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Induction of autoimmunity after allotransplantation

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1. ABSTRACT

Our studies show that activated autoreactive inflammatory T cells specific and autoantibodies to collagen (V) and cardiac myosin are consistently detected after lung and heart transplantation, respectively. Clonal expansion of these T cells occurs only after an alloresponse, but once activated they can induce on their own rejection of allogeneic and even syngeneic transplants. Indirect rather than indirect alloresponse triggers autoimmunity after transplantation presumably via antigen mimicry between autoantigen peptides and donor MHC peptides. Also, it is plausible that inflammation and tissue damage associated with initial alloresponse to donor MHC antigens causes the release of formerly sequestered autoantigens. This may result in the presentation of some cryptic self-determinants thereby triggering an autoimmune process at the site of the graft. Finally, tolerance induction to cardiac myosin and collagen (V) results in long-term survival and reduced pathogenesis of heart and lung allografts, respectively. This suggests that, after transplantation, the inflammatory alloresponse to donor MHC triggers a cascade of events including autoimmunity to tissue antigens, a phenomenon that is essential to the actual rejection.

2. INTRODUCTION

The transplantation of allogeneic organs initiates a potent inflammatory immune response in which recipient T lymphocytes directed to donor MHC molecules become activated. Allorecognition takes place primarily in the recipient lymph nodes and spleen where T cells interact with intact alloMHC molecules present on donor dendritic cells (direct allorecognition) (1-3) and with donor MHC peptides processed and presented by recipient APCs (indirect allorecognition) (4-8). In addition, minor histocompatibility antigens defined as peptides derived from a non-MHC donor polymorphic protein, are also regularly presented either directly or indirectly and can trigger an alloimmune response (4-11). Activation of alloreactive $CD4^+$ T cells triggers a cascade of events including cytotoxic T cell differentiation, DTH reactions and anti-donor antibody production (12). However, whether the immune response to donor MHC molecules truly represents the main and only driving force behind allograft rejection remains open to question. Here, we review recent studies showing the spreading of alloimmunity to tissue-specific antigens after transplantation of allogeneic hearts and lungs. These studies support the view that such breakdown of tolerance to autoantigens triggers an

