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HLA Class I-Mediated Induction of Cell Proliferation Involves Cyclin E-Mediated Inactivation of Rb Function and Induction of E2F Activity

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Chronic rejection of transplanted organs is manifested as atherosclerosis of the blood vessels of the allograft. HLA class I Ags have been implicated to play a major role in this process, since signaling via HLA class I molecules can induce the proliferation of aortic endothelial as well as smooth muscle cells. In this study, we show that HLA class I-mediated induction of cell proliferation correlates with inactivation of the Rb protein in the T cell line Jurkat as well as human aortic endothelial cells. HLA class I-mediated inactivation of Rb can be inhibited specifically by neutralizing Abs to basic fibroblast growth factor (bFGF), suggesting a role for FGF receptors in the signaling process. Signaling through HLA class I molecules induced cyclin E-associated kinase activity within 4 h in quiescent endothelial cells, and appeared to mediate the inactivation of Rb. A csk inhibitor, Olomoucine, as well as a dominant-negative cdk2 construct prevented HLA class I-mediated inactivation of Rb; in contrast, dominant-negative cdk4 and cdk6 constructs had no effect. Furthermore, there was no increase in cyclin D-associated kinase activity upon HLA class I ligation, suggesting that cyclin E-dependent kinase activity mediates Rb inactivation, leading to E2F activation and cell proliferation. The Journal of Immunology, 1999, 162: 5351–5358.

T he cell cycle regulatory machinery can respond to a wide array of extracellular signals and modulate the proliferative state of cells accurately (1). The ability of the cell cycle machinery to respond differentially to various extracellular signals enables cells to undergo proliferation, differentiation, apoptosis, or remain in a quiescent state, as appropriate (2, 3). An understanding of how extracellular signals received at the cell surface contact the cell cycle machinery would enable us to modulate such processes for therapeutic purposes (4).

Recent studies have demonstrated that multiple signal transduction cascades can target the Rb protein, which is the major negative regulator of cell cycle progression (5–7). Earlier studies had indicated that growth-factor stimulation of quiescent cells leads to the inactivation of Rb through the mediation of cyclin-dependent kinases (8–10). This observation was further extended to other signaling pathways initiating from other types of receptors, and such signals were also observed to converge on Rb (11). The normal function of the Rb protein is regulated by kinases associated with cyclins D and E, and phosphorylation of Rb by such kinases in mid-to-late G1 phase of the cell cycle leads to its inactivation (12–15). The interaction between Rb and its major downstream target, the E2F transcription factor (16–18), is disrupted upon the inactivation of Rb, and this facilitates the entry of cells into the S phase (10). Rb and its downstream target E2F transcription factor have been found to respond to various signaling events facilitating proliferation, apoptosis, or differentiation, and are believed to regulate the genes expressed during such processes (19–22).

It has been suggested that Rb and E2F function can be modulated by extracellular signals independent of the cyclin/cdk pathway (23–25); for example, we have found that the signaling kinase Raf-1 physically interacts with Rb and regulates its function (26). The Raf-1/Rb interaction occurs in response to mitogenic stimuli and leads to an inactivation of Rb function. Signals that are not proliferative have also been found to inactivate Rb (27, 28); furthermore, we find that stimulation of the Fas receptor in Jurkat cells leads to an inactivation of Rb within 30 min, and this occurs independent of cyclins and cyclin-dependent kinases. Fas-mediated inactivation of Rb occurs through the mediation of the p38 kinase, a member of the mitogen-activated protein kinase family. p38 kinase can directly phosphorylate Rb and can inactivate Rb in the presence of dominant-negative cyclin-dependent kinases. In addition, nonproliferative signals like cytokines can inactivate E2F1 through the mediation of JNK1/SAP1 (c-Jun N-terminal kinase/stress-activated protein-1) kinase (69).

