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Divergence in Activation by Poly I:C of Human Natural Killer and Killer Cells

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Summary. *Interferons consistently enhance spontaneous cellular cytotoxicity (SCC) mediated by natural killer (NK) cells. More controversial is the ability of interferons to enhance antibody-dependent cellular cytotoxicity (ADCC) mediated by killer (K) cells. Since NK and K cells appear to represent overlapping subpopulations of lymphocytes, the present study was undertaken to examine in greater detail the relationship between NK and K cell functional modulation by the potent interferon inducer, poly I : C. Utilizing peripheral mononuclear cells from a panel of 21 healthy individuals, treatment in vitro with poly I : C resulted in modulation of both SCC and ADCC. SCC was significantly enhanced in 52 of a series of 55 trials (95%), whereas ADCC was significantly enhanced in parallel in only 18 of the trials (33%). Cells which mediated enhanced ADCC were plastic-nonadherent, which is characteristic of K cells. SCC was consistently enhanced in all but two of the 14 individuals who were tested two or more times. By contrast, the ability of poly I : C to enhance ADCC varied between trials in 11 of these individuals. In the other three, ADCC enhancement never occurred. No correlation existed between SCC and ADCC augmentation despite use of the same target cell to assess the two lytic activities in parallel. Poly I : C exclusively enhanced SCC in 36 trials (65%) and exclusively enhanced ADCC in two trials (4%). Discordance between SCC and ADCC enhancement also occurred in three of eight trials (38%) in which lymphocytes were treated directly with interferon α. Results in long-term (18-h) ^{51}Cr-release assays indicated that poly I : C accelerated the kinetics of ADCC without affecting the proportion of target cells lysed by K cells. By contrast, an increased proportion of target cells was killed by poly I : C-stimulated NK cells. These results suggest that the controversy concerning relative interferon effects upon NK and K cells derives from differences both quantitative and qualitative in nature. K cell activity is enhanced but at a relatively low frequency. Enhancement of NK cell activity is selective in the sense that it occurs independently of and with greater frequency than enhancement of K cell activity. Distinct biological mechanisms may, therefore, be involved in regulation and expression of NK and K cell activation by interferons.*

Introduction

Natural killer (NK) cells, mediators of spontaneous cellular cytotoxicity (SCC), and killer (K) cells, mediators of antibody-dependent cellular cytotoxicity (ADCC), represent potentially important effectors of tumor immunity. The relationship between NK and K cells has not been clearly defined. Both possess similar cell surface antigens [6, 10]. Simultaneous NK and K cell deficiencies occur in otherwise immunologically normal Chediak-Higashi patients. K cell activity is diminished by procedures which specifically remove or interfere with lymphocyte binding to NK-sensitive target cells [3, 9]. These findings suggest that the ability to mediate SCC and ADCC resides in a single effector cell. Conversely, enzymatic [11, 20] and pharmacologic [19] reagents, as well as modulatory cell subpopulations [4, 14, 16], differentially affect the expression of SCC and ADCC. Furthermore, K cells have been reported to be separable from NK cells on the basis of differences in binding affinities of cell surface IgG Fc receptors [17].

Interferons and interferon inducers such as polyriboinosinic : polyribocytidylic acid (poly I : C) stimulate NK cells in vitro to lyse fresh and cultured allogeneic tumor cells [7, 26, 28–30], whereas conflicting results have been obtained using fresh autologous tumor cells as targets [15, 28]. These agents also enhance K cell activity [5, 18], although in some studies this did not occur [12, 26].

Peripheral mononuclear cells (PMC) from a panel of healthy human volunteers were tested, in some instances repeatedly, to determine the relationship between NK and K cell responsiveness to treatment with poly I : C. Our in vitro experimental model involved assessing the concomitant expression of NK and K cell activity against the same target cell. This approach, in contrast with one using different target cells to separately assess SCC and ADCC, eliminated differences in target cell fragility as a factor in the interpretation of results. Biological and experimental parameters which affected NK or K cell immunomodulation by poly I : C were defined.

Materials and Methods

Effector Cells. Ficoll-Hypaque-purified PMC ($5-10 \times 10^6$), obtained from healthy volunteers 18–40 years old, were incubated at 37° C for 18–20 h with 100–250 μg poly I : C/ml (Miles Laboratory, Elkhart, IN, USA) or with 800 international units interferon α/ml [2] in upright plastic flasks containing 2.5 ml RPMI 1640 medium supplemented with 10% fetal calf serum and 25 mM HEPES (GIBCO, Grand Island, NY, USA). These conditions were predetermined to result in optimal enhancement of both SCC and ADCC. PMC were then washed 2 × by centrifugation before testing.