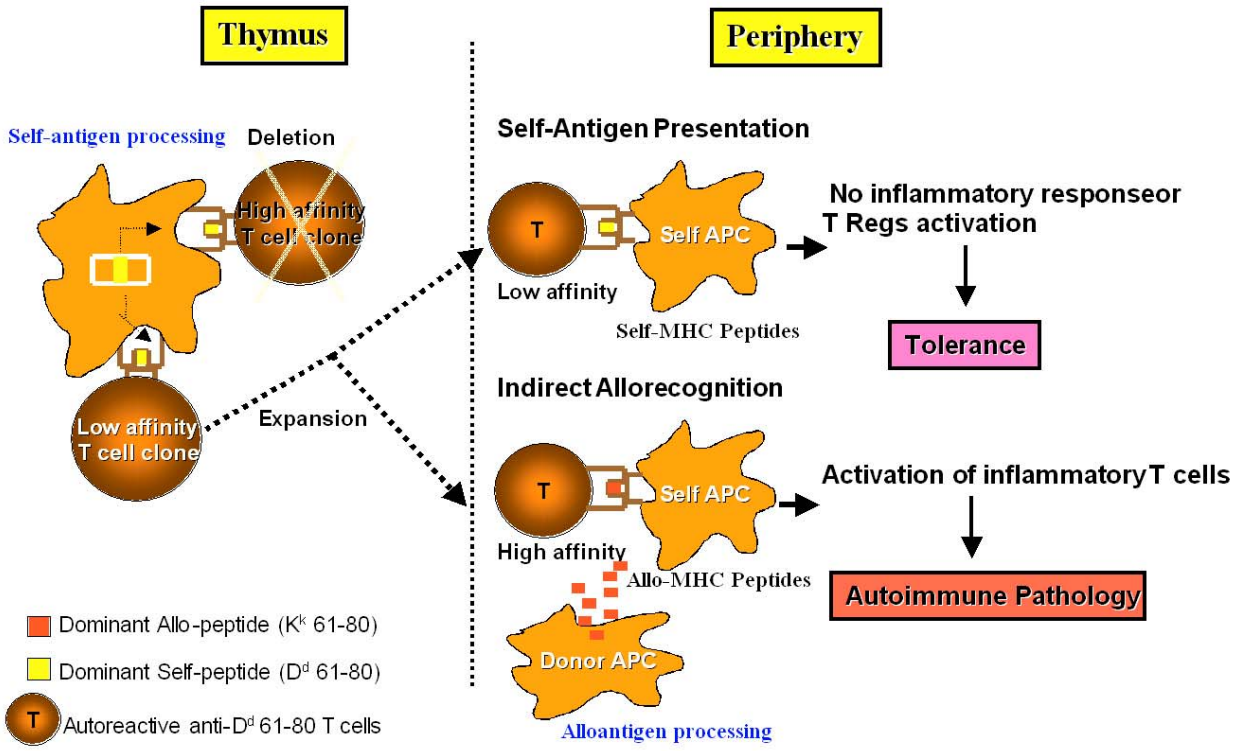

Figure 1. Model for induction of autoimmunity via indirect allorecognition of donor MHC peptides

inflammatory response that is likely to play a key role in acute and chronic rejection of allografts.

3. DEVELOPMENT OF INFLAMMATORY AUTOIMMUNE RESPONSES AFTER ALLOTRANSPLANTATION

The initial observation that allotransplantation can result in the breakdown of T cell tolerance to self-antigens was made in a study exploring the immunogenicity and tolerogenicity of MHC class I peptides in mice. BALB/c (H-2d) mice are tolerant to the self-peptide, Dd 61-80, derived from the □1 domain of MHC class I Dd autoantigen (13-15). Dd 61-80 peptide binds with high affinity to Ad MHC class II protein and it is regularly processed and presented at the surface of BALB/c APCs, a feature which accounts for its ability to tolerize corresponding T cells during development (13-15). Consequently, subcutaneous immunization of BALB/c mice with this self-peptide along with CFA never triggers a CD4+ T cell response. Based on these results, we hypothesized that Dd 61-80-specific autoreactive T cells were deleted in the developing thymus. Unexpectedly, observations in mice sensitized to H-2a alloantigens showed that this assumption was incorrect. We observed that transplantation of BALB/c mice with allogeneic B10.A (H-2a) splenocytes could, in fact, induce an autoimmune T cell response towards this Dd 61-80 self-peptide (16). These transplanted mice also mounted vigorous indirect alloresponses to another peptide derived from the donor MHC class I molecule, Kk 61-80. Given their sequence homology, it was possible that indirect response to K^k 61-80 had broken T cell tolerance to its counterpart peptide on self-MHC class I, Dd 61-80 (Figure 1). This was confirmed by the fact that immunization with Kk 61-80 was sufficient to trigger autoimmunity to the self-Dd 61-80 peptide in BALB/c mice (16). This study demonstrated that generation of an indirect alloresponse to the donor MHC peptide could abrogate tolerance to its crossreactive homologous peptide on self-MHC, thereby breaking self-tolerance in adult mice.

The study in the MHC class I peptide model prompted us to investigate whether autoimmunity is regularly induced after transplantation of allogeneic tissues and organs. We found the presence of autoimmune responses in rodents that had been transplanted with allogeneic hearts and lungs. In the heart transplant model, we showed that in a MHC class I disparate combination, T cell response to donor MHC molecules was followed by an autoimmune response to cardiac myosin (CM), a contractile protein expressed by cardiomyocytes (17). Activated MHC class II-restricted CM-specific CD4+ TH1 cells mediated anti-CM response. High titers of IgG1 anti-CM autoantibodies were detected in the serum of heart-transplanted mice. No response to CM was detected in non-transplanted mice, in recipients of a syngeneic graft and in mice engrafted with an allogeneic skin from the same donor (17). This clearly indicates that initiation of CM autoimmunity necessitates the concomitant presentation of both donor MHC alloantigen and CM cardiac antigen on the transplant. It is noteworthy that patients originally diagnosed with chronic myocarditis experience more frequent and severe rejection episodes than patients with other heart diseases (18). In addition, increases in the amounts of circulating CM

following transplantation have been correlated with poor prognosis for cardiac transplant survival (19). Most importantly, Warraich et al. recently reported the presence of anti-CM autoantibodies during acute rejection of heart transplants in patients with dilated cardiomyopathy (20). These different studies support the relevance of anti-CM autoimmunity to clinical cardiac transplantation.

