



XXVI
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Alloreattività KIR tra laboratorio e trapianto di CSE

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*CENTRO REGIONALE IMMUNOEMATOLOGIA
E TIPIZZAZIONE TISSUTALE*

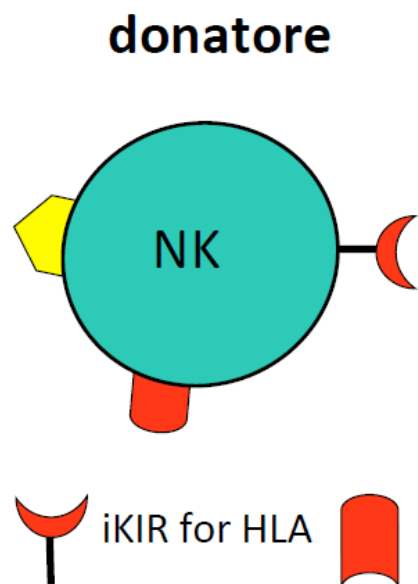


Materiali

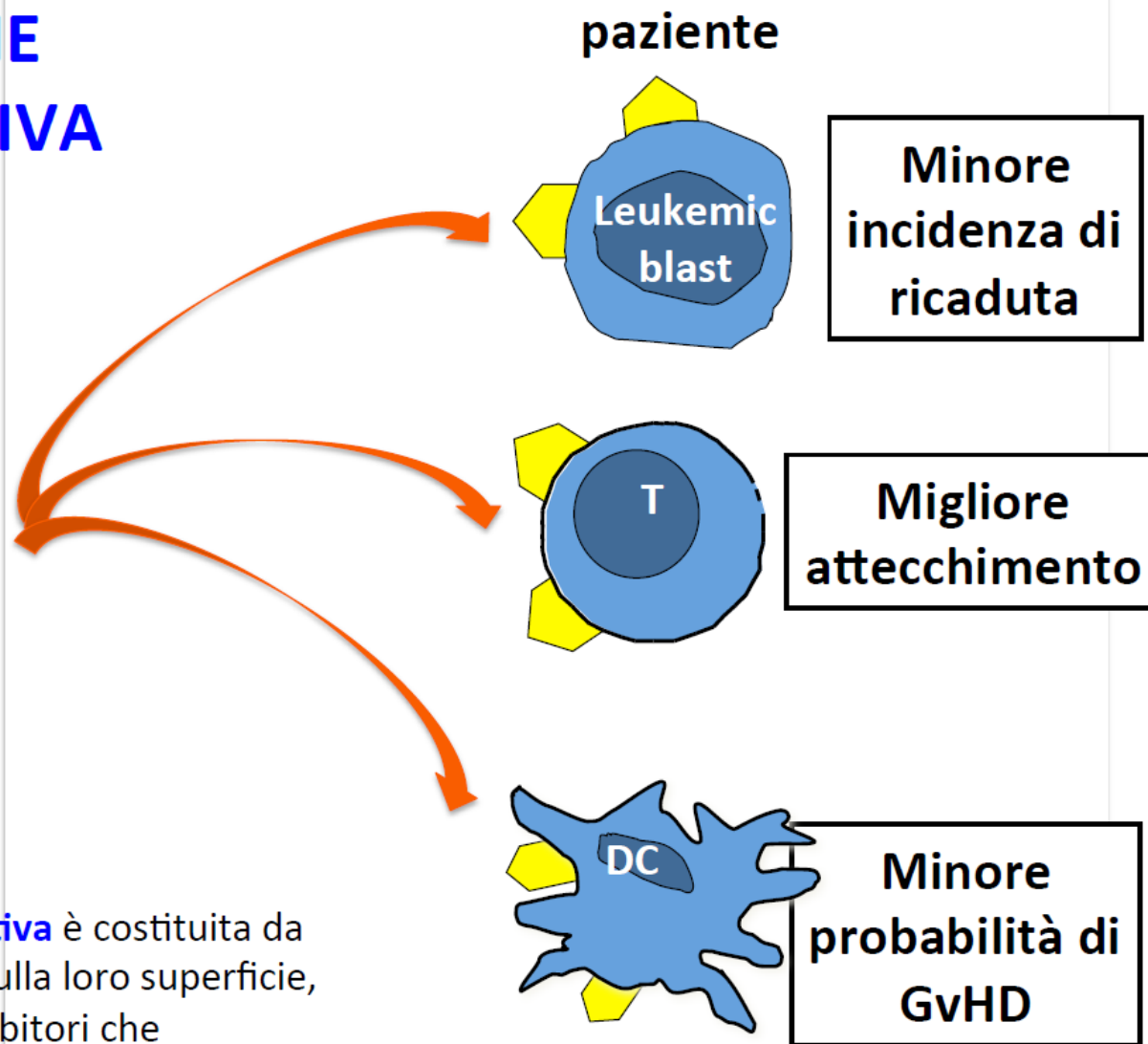
- 55 pazienti sottoposti a trapianto aploidentico di CSE
- 27 coppie studiate per alloreattività KIR e Bcontent
- Follow-up di almeno 6 mesi
- regime di condizionamento mieloablativo standard (TBF-MAC) (n.33 pazienti) o a ridotta intensità (TBF-RIC) (n.22 pazienti) e profilassi GvHD (Ciclosporina + Methotrexate + ATG + Basiliximab + Micofenolato Mofetile)
- Senza deplezione dei linfociti T

