

Review

The Role of CD2 Family Members in NK-Cell Regulation of B-Cell Antibody Production

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Received: 16 October 2013; in revised form: 13 December 2013 / Accepted: 13 December 2013 /

Published: 19 December 2013

Abstract: Natural Killer (NK) cells, an important component of the innate immune system, can mount much more rapid responses upon activation than adaptive antigen specific responses. Among the various functions attributed to NK cells their effect on antibody production merits special attention. The modification of IgG subclasses distribution as well as the amplification of the B cell response can be functionally relevant both for mediation of antibody-dependent cellular cytotoxicity (ADCC) and for control of dysregulated autoantibody production. In this review recent experimental evidence for the mechanistic basis of the effect of NK cells on B cell-responses will be covered. Thus, it will be shown that these effects are mediated not only via activation of cytokine and Toll-like receptors (TLR), but also by direct receptor-ligand interactions. Importantly, the function of these receptor/ligands, CD48 and CD244, do not require recognition of class I-MHC molecules but are more dependent on inflammatory conditions brought about by infection or oncogenesis.

Keywords: NK cells; B lymphocytes; CD244; CD48; TLR7

1. Introduction

The production of antibodies by B cells is an important arm of the adaptive immune response. Induction of B cells to secrete antigen specific immunoglobulin (Ig) can be mediated by a number of stimuli including direct cell-cell interactions as well as activation by cytokines and TLR ligands. In addition, factors that dictate preferential expression of different isotypes influence the ultimate functional effectiveness of the antibodies. In this review the evidence for Natural Killer (NK) cells, an

important arm of the innate immune system, to influence B cells Ig production will be presented. There is much evidence indicating that upon activation by inflammatory cytokines NK cells can alter the isotype selection via production of their own cytokines. Recent findings also show that NK cells can stimulate B cells via direct contact. Importantly, because of the more rapid activation of NK cells such interaction can occur prior to the participation of T cells although the extent of this interaction is governed by the proximity of the two cell types. Given that NK cells can influence the production of antibodies by B cells it is likely that they can play a role in the dysregulated production of autoantibodies from B cells that have escaped tolerance. Experimental evidence for such effects is also presented in this review.

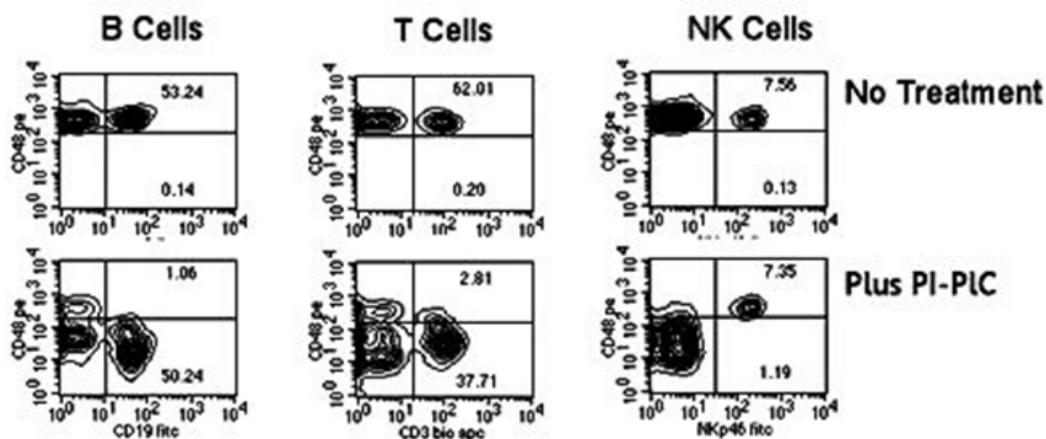
2. Evidence for NK-Cell Regulation of B-Cell Responses

Early evidence for the effect of NK cells on B cell responses are based mostly on studies investigating the results of *in vivo* NK cell depletion [1–7]. Most of the results point towards an indirect effect due to activation of accessory cells by either infectious agents or by specific antigens that mimic these agents. In these scenarios proinflammatory cytokines such as IL-12 or IFN- α/β produced by accessory cells stimulated via Toll-like receptors (TLR) can activate NK cells resulting in the production of IFN- γ which can amplify the cytokine circuit [8–17]. Expression of TLRs on NK cells themselves [18,19] may also affect the extent of crosstalk between various cell types upon encounter with pathogens. For B cells in particular the production of IFN- γ would be instrumental in directing the isotype preference of B cell immunoglobulin (Ig) production towards IgG2a/c.