Since Rb and E2F are vital regulators of cell proliferation (29, 30), we attempted to evaluate whether they mediate proliferation induced by specific signals of the immune system. Attention was focused on HLA class I-mediated signaling, which has been demonstrated recently to induce proliferation of human endothelial cells (EC)4 and smooth muscle cells (SMC) (31–33). This signaling cascade may be of particular importance in the process of chronic rejection that is caused by the proliferation of EC and SMC of the vasculature, leading to obstruction of the vessels of the allograft (34, 35). Earlier work demonstrated that cross-linking of HLA class I molecules leads to an induction of FGF receptors as...
Materials and Methods

Cell culture and transfections

Normal human aortic EC (lot 2709) were obtained from Clonetics (San Diego, CA) and maintained in EC growth medium (EGM), as described earlier (31, 32), and transfected by calcium phosphate precipitation method. Jurkat cells grown in RPMI containing 10% FBS were electroporated using a Bio-Rad (Richmond, CA) Gene Pulser; cells were harvested 72 h after transfection, and assayed for chloramphenicol acetyltransferase (CAT) and ß-galactosidase were performed using standard protocols. A pSV-ß-gal vector was included in all transient transfections as internal control. Constructs pDE2F1, pE2CAT, and pSVRb (68) as well as dominant-negative cdk2, cdk4, and cdk6 have been described before. A total of 2 μg each of E2-CAT, pDCE2F1, and pSVRb was used in all transfections.

HLA class I, bFGF, and Fas stimulation

Jurkat cells grown in RPMI containing 10% FBS were stimulated with 50 ng/ml of an anti-Fas Ab (MBL Laboratories, Watertown, MA) for 6 h before harvest. A total of 200 μM of Olomoucine or 10 μM of SB203580 was included in the culture medium during stimulation when appropriate. Stimulation with 10 ng/ml of 12-O-tetradecanoylphorbol-13-acetate (TPA) and 10 μg/ml of W6/32, an IgG2b murine mAb that binds to a monomorphic epitope on HLA class I Ags (American Type Culture Collection, Manassas, VA), was conducted for 6 h before harvest. Similarly, aortic EC were stimulated with 0.6 ng/ml of BFGF for 6 h. Neutralizing Abs to cyclins D and E were obtained from Santa Cruz Biotechnologies (Santa Cruz, CA). For immunoprecipitations, 200 μg of cell lysates prepared in M2 buffer (20 mM Tris (pH 7.6), 250 mM NaCl, 3 mM EDTA, 0.05% EDTA, harvesting, and scintillation counting on a LKB Beta Plate Cell Harvester. All data are expressed as the mean cpm of triplicate determinations of control cultures).

Results

HLA class I stimulation leads to Rb inactivation in Jurkat T cells

Experiments were designed to evaluate whether treatment of Jurkat T cells with an anti-HLA class I Ab could inactivate Rb. The strategy was to use E2F1-mediated transcriptional activity as a measure of Rb function. Transfection of an E2F1 expression vector along with an E2-CAT reporter construct led to a high degree of transcriptional activity in Jurkat cells (Fig. 1A, lane 2). Cotransfection of a human Rb expression vector could completely inhibit E2F function (Fig. 1A, lane 5), as has been found in various other cell lines. There was no significant effect on the transcriptional activity of E2F when cells transfected with E2-CAT and E2F1 were treated with either TPA alone or with W6/32, a murine mAb specific for a nonpolymorphic region on class I molecules (Fig. 1, lanes 3 and 4). Similarly, TPA treatment of cells cotransfected with Rb had no effect on Rb function (Fig. 1, lane 6). In contrast, when cells cotransfected with Rb were treated with a combination
of TPA and mAb W6/32, Rb-mediated repression of E2F activity was efficiently released (Fig. 1, lane 7). This experiment indicates that signaling pathways triggered through ligation of HLA class I molecules can effectively overcome Rb-mediated regulation of E2F1. Since Rb is known to exert its growth regulation at least in part by targeting E2F, deregulation of Rb appears to be a mechanism involved in HLA class I-mediated induction of cell proliferation.

To determine the kinetics of Rb inactivation, a similar transient transfection experiment was conducted in Jurkat cells, but the cells were treated for different periods of time with TPA and anti-HLA Abs. As shown in Fig. 1B, E2F-mediated transcription started to appear 2 h after anti-HLA class I stimulation. Full reversal of Rb-mediated inhibition was not observed until after 6 h. This suggests that HLA class I-mediated inactivation of Rb is not an immediate event in the signaling pathway. This is in contrast to Fas-mediated reversal of Rb function in Jurkat T cells, which occurred within 30 min (69). This indicates that different signaling cascades can target the Rb-E2F regulatory pathway through different molecular mechanisms.