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Monocytes were quantitated as the percent of non-specific acid esterase-positive cells [27] present in at least 200 enumerated PMC.

Cytotoxicity Assays. Chang cell monolayers were dissociated with trypsin-EDTA, then single-cell suspensions were labeled with $Na_2{}^{51}CrO_4$, washed, and added to round-bottom microtiter wells (2×10^3 cells/well) containing sufficient PMC to result in effector-target ratios of 12.5 : 1, 25 : 1, and 50 : 1 [1]. SCC and ADCC were assessed in parallel by adding either medium or rabbit anti-Chang cell antiserum (final dilution = 10^{-5}) to appropriate wells, respectively. After 6 or 18 h, supernatants were harvested using a Titertek collection system (Flow Laboratories, Rockford, MD, USA) and counted in a gamma counter. Percent specific ^{51}Cr release (SCC) was calculated as follows:

$$\frac{\text{cpm test release} - \text{cpm spontaneous release}}{\text{cpm maximum release} - \text{cpm spontaneous release}} \times 100 .$$

Percent specific ^{51}Cr release mediated by K cells (ADCC) was calculated by correcting for SCC against the same target measured in parallel, as follows:

$$\frac{\begin{array}{c}\text{cpm test release with antiserum present} \\ - \text{cpm parallel SCC release}\end{array}}{\text{cpm maximum release} - \text{cpm parallel SCC release}} \times 100 .$$

'Spontaneous' and 'maximum release' are cpm released from target cells incubated in medium or in 4% Cetrimide, respectively. Each measurement represents the mean of quadruplicate determinations.

Statistical significance of each difference in cytotoxicity between treated and untreated cells was determined using Student's two-tailed *t*-test. ^{51}Cr release data were subjected to logarithmic transformation prior to significance testing in order to normalize variance and to remove the correlation which existed between means and standard deviations in untransformed data.

Retrospective analysis of data from all trials indicated that ^{51}Cr release in excess of 70% was sufficiently proximal to the plateau region of the cytotoxicity response curve for enhanced cytotoxicity to be unlikely to be detected if it occurred. Therefore, ten trials in which basal cytotoxicity in the presence of antiserum equaled or exceeded 70% (prior to subtraction of parallel SCC) were excluded from the following analysis.

Chang cells and anti-Chang cell antiserum were gifts from Dr Steven Shore [24].

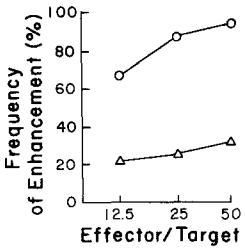

Fig. 1. Relationship between effector-target ratio and detection of poly I : C-mediated enhancement of cytotoxicity. In 55 trials, peripheral mononuclear cells were incubated 18–20 h with poly I : C, then tested for cytotoxicity in 6-h ^{51}Cr-release assays. The % of trials in which poly I : C significantly ($P < 0.05$) enhanced SCC (○–○) or ADCC (△–△) was calculated as follows: (no. of trials in which cytotoxicity was enhanced/total no. of trials ×100

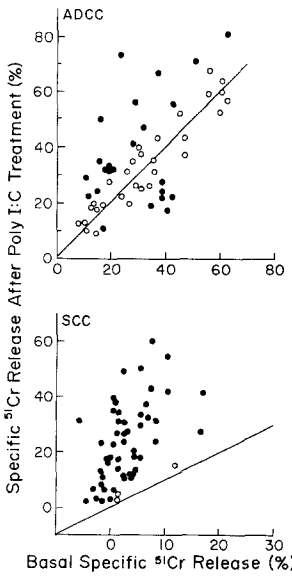

Fig. 2. Effects of poly I : C upon SCC and ADCC in individual trials. Cytotoxicity mediated by poly I : C-treated mononuclear cells was compared with basal cytotoxicity of untreated cells in ADCC (*top panel*) and SCC (*bottom panel*) assays. *Diagonal lines* represent loci at which cytotoxicity of treated and untreated cells are equal. Each *point* represents an individual trial in which cytotoxicity was (●) or was not (○) significantly changed ($P < 0.05$). Effector-target ratio = 50 : 1

Results

Parameters Affecting Enhancement of Cytotoxicity

In 55 trials using cells from 21 healthy individuals, poly I : C enhanced both SCC and ADCC. The frequency with which significant ($P < 0.05$) enhancement of cytotoxicity occurred was dependent upon the effector-target ratio at which poly I : C-treated cells were tested (Fig. 1). Both SCC and ADCC were augmented most frequently (in 94% and 33% of trials, respectively) when the effector-target ratio was 50 : 1. Because of the evidently greater sensitivity for detecting enhanced responses, results obtained at this ratio were selected for detailed analysis.