In vitro experiments were also performed to investigate whether there are additional interaction molecules that would allow NK cells to regulate B cell activity in addition to the non-specific effect of cytokines [20–26]. These experiments utilized purified *in vitro* IL-2 propagated NK cells which were partially activated in that they expressed activation markers but produced only minimal amounts of cytokines. Whereas co-incubation of these NK cells with purified, resting, B lymphocytes can result in the skewing of B cell Ig synthesis predominately towards IgG2a/c, interestingly however, this effect can also be mediated in the absence of IFN- γ but requires direct cell contact between the two cell types [27]. Further investigations revealed that the critical interactions molecules consisted of CD2 or CD244 on NK cells and their ligand, or counter receptor, CD48, on B cells [25].

From these results, one would expect that stimulation of B cells with antibodies against the receptor could achieve the same effect as co-incubation with NK cells. However, anti-CD48, either in soluble form or immobilized on plastic, has no effect on B cells. Surprisingly, however, anti-CD48 immobilized on plastic, can stimulate NK cells to augment their production of cytokines. The activation requires the translocation of CD244 on the same cell [28] suggesting that the stimulation occurs via CD244, which, unlike CD48, can signal via intracellular kinases [29]. There is further indication that the manner of anchoring of CD48 on NK cells differs from that on B cells. Whereas B cell CD48 can be easily removed by phosphoinositide phospholipase C (PI-PLC), on NK cells the glycosylphosphatidylinositol-anchored receptor is totally resistant (Figure 1) leading to the intriguing suggestion that linkages with other molecules prevent accessibility by the enzyme. Prior to stimulation, the linkage does not involve either CD244 or CD2 because similar experiments examining NK cells from CD2-CD244-double deficient mice showed that CD48 was equally resistant to digestion [30].

Figure 1. Resistance of NK-CD48 to removal by PI-PLC. Splenocytes isolated from BALB/C mice were incubated with 1.0 units of PI-PLC for 2 h at 37 °C. Subsequently the cells were stained with B- (CD19), T- (CD3), and NK- (NKp46) cell specific reagents together with anti-CD48 antibodies to assess decrease in CD48 levels in comparison to non-treated control cells.