During lung transplant rejection, we detected an autoimmune response to collagen type V (col (V)); a protein located in the perivascular and peribronchiolar connected tissues (21-23). In lung-transplanted patients, the presence of anti-Col (V) autoantibodies displaying IgG2 isotype was consistently found (23). In addition, peripheral blood T cells from these patients were shown to induce potent DTH responses against Col (V) using a human to SCID mouse trans-in vivo DTH assay (23). In this study, no response was found to control collagen (II). Next, we used the rat model of lung transplantation to investigate the immunopathogenesis of allograft rejection in which F344 (RT1lv1) lung allografts or WKY (RT1l) lung isografts were transplanted orthotopically into WKY recipients. Using this model, we investigated the presence of cellular immune responses to col (V) in lung allografts during rejection and the role of col (V)-specific T cells in the development of the pathology of lung allograft rejection. Autoimmune responses to Col (V) were consistently detected in rats transplanted with allogeneic lungs or administered with allogeneic cells from bronchoaleolar lavages. This response was restricted to Col(V) in that no response was detected to other collagen types (21-23).Initial Col(V) cell lines propagated from lung allograft infiltrating lymphocytes were Th1 type producing copious amounts or γIFN and TNF-α (21). More recent studies show that pathogenic T cells that result from Col (V) immunization produce IL-17 (TH-17), and low levels of IFN (24). These data suggest that screening for T cells that produce IL-17 in response to Col (V) may indicate the onset of anti-Col(V) immunity in the lung transplant recipients. In addition, these studies highlight further another autoimmune pathology related to TH IL-17 type T cells (25, 26).

Following our initial reports in the mouse heart and lung transplant models, the presence of de novo immune responses to various autoantigens including heat shock proteins (HSP), vimentin, and intra-retinal binding protein (IRBP) have been reported after transplantation of skin, kidney and retinas, respectively (27-33). The presence of autoimmunity post-transplantation has been detected in both experimental rodent models and in patients. Therefore, development of autoimmunity represents a general phenomenon in allotransplantation.

4. CAN AUTOREACTIVE T CELLS ACTIVATED AFTER TRANSPLANTATION REJECT AN ALLOGRAFT?

Cardiac myosin represents the target autoantigen in a T cell-mediated autoimmune disease, experimental autoimmune myocarditis (EAM) (34-38). Two observations suggested that anti-CM autoimmunity induced after cardiac transplantation could contribute to heart tissue damage in a fashion similar to that observed during autoimmune myocarditis. 1) Histological analysis revealed the presence of epicardial and endocardial interstitial inflammatory cell infiltrates, myocyte dropout and necrosis in both transplanted and myocarditic hearts. 2) Similar to transplanted mice, B cell response in EAM is characterized by high titers of anti-CM IgG1, a set of antibodies which have been shown to play an important role in the autoimmune pathogenesis (39-41). Two sets of experiments indicated that anti-CM autoimmunity induced after cardiac transplantation is likely to contribute to the rejection of these grafts. First, pre-transplantation sensitization with CM invariably resulted in accelerated rejection (no treatment: 9.4 ± 0.3 ; control antigen (OVA) treatment: 9.5 ± 0.6 days ; CM treatment: 5.2 ± 0.6 days, $p< 0.001$) (17). Second, mice immunized with CM and then grafted with a syngeneic heart rejected their transplants within 40 day (17). Histological examination of cardiac tissue revealed massive lymphocytic infiltration as well as myocyte dropout and necrosis typically observed in acutely rejected allotransplants. In the lung transplant study, two lines of evidence supported the view that autoreactive T cells specific to Col(V) can contribute to the rejection of these transplants: 1) instillation of syngeneic BAL cells pulsed with Col(V) was sufficient to cause rejection of lung allotransplants, 2) adoptive transfer of anti-Col(V) cell lines (isolated from allogeneic lungs undergoing rejection) into naïve rats caused marked peribronchiolar and perivascular inflammation in lung isografts (21-23, 42). Altogether, the experiments in the heart and lung transplant models support the view that the induction of an autoimmune response after transplantation is likely to contribute to the rejection process.