**FIGURE 2.** Inactivation of Rb by HLA class I and Fas involves different pathways. A, Jurkat cells were transiently transfected with E2CAT, E2F1, and Rb in the indicated lanes. Stimulation of the transfected cells with HLA class I Ab and TPA reverses Rb (lane 4); treatment of cells with 200 μM Olomoucine during stimulation abolishes inactivation of Rb (lane 5). HLA class I stimulation in the presence of SB203580, a p38 kinase inhibitor, has no effect (lane 6). A similar experiment, in which an anti-Fas Ab was used to inactivate Rb. In this case, SB203580 could block Rb inactivation (lane 5), but Olomoucine had no effect (lane 6).

**FIGURE 3.** HLA class I-mediated inactivation of Rb in EC requires FGF receptor activity. A, EC2709 cells were transiently transfected with E2-CAT, E2F1, and Rb, as indicated. Stimulation with anti-HLA class I Ab for 6 h reversed Rb-mediated repression of E2F1 activity (lane 4). Inclusion of a blocking Ab to FGF (lane 5) prevented HLA-mediated inactivation of Rb; blocking Abs to PDGF, TGF-β, or a normal mouse IgG had no effect (lanes 6–8).

**Signaling through HLA class I molecules and Fas inactivates Rb by different mechanisms**

Although cyclins and cyclin-dependent kinases are the major mediators of Rb inactivation, we have found that other kinases such as the p38 kinase can efficiently inactivate Rb (69). Efforts were made to assess whether HLA class I-mediated inactivation of Rb involves cyclin-dependent kinases or occurs through mechanisms independent of them. The experimental design was to transiently transfect Jurkat cells with E2-CAT, E2F1, and Rb, and stimulate the cells with anti-HLA Abs in the presence or absence of Olomoucine, which is a cdk inhibitor, or SB203580, a specific inhibitor for p38 kinase. As shown in Fig. 2A, ligation of HLA class I molecules with mAb W6/32 reversed Rb-mediated inhibition of E2F within 6 h (Fig. 2A, lane 4). Treatment of the cells with Olomoucine during HLA stimulation totally prevented Rb inactivation (Fig. 2A, lane 5). Since Olomoucine is a specific inhibitor of cdk2 and cdc2, it appears that these kinases are involved in HLA class I-mediated inactivation of Rb. Since cdk2 in association with cyclin E is known to inactivate Rb during growth-factor-mediated stimulation of cell proliferation, it is likely that the same kinase is involved in inactivating Rb in response to HLA class I as well. Interestingly, the p38 kinase inhibitor SB203580 had no detectable effect on HLA class I-induced inactivation of Rb function.

In contrast, Fas-mediated reversal of Rb function could be efficiently blocked by the p38 inhibitor, but not Olomoucine (Fig. 2B) (69). Thus, it appears that different signaling pathways can target Rb protein, and thus E2F activity through the mediation of different kinases.
inactivation was dependent on the binding of bFGF to EC. For these experiments, EC were transiently transfected with E2-CAT, E2F1, and Rb, followed by stimulation with mAb W6/32. As shown in Fig. 3, similar to the results obtained using Jurkat cells, Rb-mediated repression of E2F1 activity in EC could be efficiently reversed by the addition of Olomoucine, a cdk inhibitor, preventing this inactivation (lane 5), but a p38 inhibitor had no effect (lane 6). B, Induction of cyclin E-associated kinase activity upon HLA class I stimulation. Extracts from EC2709 cells prepared after stimulating with anti-HLA class I Ab for the indicated periods of time were immunoprecipitated with Abs to cyclin D or cyclin E. The kinase activity was assessed by performing an in vitro assay using histone H1 as a substrate. Cyclin E-associated kinase activity is induced within 4 h of stimulation, but there is no change in kinase activity associated with cyclin D. C, A similar experiment as in A, but 0.6 ng/ml of bFGF was used to stimulate the cells for 6 h instead of HLA class I Ab. BFGF could inactivate Rb by itself efficiently (lane 4), and it was inhibited by Olomoucine (lane 5), but not SB203580. D, A dominant-negative cdk2 construct can prevent HLA class I-mediated inactivation of Rb. EC2709 cells were transfected with E2-CAT, E2F1, and Rb. A dominant-negative cdk2 construct (6 µg; lane 5) or a combination of cdk4 and cdk6 (6 µg each; lane 6) was cotransfected as indicated; stimulation of HLA class I inactivates Rb (lane 4), but this is blocked by the dominant-negative cdk2, but not cdk4/6 (lanes 5 and 6).