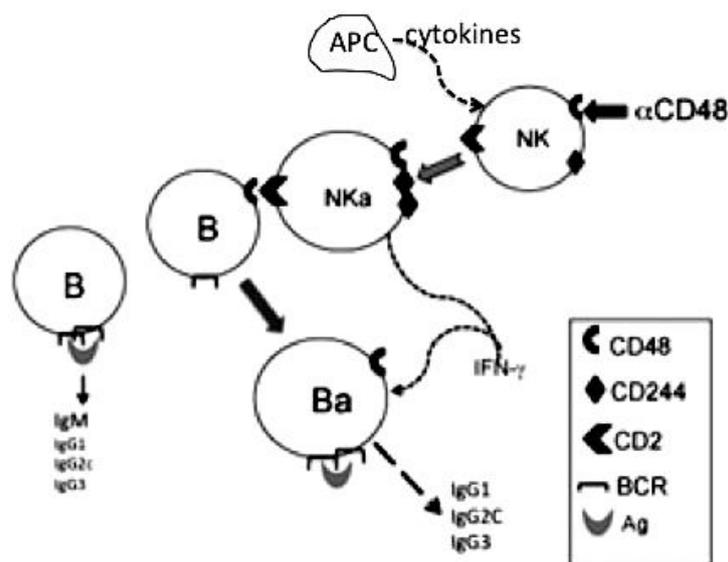


These findings suggested that it might be possible to test whether NK cells can exert direct effects on B cell Ig production *in vivo* by examining the outcome of introduction of anti-CD48 antibodies. In confirmation of the *in vitro* results, shortly after injection, anti-CD48 was found to activate NK cells but not B cells. Furthermore, the activation of NK cells was instrumental in altering the isotype selection of B-cell Ig produced as a result of stimulation by a T independent antigen (TI), NP-Ficoll [31]. A TI antigen was chosen since the presence of anti-CD48 would likely block a T dependent response that requires help from antigen presenting cells [26,32]. The requirement for NK cells was ascertained by specific depletion of the cells prior to anti-CD48 injection. Most importantly, similar effects could not be achieved by the introduction of anti-CD48 into CD244 or CD2-deficient mice. Thus, anti-CD48 stimulated NK cells can only stimulate B cells via the CD244 or CD2 counter-receptor. These results confirm the requirement for direct contact between the two cell types. Thus, in addition to indirect effects of cytokines, NK cells can regulate B-cell Ig production via direct cell-cell interaction. Nonetheless, the contribution exerted by such direct cell contact would be determined by the extent of appropriate localization of the two cell types in selected sites of infection or malignancy [33]. Thus, it is relevant that, real-time imaging of lymph nodes have shown that resident NK cells are relatively immotile but are much increased upon activation [34]. Activated NK cells have also been shown to migrate from the red pulp into the marginal zone areas of the spleen [35]. In this respect it is interesting that NK activation of rapid B cell IgM production in the marginal zone was found to require direct cell contact [36].

A possible scenario of these interactions is diagrammed in Figure 2, illustrating the consequence of anti-CD48 stimulation in the presence of a T independent antigen that can crosslink the B cell receptor. Thus, whereas some B cells can be stimulated by a TI-II antigen to produce a basal level of Ig, the extent of the response is low. Upon stimulation by anti-CD48, NK cells are activated, resulting in an alteration of CD244 which is required before the CD2 expressed on NK cells can become effective stimulators (NKa) of B cells via their counter-receptor CD48 [25]. These partially activated B cells (Ba) can proceed to Ig secretion upon encounter with antigen. It is also possible that NK stimulation can

alter the differentiation pathway of B cells that have already been activated by antigen. The downstream effects of stimulation of NK cells via anti-CD48 may differ from induction via proinflammatory cytokines produced by accessory cells. As shown recently, activation markers on NK cells induced by cytokines differs from those arising from activation via recognition of the viral antigen m157 [37]. Therefore, it would be interesting to determine if such differences also occur between those NK cells stimulated via CD48/CD244. An important question remaining is the configuration of the cellular ligand for CD48 on NK cells that would crosslink the molecule in the same manner as anti-CD48.

Figure 2. Scenario for the most likely interaction between NK and B cells induced by anti-CD48. Whereas some B cells can be stimulated by a TI-II antigen to produce a basal level of Ig, the extent of the response is low. Upon stimulation by anti-CD48, NK cells are activated, resulting in an alteration (translocation) of CD244 which is required before the CD2 expressed on NK cells can become effective stimulators (NKa) of B cells. These partially activated B cells (Ba) can proceed to Ig secretion upon encounter with antigen. Stimulation of NK cells via anti-CD48 may differ from stimulation via cytokines produced by accessory cells.



Similar *in vitro* and *in vivo* studies have demonstrated contact dependent interactions between NK and dendritic cells [38–41] that would ultimately result in modulation of T-cell responses [42–44] and *vice versa* [45]. Recently, there is also increasing evidence for regulation by T reg cells [46–48]; The proposed mechanisms generally implicate changes in the cytokine network, in particular, the availability of IL-2, but there is as yet little evidence for direct cell contact to play a role.

3. The Role of NK Cells in the Production of Anti-Nuclear-Antibodies

NZM2410, a mouse strain that develops systemic lupus erythematosus (SLE) with fatal glomerulonephritis, has been useful for the analysis of the cellular and genetic basis for the syndrome. Part of the genetic regions responsible for the phenotype is the locus, *Sle1b*, a 900 Kb interval