Interestingly, while initiation of an autoimmune response in both lung and heart models resulted in inflammatory infiltration and tissue damage of transplants, the native heart and lung of transplanted rodents remained apparently intact. It is surprising, at first glance, that autoimmunity to CM and Col(V) had apparently not affected the native's recipient cardiac and lung tissues, respectively. We surmise that the absence of trauma and of local inflammation in the non-transplanted organ associated with the lack of chemokine and inflammatory cytokine production and of adhesion molecule upregulation could explain the absence of infiltration by activated lymphocytes. Interestingly, simultaneous transplantation of a syngeneic and an allogeneic heart in the same mouse resulted in the rejection of the allotransplant while the syngeneic one remained intact. This suggests that, unlike that observed after CM immunization with CFA, the response to CM is not sufficient to cause the rejection fo a syngeneic heart transplant. It is possible that the CM response is too weak or that CM-specific T cells are not trafficking to the syngeneic heart transplant.

4. MECHANISMS RESPONSIBLE FOR SELF-TOLERANCE DISRUPTION DURING AN ALLOIMMUNE RESPONSE

Initiation of autoimmunity is traditionally believed to originate from two processes: 1) following infection, certain microbial antigens can “mimic” self-

antigens and activate normally resting autoreactive T cells (antigen mimicry) and, 2) tissue damage associated with infection and/or inflammation can cause the release of normally sequestered autoantigens and the subsequent activation of some undeleted self-reactive peripheral T cells. We tested whether either one or both of these mechanisms could also be associated with the activation and expansion of CM-specific T cells after cardiac allografting in mice.

We first investigated whether antigen mimicry could account for induction of autoimmunity after allotransplantation. In the A/J-A.TL combination, donor and recipient differ by a single MHC class I allele (K^k vs. K^s). We reasoned that if indirect $CD4^+$ T cell alloresponse to K^k was sufficient to elicit a response to CM, K^k molecule may contain a peptide that can crossreact with a determinant on CM. Indirect alloresponse to K^k in recipient mice was directed to a dominant allopeptide corresponding to region 61-80, K^k 61-80 (GB, unpublished observations). Interestingly, we found that immunization of A.TL mice with K^k 61-80 allopeptide could on its own elicit an autoimmune response to CM, in the absence of transplantation. This showed that some alloreactive T cells directed to K^k 61-80 could also recognize a determinant on CM. This suggests that antigen mimicry could account for initiation of CM autoimmunity after engraftment of A.TL mice with an A/J heart. Identification of the CM determinant crossreacting with K^k 61-80 is in progress in our laboratory.

Another possibility was that damage and myocyte death in the grafted heart tissue mediated by the alloresponse and/or the inflammation could cause the release of CM in the extracellular milieu and in the blood. In this scenario, it is likely that circulating CM would undergo exogenous processing and MHC class II presentation by recipient "professional" APCs and subsequent T cell autoimmunity to this cardiac autoantigen. It is noteworthy that the mature form of CM is not expressed in the thymus during development (43, 44). This presumably accounts for the incomplete negative selection to this self-protein and the apparent survival of some high affinity anti-CM autoreactive T cells. Since, under normal conditions, CM is never released in the periphery, corresponding autoreactive peripheral T cells should remain silent. However, these T cells may become activated after heart transplantation if CM is released from injured cardiac muscle tissue. To address this possibility, peripheral blood samples from heart-transplanted mice were collected and tested using an ELISA assay for the presence of CM. High titers of circulating CM were detected (unpublished data), a finding that has also been reported in transplanted patients (20). No CM was detected in the blood of non-transplanted mice and skin-grafted mice. Therefore cardiac transplantation is associated with release of CM in the circulation, a process which may contribute to initiation of CM autoimmunity.

