCl is a potent inhibitor of GSK-3β and is believed to exert its anti-inflammatory effects via this inhibition. The inhibition of GSK-3β in DCs via LiCl induces IL-10 production and reduces TNF-α production by impairing the activation of NF-κB and JNK signaling cascades (Beurel et al., 2010; Woodgett and Ohashi, 2005; Beurel et al, 2011; Coant et al., 2011; Spinnler et al., 2010). Lithium also decreases the expression of pro-inflammatory cyclooxygenase-2 and inducible nitric oxide synthase. Reports also suggest that LiCl may be inhibiting GSK-3β via phosphorylation of AKT (Freland and Beaulieu, 2012). We have previously reported that AKT phosphorylation is impaired in DCs from aged subjects (Agrawal et al., 2007a). This may be therefore a mechanism for impaired IL-10 secretion in aged DCs by LiCl. However, the reason for the decrease in TNF-α and IL-6 production from LiCl treated aged DCs is not clear, though it does suggest that LiCl signals via a different pathway in aged DCs.

As is well established, the cytokines secreted by DCs dictate the Th cell polarization towards Th1/Th2/Th17/Tregs. IL-12 secretion by DCs induces IFN-γ from Th cells biasing the Th response towards Th1 whereas IL-10 along with other cytokines favors a Th2 bias and induces IL-5 secretion from T cells (Zhu et al., 2010). The culture of LiCl treated aged and young DCs with CD4 T cells displayed a Th cell polarization pattern in concurrence with DC cytokine production. Since LiCl treatment led to reduced IL-12 production by LPS-stimulated aged and young DCs, the secretion of IFN-γ from CD4 T cells was inhibited. There was a concomitant increase in IL-5 and IL-10 from T cells cultured with young DCs biasing the response towards Th2/Treg. However, CD4 T cultured with LiCl treated aged DCs displayed a modest but insignificant bias towards Th2/Treg suggesting that these DCs are also impaired in their capacity to induce IL-10 even at the level of T cells. The effect of LiCl treated DCs on T cell responses has not been investigated. Previous studies have reported that LiCl can directly inhibit GSK-3β activity in CD4 T cells and potentiate Treg cell suppressive activity by increasing Treg cell survivability. Similar increase in survival has also been reported in CD8 T cells treated with LiCl (Beurel et al., 2010).

In summary, LiCl is unable to induce IL-10 production from DCs of aged subjects and control inflammatory responses as compared to young DCs. This suggests that DCs from the aged are intrinsically defective in their capacity to produce IL-10 and the use of agents to enhance IL-10 production in aged DCs may not prove to be an effective approach to control inflammation.

**Conflict of interest**

The authors have no conflicts of interests.
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