HLA class I-mediated inactivation of Rb correlates with enhancement of cyclin E-dependent kinase activity

We attempted to examine whether reversal of RB function by HLA class I ligation in EC can also be blocked by Olomoucine, as in Jurkat cells. As shown in Fig. 4A, Olomoucine was quite effective in blocking HLA class I-mediated reversal of RB function, but the p38 kinase inhibitor had no effect. These results indicate that HLA class I-mediated modulation of RB function involves the same downstream kinases in both Jurkat and EC cells. As demonstrated...
above, HLA class I-mediated cell proliferation requires the involvement of bFGF receptors; hence, we examined whether bFGF-induced cell proliferation in the absence of anti-HLA class I Ab can be blocked by Olomoucine as well. As shown in Fig. 4C, stimulation of the EC with bFGF in the absence of HLA class I Ab resulted in an effective reversal of Rb function. This FGF-mediated inactivation of Rb could be blocked by the cdk inhibitor Olomoucine, but not the p38 inhibitor SB203580, as in the case of HLA class I. Since inactivation of Rb by HLA class I signaling can be blocked by Olomoucine in two different cell lines, experiments were designed to examine whether the activity of cdk kinases, which are the targets of Olomoucine, changes upon ligation of class I molecules. The strategy was to prepare extracts from cells stimulated with an anti-HLA Ab and immunoprecipitate cyclin D and cyclin E. Immunoprecipitations were conducted under conditions in which the cyclin-cdk complexes are not disrupted. The immunoprecipitated cyclin-cdk complexes were used to conduct in vitro kinase assays using histone H1 as a substrate.

As shown in Fig. 4B, treatment of EC with anti-HLA Abs did not have any effect on cyclin D-dependent kinase activity at the same time points when Rb was inactivated. This suggests that cyclin D-cdk4/6 complexes do not play a major role in Rb inactivation in response to HLA class I signaling. In contrast, we find that there is a two- to threefold increase in the activity of kinases associated with cyclin E within 4 h of HLA stimulation. Since cyclin E-cdk2 complexes have been shown to phosphorylate Rb, and since Olomoucine can efficiently inhibit cdk2, but not cdk4/6, it appears likely that the inactivation of Rb in response to HLA class I signaling occurs through the mediation of this kinase.

This possibility was verified by a transient transfection experiment in which EC were transfected with E2CAT, E2F1, and Rb. The aim of this experiment was to determine whether dominant-negative cdk2 or cdk4/6 could block HLA class I-mediated reversal of Rb function. As shown in Fig. 4D, overexpression of a dominant-negative cdk2 could block HLA class I-mediated reversal of Rb function. Since cdk2 is known to function in association with cyclin E, it confirms the role for cyclin E-associated kinases in mediating HLA class I-induced proliferative signals. In contrast, overexpression of dominant-negative cdk4 and cdk6, which inhibit the activity of cyclin D-associated kinases, had no effect of HLA class I-mediated reversal of Rb function.

