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CML reaction between unrelated SD and SD identical individuals.

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Introduction

From observations made by Eysvoogel et al. (1973) and Alter et al. (1973) a positive CML reaction only occurs if the two reacting cell populations differ for both the LD (MLC-s) and SD loci.
Following the work of Mawas et al. (1973) we decided to try to identify non HL-A determinants which play a role in CML. From our results collected sofar we can say that at least 5a and 5b of the group Five system is not a target for CML.

Results

We set up some family studies and one of the informative families is shown in figure 1. In this family, the father, who had died, and the mother both had a 1-8 haplotype, carrying different LD determinants. (Keuning et al. 1975) A crossing-over occurred in child 4. The 1-8 haplotype from the father, accompanied by the LD determinant 103 and the 1-8 haplotype from the mother, here accompanied by the LD determinant 102 instead of 106, was inherited.
Child 4 and child 2 are thus identical for LD. Child 2 sensitized with child 4 gives no kill in CML with child 4 or any of the other targets. For SD child 4 is homozygous 1,8 and is therefore compatible when used as a stimulator for child 2. Child 4 sensitized with child 2 could not be tested on C2 targets for technical reasons, but did not give a kill on the cells of the mother who shares the same 2-7 haplotype with child 2 and is thus SD identical with C2. This apparently confirms the necessity of LD and SD differences as found by others.

Our next step was to find out whether the locus coding for the determinants that we can identify by means of our homozygous typing cells, is the same as that, coding for the induction of effector cells. We used the following procedure:
From a group of 100 unrelated individuals which had been typed for LD, we selected 6 combinations, which shared the same two LD determinants. They were thus LD full house identical. As discussed by Keuning et al. (this issue) such unrelated LD identical individuals are not necessarily negative in the MLC test. Our findings, as shown in figure 2, were as follows: We tested 5 pairs of unrelated individuals which were identical for SD but not for LD and gave a positive MLC reaction (figure 2 group A). These combinations were all negative in CML, indicating that a SD difference is necessary for a kill and that unrelated SD identical individuals are in this respect as identical as HL-A SD identical siblings. In the same figure, group B and group C, we see the results of CML occurring after sensitization with unrelated LD identical cells while both groups differ for SD. Despite LD identity (by homozygous typing cells) when the MLR is positive, a positive CML occurs, and when the MLC is negative, there is no killing in CML.

These findings suggest that at least one other locus than the MLC-s locus, recognized with typing cells, can give rise to a positive MLC. The fact that in the case of a negative MLC, no CML was found, indicates that this second MLC locus or a locus closely linked to it,might be responsible for the induction of a CML reaction, and we might be dealing with a locus comparable to the E.C.S. locus as described by Festenstein et al. (1974) in the mouse. The probability that this locus is on another chromosome, is very small in our opinion. If this was the case, a positive MLC and CML reaction between SD identical

siblings should then be found more often.
If the CML locus is located on chromosome 6 we can say that it is probably linked to the MLC-s region, based on the results of the family shown before. Because a negative CML reaction occurred between two people who shared the same MLC-s determinant and who had a negative MLC reaction between them, but differed for the SD part of the MHC (major histocompatibility) complex, we would like to postulate, that these findings can be explained by the existence of a locus near the MLC-s locus (fig. 3) which not only governs part of the MLC reactivity but also activation of the effector arm of the CML reaction.

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Fig. 1. CML in family Br.

	SD	LD*)
Father †	1,8/2,13	103/XII
Mother	1,8/2,7	106/102
Child 1	1,8/2,13	XII/106
Child 2	1,8/2,7	103/102
Child 4	1,8/1,8	103/(102)
Child 5	1,8/1,8	103/106
Child 6	2,13/2,7	XII/102

% kill	M	C1	C2	C4	C5
$C4C1_x$	+ 18	+ 25		- 3	- 6
$C4C2_x$	- 12	- 2		- 3	- 9
$C5C2_x$	+ 79	+ 25	+ 62	- 0.7	- 10
$C2C4_x$	- 12	- 0.6		- 3	- 10
$C5C4_x$	- 5	- 4		- 0.7	- 10
$C6C4_x$	+ 22	+ 20	+ 25	+ 29	+ 26
$C2C5_x$	- 11	- 3		- 5	- 9
$C4C5_x$	- 12	- 3	- 2	- 3	- 9
$C2C6_x$	- 12	+ 18		- 4	- 9

*)workshop nomenclature (Roman numbers Leiden nomenclature)

Fig. 2.

Group A. unrelated

HL-A		S.I. in MLC			CML %		
A=B= 1,9,8,W10	AB_x	22.8	BA_x	18.4	AB_x/B	- 9	BA_x/A - 2
A=B= 1,2,5,8	AB_x	6.8	BA_x	9.3	AB_x/B	+ 5	BA_x/A + 6
A=B= 1,2,5,8	AB_x	15.9	BA_x	15.0	AB_x/B	- 2	BA_x/A - 6
A=B= 2,3,7,12	AB_x	9.0	BA_x	14.0	AB_x/B	- 1	BA_x/A + 0.6
A=B= 1,2,7,8	AB_x	17.7	BA_x	8.0	AB_x/B	+ 3	BA_x/A - 7

Group B. unrelated

HL-A	LD	S.I. in MLC		CML %	
A= 3,W26,8,13,Sl B= 1,W28,8,W22	103/XII	AB_x BA_x	18.1 8.3	AB_x/B BA_x/A	+ 79 + 51
A= 1,W29,8,12 B= 2,3,7,12	102/106	AB_x BA_x	3.6 10.2	AB_x/B BA_x/A	+ 28 + 40
A= 1,9,8,W10 B= 1,9,W5,27	103/105	AB_x BA_x	4.2 3.6	AB_x/B BA_x/A	+ 37 + 18
A= 1,2,8,W10 B= 1,11,8,W5	103/101	AB_x BA_x	7.3 2.9	AB_x/B BA_x/A	+ 84 + 31
A= 1,W24,8,W10 B= 1,11,8,W5	103/101	AB_x BA_x	2.3 2.1	AB_x/B BA_x/A	+ 30 + 37

Group C. unrelated

HL-A	LD	S.I. in MLC		CML %	
A= 1,2,8,W10 B= 1,W24,8,W10	103/101	AB_x BA_x	2.6 1.1	AB_x/B BA_x/A	- 2 - 1

Group A	Group B	Group C
SD =	SD ≠	SD ≠
LD ≠	LD =	LD =
MLC ++	MLC (++)+	MLC (±)
CML -	CML ++	CML -
N = 5	N = 5	N = 1

Fig. 3. Possible location of the CML locus in the MHC complex.