Age-related alterations of anti-tumor specific cytotoxic CD8⁺ T cells

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The incidence of cancer increases with age and at the same time, normal individuals aged over 65 years, are characterized by an extremely reduced naive CD8⁺ T cell count and an increased number of memory cells, indicating an acceleration of the decay of the immune system from this age onwards. Several reports indicate that the immune system becomes overwhelmed with memory cells (both effector memory and terminally differentiated) and this appears to be directly related with an increase in age. The aim of this study was to investigate whether in patients with lung cancer and normal healthy individuals, the frequency and the qualitative features of circulating precursor cytotoxic T lymphocytes (pCTLs) specific for naturally processed and presented peptides of human telomerase reverse transcriptase (hTERT) and MAGE-A3 could be attributed to changes related to immunosenescence.

Materials / Methods

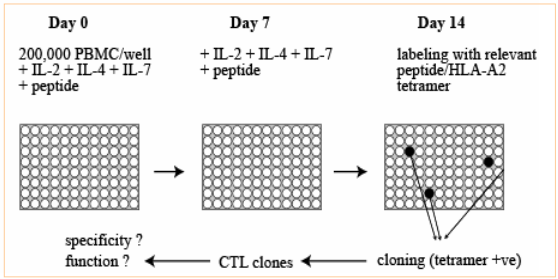
Samples

25 patients with lung cancer
(mean age: 66.2±10.0 years)

17 normal individuals
(mean age: 58.2±5.4 years)

11 normal individuals
(mean age: 27.1±3.9 years)

Antigen	Peptide	HLA-multimer
hTERT	ILAKFLHWL	A2.PE
	RLFFYRKSV	A2.PE
	VYAETKHFL	A24.PE
MAGE-A3	FLWGPRALV	A2.PE
	TFPDLESEF	A24.PE
BMLF1	GLCTLVAML	A2.APC
EBNA3C	RYSIFFDYM	A24.APC



Mixed Lymphocyte Peptide Culture (MLPC)[1]: Isolated peripheral blood mononuclear cells (PBMC) from patients with lung cancer and normal healthy individuals, were pulsed separately with test and control peptides and distributed in round bottom 96 microwell plates ($2x10^5$cells/0.2mL) in medium containing IL2, IL4 & IL7 (day 0). On day 7, cells were restimulated, and after a further 7 days (day 14), peptide specific CTLs, contained in microwells, were detected after staining with relevant HLA-multimers.

Results

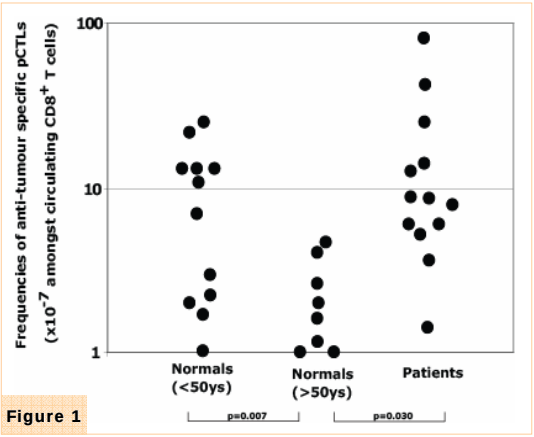


Figure 1

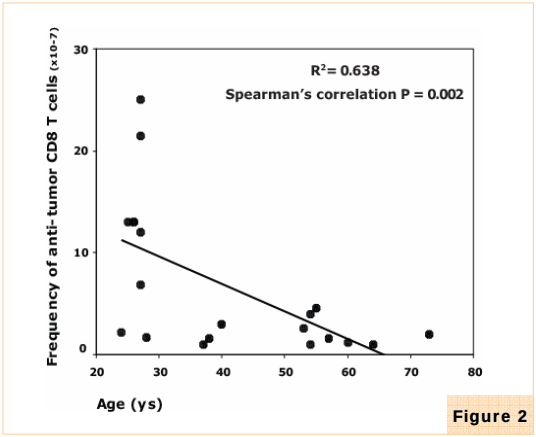


Figure 2

The estimated frequency of circulating pCTL against all tumor peptides studied was much higher in patients than in aged matched cancer-free individuals. However it was very similar to that seen from normal healthy individuals (Fig. 1).

Peptide specific pCTL frequency was inversely related to age in normal individuals (Fig. 2).

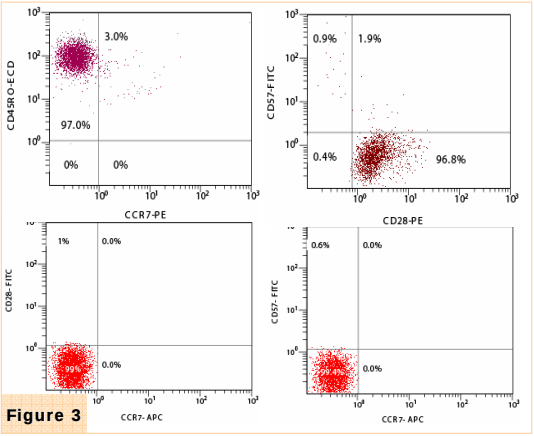


Figure 3

When the phenotypic characteristics of the *in vitro* amplified cell populations that contained multimer positive cells was examined (Fig. 3), a difference with respect to the differentiation profile according to staining with CD45RA, CCR7 and CD28 was observed between patients (upper panel) and normals (lower panel).

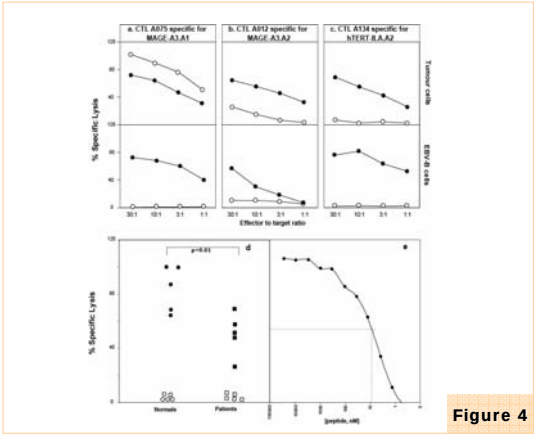
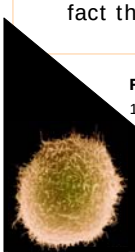


Figure 4

Isolated clones from normals displayed an overall higher lytic capacity against those isolated from patients (Fig. 4). No differences were observed with respect to secretion of cytokines .

Conclusion

An age-related decline of the frequency of anti-tumor specific pCTLs was observed for the first time in the literature[2], despite the fact that, in the presence of tumours, this response is augmented. Our observation, questions how the application of various immunostimulating protocols could prove beneficial for aged cancer patients.



References

1. Karanikas V et al. Baseline levels of CD8+ T cells against survivin and survivin-2B in the blood of lung cancer patients and cancer-free individuals. Clin Immunol 2008;129:230-40.

2. Karanikas V et al. Frequency and function of naturally occurring cytolytic CD8⁺ T cell precursors against multiple tumor antigen peptides in lung cancer patients and healthy individuals *Cancer Research* (in press)

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