containing 24 expressed genes, including 7 members of the SLAM/CD2 gene cluster. This cluster encodes a family of costimulatory/adhesion receptors that includes SLAM (CD150, SLAMF1), Ly108 (NTB-A, SLAMF6), CD84 (SLAMF5), CRACC (CS1, SLAMF7), Ly9 (CD229), 2B4 (CD244), and CD48 [49]. The *Sle1b* cluster was introduced to a C57BL/6 background [50] in order to analyze its effects in a strain that does not exhibit autoimmunity. Interestingly, the presence of this interval alone was found to be sufficient to result in high levels of ANA production [51]. Importantly, the effect is limited in that, unlike the parental strain, other deleterious manifestations of lupus such as glomerulonephritis do not appear. Therefore animal survival is not affected. Further experiments showed that transfer of only B cells from the B6.*Sle1b* strain is sufficient for ANA production and that while T cell help modulates the response the presence of T cells from *Sle1b* mice is not required [52]. Therefore the B6.*Sle1b* strain is ideal for the study of dysregulated B- cell-Ig production. The cell surface molecules that are encoded by the *Sle1b* segment are ubiquitously expressed on hematopoietic cells. With the exception of CD244 in that it is expressed only on NK cells and a restricted population of CD8 T cells, the other receptors/counter-receptors regulate homophilic interactions between cells. The original analysis of CD244 showed it to be an activation molecule for NK cells [53–55]. However, further investigations indicated that the receptor can also exert an inhibitory role [56]. These dramatically opposing functions may be attributed to different splice forms of the transcript that result in alternative intracellular signal transduction [57]. However, the presence of the ligand, CD48, for the receptor, on the same cell may also affect its function depending on the extent of intra vs. intercellular crosslinking that may be modulated by interaction with other cell types that express CD48 [28,58–60]. It is interesting that the cell surface molecule, CD48 is also encoded within the *Sle1b* locus and a number of reports have indicated NK cell-interactions between CD244 and CD48 expressed on other NK cells as well as on other cell types that may be manifested in functional sequelae [61–63]. The evidence that direct NK-B cell interactions involve CD48 and CD244 suggests that regulation of or by NK cells may play a role in the initiation or progression of ANA in the B6.*Sle1b* strain.

The increased abundance of ANA in these mice do not occur until later in life and is even less pronounced in male mice; therefore to test the effect of this locus on B cell responses prior to development of the symptoms of SLE, young male animals can be tested. Interestingly, already at this stage the responses to antigenic challenge were found to be significantly altered from that of control B6 animals [64]. Furthermore and significantly, prior depletion of NK cells normalized the responses. These results suggest that molecules encoded in the *Sle1b* locus that direct NK-B cell interactions may be involved in the initiation of ANA production.

The critical time period required for the initiation of ANA production is not known. Therefore, in order to delineate a role for NK cells for the accumulation of ANA it was necessary to utilize a model by which NK cells can be chronically depleted without effects on other cell types. This was accomplished by transplantation experiments in which bone marrow precursors from the B6.*Sle1b* strain were transferred into irradiated recipients in which NK cells were chronically depleted resulting from the continued production of anti-NK1.1 antibodies derived from a transgene [7]. The results of these experiments showed that depletion of NK cells did not alter the course of development of ANA [65]. Thus if NK cells were involved their absence may have been compensated by, most probably, T cells.

Many of the receptors encoded by the *Sle1b* gene segment signals via the SLAM associated protein (SAP). This transducer has been shown to be critically important in T cell help for B cell responses [66].

Disruption of the gene encoding the protein (*Sh2d1a*^{-/-}) dramatically compromises the interaction between T and B cells with a resultant deficiency in T dependent antibody responses and production of T cell derived cytokines [66,67]. In order to analyze the role of this T cell function for the development of ANA the SAP-deficient strain was crossed with the B6.*Sle1b* strain. The results showed that although ANA continued to be made the penetrance was significantly reduced [64]. Furthermore because of the *Sh2d1a* disruption the subclass of antibody most dependent on T cell help, IgG1, was eliminated whereas IgG2C, the class of antibody produced in response to T independent antigens was only partially reduced. These results suggest that T cell help is not absolutely required for the induction of much of the ANA in B6.*Sle1b* mice. Furthermore, since mice with the SAP deficiency also have a total deficit of invariant NKT (iNKT) cells [68], the residual ANA production must be initiated from B cell responses that also do not require iNKT-cell involvement but may however derive help from other sources such as NK cells. Indeed, when NK cells were chronically depleted from the B6.*Sle1SAP*^{-/-} strain, the production of IgG2c ANA was significantly reduced [65]. Thus, whereas in intact animals where T cell help for the initiation of ANA is sufficient, the role of NK cells cannot be easily demonstrated. However, their functional relevance can be revealed when T cell help is compromised. The decrease in IgG subclasses that characterizes T independent responses confirms previous findings that B cell help from NK cells are more pronounced for T independent responses. Because appearance of ANA takes many weeks it is important to note that antibody producing plasma cells derived from T independent activation can also have long half-lives [33].