TBF= tiotepa, busulfano e fludarabina

POPOLAZIONE NK ALLOREATTIVA



La **popolazione NK alloreattiva** è costituita da cellule NK che esprimono, sulla loro superficie, unicamente recettori KIR inibitori che riconoscono KIR-L presenti nel donatore (educazione dei KIR) e non nel ricevente.





KIR Ligand Calculator

Recent transplant strategies based on KIR-ligand mismatch to predict NK cell alloreactivity have resulted in less relapse, less GvHD and better overall survival in patients with Acute Myeloid Leukaemia (AML) (1). KIR-ligands are HLA molecules that can be grouped into three major categories based on the amino acid sequence determining the KIR-binding epitope in HLA-C and HLA-B molecules. All expressed HLA-C alleles are of the C1 or C2 group (2) and most HLA-B alleles can be classified as either Bw4 or Bw6 (3). The grid below shows how the tool defines these groups. Killer-immunoglobulin receptors KIR2DL1, KIR2DL2 and KIR3DL1 bind KIR-ligand C2, C1 and Bw4 respectively, resulting in inhibition of NK cell mediated lysis.

Locus	Motif	77	80
HLA-B	Bw4	N (Asparagine)	I (Isoleucine)
HLA-B	Bw4	N (Asparagine)	T (Threonine)
HLA-B	Bw4	D (Aspartic acid)	T (Threonine)
HLA-B	Bw4	S (Serine)	T (Threonine)
HLA-B	Bw6	G (Glycine)	N (Asparagine)
HLA-B	Bw6	S (Serine)	N (Asparagine)
HLA-C	C1		N (Asparagine)
HLA-C	C2		K (Lysine)

The IPD-KIR Ligand Calculator has been written in collaboration with Jeff Miller, University of Minnesota, USA.

Il paziente ha attecchito

Predicted Ligands for Patient				
Typing	B*44:03	B*57:01	C*06:02	C*16:01
Alleles	Allele listing	Allele listing	Allele listing	Allele listing
Ligand	Bw4 - 80T	Bw4 - 80I	C2	C1
Exceptions				
Predicted Ligands for Donor				
Typing	B*57:01	B*57:01	C*06:02	C*06:02
Alleles	Allele listing	Allele listing	Allele listing	Allele listing
Ligand	Bw4 - 80I	Bw4 - 80I	C2	C2
Exceptions				
Mismatching in the GvH Direction				
HLA-B	KIR ligands are matched			
HLA-C	KIR ligands are matched			
Mismatching in the HvG Direction				
HLA-B	KIR ligands are matched			
HLA-C	KIR ligands are (mis)matched in the HvG Direction (C1)			

In summary, these ligands will be matched in the GvH direction and (mis)matched in the HvG direction.

Il paziente ha avuto GvHD di 2° grado

Predicted Ligands for Patient				
Typing	B*35:03	B*35:08	C*04:01	C*12:03
Alleles	Allele listing	Allele listing	Allele listing	Allele listing
Ligand	Bw6	Bw6	C2	C1
Exceptions				
Predicted Ligands for Donor				
Typing	B*18:01	B*35:08	C*04:01	C*07:01
Alleles	Allele listing	Allele listing	Allele listing	Allele listing
Ligand	Bw6	Bw6	C2	C1
Exceptions				
Mismatching in the GvH Direction				
HLA-B	KIR ligands are matched			
HLA-C	KIR ligands are matched			
Mismatching in the HvG Direction				
HLA-B	KIR ligands are matched			
HLA-C	KIR ligands are matched			

In summary, these ligands will be matched in the GvH direction and matched in the HvG direction.