Disregarding statistical significance, poly I : C elevated SCC above basal levels in all 55 trials (Fig. 2, bottom), whereas there were only 34 trials (62%) in which ADCC was also elevated (Fig. 2, top). The observed frequency with which ADCC exceeded basal levels was significantly less than expected had poly I : C exerted corresponding effects upon SCC and ADCC ($P < 0.005$ by chi-square analysis). ADCC was lower than basal levels in 21 trials (38%); significantly so in seven of these (13%). No apparent relationship existed between the magnitude of basal ADCC and the ability of poly I : C to enhance ADCC.

Of 14 individuals who were tested two or more times, SCC was consistently enhanced in all but 2 (Table 1). The group mean SCC increased from a basal level of 3% up to 23% ^{51}Cr release as a result of poly I : C treatment. In comparison, enhancement of ADCC was a relatively infrequent event, which occurred in 50% or fewer trials in all but one individual.

Table 1. Results of repeatedly testing individuals for responsiveness to poly I:C

Effector cell source	SCC			ADCC		
	Specific ^{51}Cr release (%)[a]		Enhancement frequency[b]	Specific ^{51}Cr release (%)		Enhancement frequency
	− Poly I : C	+ Poly I : C		− Poly I : C	+ Poly I : C	
BE	7	41	6/6	31	36	2/6
ML	0	19	5/5	31	32	1/5
TH	0	17	4/4	30	39	1/4
AL	1	15	3/4	35	41	2/4
BM	5	23	4/4	25	22	1/4
JN	−1	4	4/4	34	50	3/4
BP	6	31	4/4	30	29	1/4
RT	5	33	3/3	13	18	1/3
EB	2	17	3/3	42	40	0/3
EO	7	30	3/3	41	44	0/3
JM	−2	21	2/2	25	34	1/2
SB	9	20	2/2	23	37	1/2
DG	1	30	2/2	47	45	0/2
MD	6	16	1/2	25	35	1/2
Group means	3	23	46/48 (96%)	31	36	15/48 (31%)

[a] Mean specific ^{51}Cr release for all trials at an effector-target ratio of 50 : 1
[b] No. of trials with significantly ($P < 0.05$) enhanced cytotoxicity/total no. of trials

In three individuals (EB, EO, and DG), ADCC was never significantly enhanced. Reflecting these low frequencies of enhancement, the group mean ADCC resulting from poly I : C-treated cells (36% specific ^{51}Cr release) was only slightly above the group mean basal ADCC (31% specific ^{51}Cr release). However, on the basis of paired comparisons of means from each individual, there was a significant overall enhancing effect of poly I : C upon both SCC and ADCC ($P < 0.001$ and $P < 0.025$, respectively, by Wilcoxon's signed ranks test).

Relationship Between SCC and ADCC Enhancement

In repeatedly tested donors, poly I : C exerted similar effects upon SCC and ADCC in some trials, but not in others. To examine the relationship between enhancement of SCC and ADCC, cells from pairs of individuals were tested under identical experimental conditions. In three such experiments representative of seven performed (Table 2), different combinations of poly I : C effects occurred: parallel enhancement of SCC and ADCC (SB in expt 1, BE and JN in expt 2, BP in expt 3), exclusive enhancement of SCC (BE in expt 1), and exclusive enhancement of ADCC (MD in expt 3).

Differences in poly I : C effects were also observed between paired individuals compared in the same experiment. SCC was enhanced in one donor, but not the other (expt 3), and likewise for ADCC (expt 1 and two other experiments not shown). Differences in poly I : C effects upon ADCC also occurred when one individual was tested twice in separate experiments (BE in expt 1 and 2) despite the demonstrated ability of poly I : C to enhance ADCC in the paired individual in both experiments. These results indicated that SCC and ADCC could be differentially modulated by poly I : C. Moreover, they suggested that the receptivity of ADCC effector cells to poly I : C stimulation was subject to variation in the same individual.