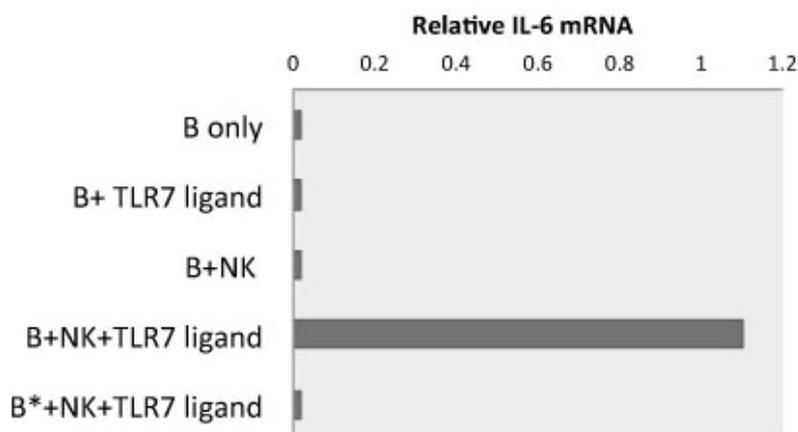
There is clear evidence that other genes included in the *Sle1b* region, most notably *Ly108* play a role during both B [69], T [70] as well as iNKT-cell [71] development such that a greater proportion of emergent cells escape tolerance. The role of NK cells appears to function at a later stage when these aberrant cells encounter stimulatory signals. Therefore the *Sle1b* locus is relevant for both the initiation as well as the progression of ANA production.

Whereas the *Sle1b* locus is sufficient for ANA production the introduction of other epistatic loci such as the Y-linked autoimmune accelerating (*Yaa*) locus can exacerbate symptoms resulting in more aggressive disease [72]. The *Yaa* locus consists of a duplication of a chromosomal segment which includes the TLR7 gene [73]. The upregulation of TLR7 expression has special consequences for the regulation of ANA production because of the key role of this receptor in regulation of responses to self antigens [74]. Self-RNA can act as TLR7 ligands [75], therefore, TLR7 stimulation is suggested as an additional signal contributing to activation and/or modulation of the aberrant immune response [76,77]. Duplication of the gene encoding TLR7 has indeed been shown to be responsible for increased responses to RNA protein complexes resulting in progression to kidney disease when it was introduced into the B6.*Sle1b* strain [78].

In this respect, it may be relevant to note the results of a recent survey, by means of microarray analysis, of all the transcripts that could be altered as a result of interactions between B and activated NK cells [79]. The most prominent class of up-regulated transcripts in B cells belongs to the Interferon Responsive Gene family that is typically initiated by Type I IFN produced by accessory cells. An outstanding transcript of this family, confirmed by RT-PCR analysis, is TLR7. Significantly, by the use of B cells from IFN α/β -deficient mice it was shown that the cascade initiated by NK cell signaling does not occur via IFN Type I or Type II but via Type III [80,81]. Thus, in addition to IFN- α , produced by accessory cells [82–85] that can increase TLR7 expression, NK cells are able to activate

B cells via an alternative pathway. The transcriptional up-regulation of TLR7 is functional in that addition of the ligand for this receptor on B cells results in the activation of IL-6 gene expression (Figure 3). This activation of IL-6 may be instrumental in the augmentation of help from T cells for increased production of Ig [86] and exacerbating various autoimmune states [87]. Indeed increased IL-6 levels have been found in the B6.*Sle1b.Yaa* strain [88]. Thus, the effect of increased transcription of this receptor as a result of NK interaction with B cells may approach conditions similar to the duplication of the TLR7 gene in the B6.*Sle1b.Yaa* strain. It should be noted, however, that the enhancement of B-cell TLR7 expression requires activated NK cells. Thus only under conditions that can sufficiently activate NK cells can more aggressive disease symptoms be elicited in the B6.*Sle1b* strain.