We investigated the involvement of direct and indirect allorecognition pathways in the onset of CM response following heart transplantation. In the A/J-AT.L model, donor and recipient differ by a single MHC class I allele (K^s vs. K^k). In this type of combination, we have shown that $CD4^+$ T cell alloresponse is primarily mediated via indirect pathway (45) and a response to CM is regularly detected. In this model, antibodies to recipient but not donor MHC class II blocked CM response. In another set of experiments, BALB/c mice were transplanted with hearts derived from B6 mice devoid of MHC class II molecule (MHC class II knockout ; a setting in which $CD4^+$ T cell response is restricted to the indirect pathway (46-48). We observed that BALB/c mice transplanted with B6 class II KO hearts mounted a potent anti-CM response (45). This finding was confirmed by A. Valujskikh who reported that MHC class II KO skin grafts induce potent autoimmune responses in recipients (49). Autoreactive T cells activated as a consequence of indirect allorecognition were shown to reject syngeneic skin transplants (49). Altogether, these studies demonstrate that indirect alloreactivity mediated by $CD4^+$ T cells is necessary and sufficient to elicit autoimmunity after transplantation of allogeneic tissues.

Col(V) is considered a "sequestered" antigen, intercolated within type I collagen [col(I)], the major lung collagen. Accordingly, col(V) could be hidden from the immune system and only exposed in response to interstitial remodeling that may occur during lung injury. To test this hypothesis, we isolated T cells from WKY rats immunized with col(V), and adoptively transferred these cells to normal WKY rats or WKY rats that received lung isografts. By conducting the experiments in this manner, any anti-col(V)-induced pathology would be the result of autoimmunity without elements of alloimmunity. Interestingly transfer of Col (V)-reactive lymphocytes did not induced any pathology in lungs of normal rats. In contrast, isograft lungs redeveloped perivascular and peribronchiolar infiltrates consistent with grade 2 acute rejection within five days after cell transfer (24).

Data showing that transfer of col(V)-reactive cells induces "rejection" pathology in transplants but not normal lungs suggest that the transplant procedure, itself, may have unmasked antigenic Col (V). Indeed, Col(V) fragments are readily found in isograft bronchoalveolar lavages by western blotting (21). Col(V) is also detected by immunhistochemistry in the peribronhiolar and perivascular lung tisssues at five days post transplantation. In contrast, similar staining is not present in normal lungs (24). Although the lung isografts are histologically normal 30 days post transplantation, the presence of col(V) is consistently observed by immunohistochemistry at this time point (24). Detecting col(V) at 30 days suggests that the lung is well healed from any injury that may have occurred from ischemia and reperfusion but it may still be susceptible to anti-Col (V)-mediated pathology. Indeed, transfer of Col (V)-reactive lymphocytes to rats 30 days post-transplantation induced (grade 3) "rejection" pathology in the isograft (24). Collectively, these data suggest that inflammation that results from ischemia reperfusion injury (IRI), which is an invariable consequence of the transplantation procedure, results in exposing antigenic Col (V) epitopes. This implies that interventions able to reduce/prevent IRI may protect the lung from anti-col(V)-mediated injury.

6. MODULATION OF T CELL RESPONSES TO AUTOANTIGENS IN HEART AND LUNG TRANSPLANTATION MODELS

The most compelling evidence of the role of autoimmunity in allograft rejection has been obtained through experiments designed to modulate the inflammatory T cell responses to autoantigens. In the lung transplant model, Mares et al. initially reported that intratracheal instillation of rats with Col(V) prior to nasal insufflations of allogeneic BAL cells prevented the development of rejection pathology and apoptosis and abrogated the proliferation of alloreactive T cells (via direct allorecognition) and markedly reduced macrophage infiltration and local production of TNF□(42, 50). These observations were extended in a subsequent study in which WKY rats were fed with 10 □g Col(V) every other day for two weeks prior to transplantation with an allogeneic F344 lung. Col(V)-treated rats were tolerant to lung allografts in that they displayed reduced DTH responses to alloantigens and prolonged graft survival associated with mild perivascular and peribronchial mononuclear cell infiltration. No effects were observed with control collagens (II and XI). In addition, Col(V)-fed recipients displayed intact responses to nominal antigens. In this model, prolongation of lung allograft survival was associated with a systemic production of transforming growth factor (TGF)-□ but not IL-4 and IL-10 (42, 50). Neutralization of TGF-□ restored the DTH alloresponse thereby confirming the involvement of this cytokine in the oral tolerization process (42, 50).