Risultati 1

- KIR2DL1+/C2+
 - 27 coppie: 16(59.2%) C1/C2, 7(25.9%) C2/C2, 4 (14.8%) C1/C1
 - Rec. 9 (39.1%)
 - No Rec. 14 (60.9%)

Software svincolato dalla reale presenza dei KIR_inib o dall'educazione dei KIR

B content

Prospective Donor KIR Typings															
Prospective Patient ID xxyy01															
Prospective Donor 1															
CEN genes						TEL genes		CEN or TEL genes				Framework genes			
2DS2	2DL2	2DL3	2DP1	2DL1	3DL1	2DS4	3DS1	2DS1	2DL5	2DS3	2DS5	3DL3	3DP1	2DL4	3DL2
<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<p>Warning! - The KIR genotype entered does not match any of those stored in our library of known KIR genotypes. This may be a rare genotype or there are gaps or typographical errors in the typing. A predicted assignment may be possible, but further typing of the sample should be performed.</p> <p>The Predicted KIR B-content group for prospective donor 1 is: Neutral.</p>															

Il paziente ha avuto GvHD di 1° grado, poi ha recidivato

B content 2

Prospective Donor KIR Typings															
Prospective Patient ID															
Prospective Donor 1															
CEN genes				TEL genes				CEN or TEL genes				Framework genes			
2DS2	2DL2	2DL3	2DP1	2DL1	3DL1	2DS4	3DS1	2DS1	2DL5	2DS3	2DS5	3DL3	3DP1	2DL4	3DL2
<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
The Predicted KIR B-content group for prospective donor 1 is: Better.															

Il paziente non ha avuto GvHD nè recidiva

Risultati 2

B neutral		B best/better	
GvHD +	GvHD -	GvHD +	GvHD -
8 (61.5%)	5 (38.5%)	3 (21.4%)	11 (78.5%) *
Recidiva +	Recidiva -	Recidiva +	Recidiva -
6 (42.9%)	8 (57.1%)	4 (31%)	9 (69%) #
<ul style="list-style-type: none"> • P corr Fisher 0.04 			
# OR = 1.6			

Statistics for Release 2.8.0 (November 2018)

The numbers below represent the number of named alleles for each gene. This number includes alleles which have been named but whose sequences is still held as confidential. This means that the number of sequences found in some files may differ to the numbers printed in this table. These numbers do not include the names of any deleted alleles.

Allele Information	
KIR Alleles:	977

Considerazioni

KIR Alleles								
Gene	2DL1	2DL2	2DL3	2DL4	2DL5	2DS1	2DS2	2DS3
Alleles	64	33	59	70	54	16	24	16
Proteins	36	15	34	41	24	8	9	7
Nulls	2	0	1	0	0	0	0	1
Gene	2DS4	2DS5	3DL1	3DS1	3DL2	3DL3	2DP1	3DP1
Alleles	37	24	147	39	161	164	40	29
Proteins	16	17	91	22	111	92	0	0
Nulls	0	0	3	1	1	0	0	0

Considerazioni

- Quindi allelismi probabilmente con funzione diversa o con diversa espressione
- Differenza di attività KIR nelle diverse patologie: ALL minore influenza dei KIR, AML maggior influenza dei KIR
- T non depleti bloccano l'azione dei KIR
- Gli Ag HLA-C potrebbero essere ipoespressi nelle cellule leucemiche
- Il sito web non valuta alcune alloreattività: B*73:01/B*46:01 (C1+), B*13:01, *13:02 sono erroneamente considerati come lig. KIR₃DL₁; A*23, *24, *32 (Bw4+) non sono considerati per KIR₃DL₁.

Conclusioni

- Sicuramente i KIR sono importanti nel trapianto di CSE ma è necessaria una più approfondita valutazione della loro funzione sulla base delle nuove conoscenze della genetica e dell'azione dei KIR.
- Sarebbe auspicabile uno studio multicentrico per avere un significativo numero di osservazioni.