Figure 3. Induction of IL-6 mRNA by NK cells in the presence of TLR7 Ligand. IL-2 propagated NK cells were cultured with purified, resting B cells for 24 h before TLR7 ligand (Gardiquimodtm InvivoGen., San Diego, CA, USA) was added for another 24 hours. Levels of IL-6 mRNA was assessed by semi-quantitative RT-PCR analysis and normalized to the levels of MHCII mRNA in each culture. B* indicates B cells isolated from TLR7-deficient mice.



4. Functional Relevance of Preferential IgG Subclass Switch

The tendency of activated NK cells to program the B cell IgG switch to IgG2a/c and IgG3 should be clinically relevant. Clearly this switch preference is similar to that directed by Th1 responses; however, the ability of NK cells to utilize the antibodies for ADCC adds an additional factor in the armamentarium for combating diseases. A number of early reports have provided evidence for the greater efficacy of IgG2 and IgG3 (IgG1, IgG2 and IgG3 in humans [89]) to mediate ADCC [90–92] due to the difference from IgG1 (IgG4 in humans) in the Fc region. This difference has been taken into consideration in the optimization of therapeutic antibodies [93–95] and in many cases ADCC has been shown to increase the effectiveness of the antibodies.

Comparisons have been made for the relative effectiveness of CD8 T *vs.* NK cells, both of which can mediate cellular cytotoxicity. NK cells have been considered to be more advantageous during early responses because they can be activated prior to the activation of antigen specific T cells. Furthermore, there is now mounting evidence for the existence of memory NK cells with the capacity for increased response upon a second encounter [96–98]. However, the recent finding that memory T cells can be

activated without clonal restriction and can initiate cytokine production as well as cytotoxicity as rapidly as that by NK cells [99] seems to render the latter somewhat irrelevant in the case of secondary responses to most infections. However, even in this case the ability of NK cells to mediate ADCC may confer some additional advantage over that of CD8 T cells.

5. Conclusions

In this review, which is restricted to the effect of NK cells on B-cell Ig production, experimental results have been summarized to show that not only do NK cells influence the Ig isotype selection via the cytokine circuit they may also directly interact with B cells. However, since resting NK cells have limited mobility the time course of induction of increased motility to allow for cell contact as well as site of interaction is an important aspect of the effectiveness of NK stimulation which requires further investigation. NK cells have traditionally been considered to be a part of the innate immune system due to their rapid response to bodily insult. They are, however, also tightly regulated via inhibitory receptors to maintain their tolerance to self [100,101]. This homeostasis is further modulated by the availability of cytokines that can break tolerance [102] and others such as IL-2 that modulate the activity of T reg cells [47]. For this reason studies that attempt to pinpoint the effect of NK cells on B-cell Ig production is complicated by the many other elements that impact the response of B lymphocytes. Therefore, it may be for this reason that results of experimental manipulations are seldom found to be totally unambiguous but are instead, revealed as a 2 or 3-fold enhancement or reduction, which are nonetheless statistically significant.

NK cells may also contribute to dysregulated antibody production. Although NK-cell influences have been documented in other mouse models for SLE [103–106], mechanistic analysis has been complicated by the contribution of other cell types. Thus the B6.*Sle1b* model was useful for restricting the genetic components; however, it should be borne in mind that the transferred gene segment contains three copies of the CD244 gene whereas there is only one copy in the B6 genome [107]. In this respect it is interesting that the effect of Ig production by injection of anti-CD48 antibodies was shown to be strain dependent in that depletion of NK cells only normalized the response in B6 but not BALB/C mice [31]. One reason for the difference may be attributed to the balance between inhibition vs. activation capacities of the CD244 receptor due to the difference in copy numbers in the two strains.

In conclusion, whereas it is clear that NK cells are not absolutely required for B-cell Ig production the experiments summarized in this document clearly show that they can modify B-cell responses under certain conditions. Thus, the limited effect of NK cells on B lymphocytes shown in mouse models correlate with the fact that human NK-cell deficiencies have not been found to be as deleterious as other B or T cell defects [108]. Nonetheless, when combined with other causes of immune dysregulation the effect may not be trivial.

Acknowledgements

The author is grateful to members of her laboratory for scientific contributions that helped to solidify the concepts proposed in this review. Special thanks goes to Paula Jennings for careful review of the manuscript. The work was supported by the National Institutes of Health.

Conflicts of Interest

The authors declare no conflict of interest.

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