Olomoucine, but not SB203580, blocks HLA class I-mediated cell proliferation

Since we found that different kinases are involved in Fas-mediated and HLA class I-mediated reversal of Rb function, attempts were made to assess which kinases are involved in class I induction of cell proliferation. Previous studies have shown that ligation of class I molecules with mAb W6/32 could stimulate S-phase entry within 24 h in growth factor-deprived EC, as measured by tritiated thymidine incorporation (31, 32). To determine whether p38 kinase is involved in HLA class I-mediated growth induction, or whether the entire class I-mediated signaling occurs through cyclin-dependent kinases, EC were treated with mAb W6/32 in the presence of Olomoucine or SB203580, the p38 inhibitor. As shown in Fig. 5A, Olomoucine totally eliminated HLA class I-mediated S-phase entry. In contrast, SB203580 did not inhibit cell proliferation and, in fact, augmented W6/32-induced proliferation. These results suggest that HLA class I-induced cell proliferation is primarily regulated by cyclin-dependent kinases. Additional experiments were conducted in which bFGF was used to induce cell proliferation, in the presence or absence of anti-HLA class I Abs. As shown in Fig. 5B, bFGF-induced cell proliferation was augmented by costimulation with the HLA class I Ab W6/32. Olomoucine efficiently inhibited the combined proliferative effects of bFGF receptor and HLA class I signaling, whereas SB203580 enhanced the proliferative effects of bFGF alone or in combination with Abs to HLA class I. These results show that there is a close parallel between HLA class I-mediated induction of cell proliferation and its effects on Rb function, suggesting that Rb inactivation is a vital component of HLA class I-mediated proliferation.

Discussion

HLA class I Ag signaling pathways have been implicated in the proliferation of vascular EC, SMC, T and B cells, as well as apoptosis of activated B and T cells (31–33, 36–47). Although the mechanisms and molecules involved in the HLA-mediated apoptosis are emerging, such information is scanty on HLA class I-mediated cell proliferation. The studies described in this work attempt to elucidate the mechanisms by which the cell cycle machinery is manipulated by HLA class I signaling. We were able to focus specifically on the cell proliferation aspect because the anti-HLA class I Ab used in this study does not induce apoptosis (31–33, 38, 47).

Attention was focused on Rb protein and its downstream target, the E2F transcription factor, for two reasons: first, Rb is the main regulator of G1/S transition in mammalian cells (5, 10); second, we had observed that various signaling pathways target the Rb protein, whether the signals are proliferative or apoptotic. As mentioned in the introduction, we had observed that Fas-mediated signaling in Jurkat cells leads to Rb inactivation, contributing to apoptosis. This occurs through the involvement of the p38 kinase (69). In contrast, inhibitors of p38 kinase had no effect on the inactivation of Rb following ligation of HLA class I molecules with anti-HLA Abs. This result suggests that different signaling cascades can target Rb by using different cellular kinases, with the end result in one situation being apoptosis and the other, proliferation. The kinetics of Rb inactivation is also different for the two signaling pathways: whereas Fas inactivates Rb within 30 min, HLA class I stimulation leads to a partial inactivation within 2 h, and complete inactivation within 4–6 h. Since we have observed that p38 kinase is involved in inactivating Rb in response to Fas, it would be interesting to see whether the HLA class I Abs that induce cellular apoptosis in Jurkat cells affect Rb through p38 kinase.

As described earlier, the effects of HLA class I stimulation on EC and SMC were conducted with the intention of assessing the role of anti-HLA Abs in the development of transplant-related atherosclerosis. We had reported previously that ligation of HLA class I molecules with anti-HLA Abs stimulates the proliferation of EC, along with the induction of tyrosine phosphorylation of a variety of cellular proteins, inositol phosphate generation, and specific induction of the FGF receptor (31–33). HLA class I-mediated proliferation could be prevented by the addition of neutralizing Abs to bFGF, suggesting that the FGF receptor is a major coreceptor for the generation of HLA class I-mediated signals. In this study, we find that HLA class I stimulation can inactivate the Rb protein, and this could be inhibited efficiently by a neutralizing Ab to bFGF. This suggests that inactivation of Rb by HLA class I signaling is a vital step in induction of cell proliferation, and occurs subsequent to FGF receptor-mediated signaling. The current results also support our earlier observations that the FGF receptor is required for transducing HLA class I-mediated proliferative signals (32, 33).