In a subsequent study, we investigated whether generation of a type 2 anti-inflammatory T cell response to CM could impact the rejection of cardiac allotransplants in mice. Seminal studies performed in P. Lehmann's laboratory have demonstrated that administration of autoantigens along with incomplete Freund's adjuvant (IFA) polarizes the T cell response toward type 2 cytokines (IL-4, IL-5, IL10) (51-54). This procedure has been shown to reduce type 1 immunity (TNF-□, □IFN, IL-12) to pathogenic autoantigens and protects against inflammatory autoimmune diseases including autoimmune encephalomyelitis and diabetes. Based upon this principle, we hypothesized that development of a type 2 immunity (IL-4, IL-5) to CM could reduce inflammatory TH1 response to CM and thereby improve heart transplant survival. To test this, A.TL mice were injected intraperitoneally with CM emulsified in IFA and transplanted ten days later with MHC class I-disparate A/J hearts. First, anti-CM response in A.TL mice treated with CM-IFA was evaluated using ELISPOT. High frequencies of IL-4 and IL-5 producing T cells were detected in freshly isolated spleen cells from these mice. Remarkably, these mice retained donor hearts for more than 100 days, while untreated recipients and mice injected with IFA alone rejected their transplants approximately 10 days after grafting (45). While acutely rejected hearts from control untreated recipients exhibited generalized interstitial inflammatory cell infiltration and myocyte damage, donor hearts from CM/IFA-treated mice displayed well-preserved epicardium with minimal or no inflammatory cell infiltrates (45). To investigate whether type 2 T cells were actually involved in prevention of acute rejection after CM/IFA injection, we blocked in vivo IL-4 cytokine that serves as a growth and differentiation factor for Th2 cells (55). IL-4 was neutralized at the time of activation of type 2 CM-specific T cells as previously described (56). Recipient A.TL mice were injected i.p. with 4 mg of anti-IL-4 mAb one day before CM/IFA injection. Ten days after CM/IFA administration, mice were grafted with A.TL heart. Strikingly, anti-IL-4 mAb treatment prevented the prolongation of graft survival by CM/IFA (mean survival time in: 15.5 ± 0.8 days) (45). This data shows that IL-4 cytokine is a key element of the prevention of acute rejection of cardiac allografts following CM/IFA administration.

Taken together, the results obtained in both lung and heart transplants models suggest that the development of an autoimmune response after transplantation of allogeneic organs is an essential component of the rejection process. Most importantly, these studies show that tolerance induction to tissue-specific autoantigens is effective at preventing acute rejection and delaying the onset and reducing the severity of chronic rejection of allografts.

7. FUTURE PERSPECTIVES

The presence of autoreactive T cell responses to tissue specific antigens expressed by the graft has been observed after placement of different allogeneic organs and tissues in various species and therefore represents a general phenomenon in transplantation. Autoimmune T cells expand only after indirect sensitization of allospecific T cells to donor MHC antigens. However, once activated, these T cells are sufficient on their own to ensure the rejection process. This suggests that while indirect T cell response to donor MHC is necessary for initiation of the rejection, T cells recognizing graft tissue specific antigens may be the actual mediators of the rejection. The spreading of T cell alloimmunity to formerly cryptic autoantigens is likely to occur when the rejection is delayed and associated with persistence of low inflammation reactions; a phenomenon reminiscent of that observed in chronic inflammatory autoimmune diseases. This scenario suggests that post-transplant autoimmunity may play a pivotal role in chronic form of allotransplant rejection, a hypothesis supported by studies in the heart transplants model (57). The mechanisms by which indirect alloimmunity causes an autoimmune reaction are still unclear. It is likely that antigen mimicry between donor peptides and self-peptides and any injury that may cause the release of normally sequestered autoantigens may activate some undeleted autoreactive T cells in the periphery and initiate an autoimmune pathological cascade. The most compelling evidence of the role of this autoimmune process in the rejection is that tolerization of recipient T cells to cardiac myosin and Collagen (V) results in long term survival of heart and lung transplants, respectively. Moreover, Collagen (V) tolerization abrogated the development of Bronchiolitis Obliterans that is characteristic of chronic rejection in lung transplantation. It is now important to

elucidate the mechanisms by which indirect alloreactivity leads to autoimmunity and determine the actual contribution of this phenomenon to chronic rejection in clinical transplantation. As we gain insights into these questions, we will engineer appropriate strategies to accomplish transplantation tolerance.

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