Table 2. Dissociation between SCC and ADCC enhancement within individual donors

Experiment	Effector cell source	Specific ^{51}Cr release (%)			
		SCC		ADCC	
		− Poly I : C	+ Poly I : C	− Poly I : C	+ Poly I : C
1	BE	17	[41] [a]	29	26
	SB	16	[27]	16	[50]
2	BE	0	[20]	21	[40]
	JN	− 1	[2]	29	[56]
3	BP	17	[29]	10	[20]
	MD	12	16	19	[33]

[a] Boxes enclose treatment groups in which cytotoxicity was significantly enhanced ($P < 0.05$) above basal levels. Effector-target ratio = 50 : 1

To further define the relationship between SCC and ADCC enhancement, contingency tables were constructed based upon results from all parallel assays (Table 3). Trials were partitioned according to whether or not cytotoxicity mediated by poly I : C-treated cells (i) was significantly greater ($P < 0.05$) than basal cytotoxicity; (ii) exceeded basal cytotoxicity by 10% specific ^{51}Cr release; or (iii) exceeded basal cytotoxicity by 20% specific ^{51}Cr release. In no case did there exist a significant correlation between SCC and ADCC enhancement ($P \geq 0.2$ by Fisher's exact chi-square test). This suggested that poly I : C exerted independent effects upon the two cytotoxic activities.

Table 3. Lack of association between SCC and ADCC enhancement by poly I:C

I.		SCC enhanced[a]			
		No	Yes	Totals	
ADCC Enhanced[a]	No	1	36	37	$X^2 = 1.62$[b]
	Yes	2	16	18	$P = 0.20$
	Totals	3	52	55	
II.		**SCC**			
		EI[c] < 10	EI ≥ 10	Totals	
ADCC	EI < 10	8	26	34	$X^2 = 0.62$
	EI ≥ 10	7	14	21	$P = 0.43$
	Totals	15	40	55	
III.		**SCC**			
		EI[c] < 20	EI ≥ 20	Totals	
ADCC	EI < 20	27	23	50	$X^2 = 0.06$
	EI ≥ 20	3	2	5	$P = 0.80$
	Totals	30	25	55	

[a] $P < 0.05$

[b] Fisher's exact test for association between SCC and ADCC response to poly I : C treatment

[c] EI, Enhancement index = cytotoxicity of poly I : C-treated cells − basal cytotoxicity

Table 4. ADCC enhancement after depletion of plastic-adherent cells

Treatment	Specific ^{51}Cr release (%)							
	Effector cell source[a]							
	DA	HA	JG	GS	BB	PM	JN	JW
None	18	14	−2	6	21	16	37	16
Poly I : C	8	[48][b]	[70]	[12]	23	[29]	30	11
Interferon-α	20	[35]	[51]	[22]	[39]	[46]	[60]	12

[a] After three cycles of PMC adsorption to plastic surfaces (30 min, 37° C, in RPMI containing 50% fetal calf serum), eluted cells containing 0.5% (DA) or less (all others) contaminating non-specific acid esterase-positive monocytes were treated with poly I : C or interferon-α. Effector-target cell ratio = 50 : 1

[b] Boxes enclose treatment groups in which ADCC was significantly enhanced ($P < 0.05$) above basal levels

Effects of Monocyte Depletion Upon ADCC Enhancement

Since monocytes were present to some extent in all cell preparations, it was important to discern whether enhanced ADCC represented stimulation of K cells [18] or monocytes [12]. Despite the reduction, by plastic adherence, of monocyte concentrations to 0.5% or less (Table 4), poly I : C enhanced ADCC in four of eight trials. This ADCC enhancement frequency (50%) was slightly greater than that which occurred when monocytes were present (Table 1). Interferon α enhanced ADCC in six of eight trials (75%). This difference in poly I : C and interferon α effects upon ADCC was not significant. Cells responsible for mediating enhanced ADCC were therefore plastic-nonadherent, a characteristic feature of K cells but not of other ADCC effector cells such as monocytes, macrophages, or granulocytes. Moreover, the lack of correspondence between SCC and ADCC enhancement remained evident. There were four of eight trials using poly I : C and three of eight trials using interferon α in which one but not the other lytic activity was significantly boosted (data not shown).