The specific molecular mechanisms involved in the activation of the bFGF receptor by HLA class I are not clear. Furthermore, the links between bFGF receptor and cyclin E-cdk2 activation remain
to be elucidated. One possibility is that the Raf-1 kinase is involved in the HLA class I-mediated inactivation of Rb also, as we had shown previously for serum stimulation of quiescent human diploid fibroblasts (26). Although this would provide an additional link between HLA class I signaling and Rb, preliminary experiments did not show any alterations in the Rb/Raf-1 interaction in EC cells upon HLA class I ligation. This needs further detailed investigation, but as of now we do not have evidence for such a direct link through the Raf-1 molecule. This is not surprising, since the cell lines used as well as the stimulus involved are qualitatively different from our earlier study on HSF-8 cells (26).

Our studies also show that the p38 kinase plays no role in Rb inactivation in response to HLA class I-mediated signaling in both Jurkat as well as EC. Furthermore, the observation that the p38 kinase inhibitor, SB203580, augments cell proliferation in collaboration with HLA class I and bFGF is intriguing. Although the p38 kinase can have proliferative effects in some cases (48), it is normally induced in response to cytokines and other signals that have antiproliferative effects (49, 50). It has been demonstrated that activation of the p38 kinase correlates with, and probably contributes to, cellular differentiation (51, 52). Hence, it is likely that SB203580 is negating such growth-inhibitory influences associated with p38 kinase, facilitating cell cycle progression. Such a collaborative induction may not be readily visible when cells are stimulated with agents that induce multiple pathways, since p38 activity is probably compromised by other means.

Studies from different laboratories have shown that proliferative signals from a variety of receptors target the Rb protein through the mediation of cyclin D and associated kinases. Indeed, it had been suggested that phosphorylation by kinases associated with cyclins D and E is required for inactivating Rb in response to serum stimulation (14, 15). We believe that signaling by HLA class I molecule is the first instance in which Rb is found to be inactivated mainly through cyclin E and associated kinases. As our results clearly indicate, there is only minimal involvement, if any at all, of cyclin D and associated kinases in HLA-mediated growth induction. It is not clear whether cyclin E-cdk2 complex alone can inactivate Rb; it is possible that other kinases may also be involved in this process. For example, our studies have shown that Raf-1 can physically interact with Rb and inactivate it. The role of such additional kinases in HLA class I-mediated signaling pathways remains to be elucidated. From another angle, the observation that
cyclin E-associated kinase activity is induced by ligation of HLA class I molecules could be significant in itself. It had been demonstrated that cyclin E/cdk2 can induce cell proliferation by pathways that are independent of Rb and E2F (53, 54), but such additional pathways remain elusive. This might mean that HLA class I signaling could possibly affect other cell cycle regulatory molecules also, which are targeted by cyclin E/cdk2.

We believe that the results described in this study have implications for the role of class I signaling in chronic allograft rejection. The histologic appearance of transplant atherosclerosis shows marked proliferation and hyperplasia of vascular SMC and EC. These findings suggest that augmented EC and SMC responsiveness to growth factors contribute to the pathogenesis of the disease. Indeed, recent studies have identified increased expression of several SMC and EC growth factors such as PDGF and FGF and their receptors in areas of intimal hyperplasia in chronically rejected heart and renal allografts (55–58). Another consistent finding in graft atherosclerotic lesions is the demonstration of Ig deposits in affected vessel walls and within the media (34, 35). Furthermore, numerous studies have found that the development of anti-HLA Abs following transplantation is positively associated with chronic rejection and transplant atherosclerosis of heart and renal allografts (59–67). Together, our previous data and the current studies indicate that chronic rejection can be mediated by anti-HLA Abs that bind to the surface of the endothelium and smooth muscle of the allograft-transducing signals that ultimately result in cell proliferation. Our results are consistent with a model in which ligation of class I molecules by anti-HLA Abs stimulates FGF receptor expression and increased ligand binding. Binding of FGF triggers a series of downstream events resulting in the activation of cyclin E/cdk2. Activated cyclin E/cdk2 relieves the inhibition exerted by Rb, causing the EC and SMC to pass the G1 checkpoint and proliferate. Since signaling through HLA class I molecules can induce the proliferation of vascular EC and SMC, agents that block this process may be useful in the prevention of transplantation-associated atherosclerotic lesions. Elucidation of the molecular processes involved in HLA class I-mediated signal transduction will be beneficial in identifying agents that would be of therapeutic value in preventing such disease processes.

References