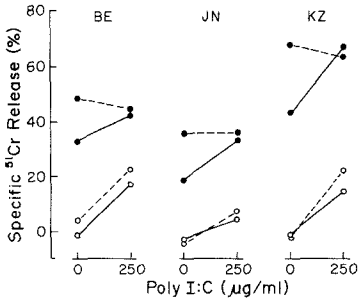

Fig. 3. Effect of duration of ^{51}Cr-release assays upon detection of poly I : C-mediated enhancement of SCC and ADCC. Monocyte-depleted lymphocyte preparations from three individuals (indicated at top) were incubated 18 h with or without poly I : C, then tested for SCC (○) or ADCC (●) which resulted after 6 h (*solid lines*) or 18 h (*dashed lines*) incubation with ^{51}Cr-labeled target cells at an effector-target ratio of 50 : 1

Relative Time-Dependence of Enhanced Cytotoxicity

Lymphocytes treated with poly I : C were assessed for SCC and ADCC in ^{51}Cr-release assays of both 6 and 18 h duration. Although stimulation of ADCC was evident at 6 h, basal ADCC increased to match levels of ADCC mediated by poly I : C-treated cells by 18 h (Fig. 3). Similar results occurred at lower effector-target ratios (12.5 : 1 and 25 : 1 not shown). By contrast, differences in SCC between treated and untreated lymphocytes either did not change or were only slightly greater by 18 h.

Discussion

In this study, we examined the relationship between SCC and ADCC enhancement by the interferon inducer, poly I : C. Whereas poly I : C augmented both SCC and ADCC, its stimulatory effects upon one cytotoxic function did not correlate with its stimulatory effects upon the other. The lack of correlation was evident in donors evaluated separately (Table 2) or as a group (Fig. 2, Table 3). Differences in poly I : C effects upon SCC and ADCC could not be attributed to differences in target cell fragility since the same target cells were used to assess both lytic activities in parallel. These results indicated that poly I : C exerted independent effects upon SCC and ADCC expression.

Interferon-enhanced ADCC has been attributed to monocytes [12], granulocytes [8], and K cells [18]. In this study, a similar degree of ADCC enhancement occurred regardless of whether or not monocytes and granulocytes were substantially depleted from effector cell preparations (Table 4). Confirming previous reports [21, 29], we found reduction of monocyte

concentration to have no effect or, in some cases, an augmenting effect upon SCC enhancement by either poly I : C or interferon (data not shown).

There has been some degree of controversy recently concerning the ability of interferons to enhance K cell-mediated ADCC [5, 12, 18, 26]. In the present study, enhancement of ADCC by poly I : C was a relatively low-frequency event, which occurred in only approximately one-third of all trials. Since SCC was enhanced in 95% of all trials, failure of poly I : C to induce interferon production was an unlikely explanation for trials in which ADCC was not enhanced. Moreover, lymphocytes treated directly with interferon α sometimes failed to exhibit enhanced ADCC (Table 4). Poly I : C infrequently resulted in significant ADCC depression (Fig. 2). This has also been reported to occur in cells treated directly with interferons [5].

Inherent differences may exist between individuals with respect to the ability of poly I : C to enhance ADCC (Table 1). However, effects of poly I : C upon ADCC, and less frequently upon SCC, were subject to variation within some individuals who were tested repeatedly. A possibly analogous situation has been reported in studies with mice, in which experimental manipulation of serum estrogen levels in vivo resulted in changes in NK cell responsiveness to poly I : C [23]. Thus, these inter-trial differences may have reflected differences in the physiological milieu of the lymphocyte donor.

When enhancement of ADCC occurred, it differed qualitatively from enhancement of SCC. Poly I : C accelerated the kinetics of ADCC expression, but did not affect the ultimate proportion of target cells killed in long-term (18-h) ^{51}Cr-release assays (Fig. 3). By contrast, poly I : C-treated NK cells lysed a greater proportion of target cells than did untreated NK cells. The increase in total NK cell cytotoxic potential was probably attributable to recruitment of 'pre-NK' cells to functional maturity [22, 25]. The differing ADCC results may, therefore, indicate that K cell activation does not include a recruitment component under the experimental conditions of the present study.

Our results suggest that NK and K cell responses to interferon-related stimuli may be determined by different biological mechanisms. Since naturally occurring regulatory cells and substances have been described which exert differential effects upon SCC and ADCC [4, 16, 19], the effectiveness with which interferons stimulate either cytotoxic function probably depends upon interaction between a diversity of factors. The biological implications of such separate fine tuning capabilities for NK and K cells remain to be defined.

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