Epigenetic drugs alter the function of anti-tumor specific CD8+ T cells

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Background

Cancer immunoepigenetics refers to an innovative approach, attempting to understand the underlying biological framework of the anti-cancer immune response. It deals with epigenetic alterations of immune or other genes in immune cells that can affect their function[1]. This study aimed to investigate whether epigenetic alterations of immune genes induced by the inhibitor of DNA methyltransferases, 5-aza-2'-deoxycytidine (5-aza-CdR), a recently FDA approved drug for MDS, affects the CD8 effector cytolytic T lymphocyte (CTL) response.

Methods

Tumor-specific CTL clones isolated from healthy individuals and patients with lung cancer and analyzed for their characteristics[2], were incubated in the presence of a subtoxic concentration of 5-aza-CdR for 5 days. Alterations in the phenotypic, lytic and functional characteristics of the clones were investigated. To determine whether culture with 5-aza-CdR had a permanent functional effect on the clones, the culture was continued for a further 6 days (Figure 1).

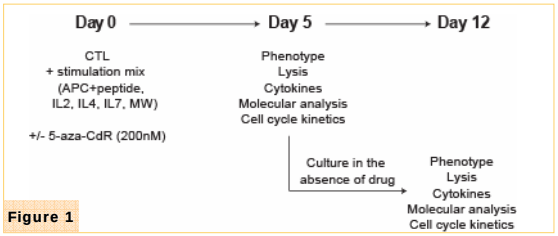


Figure 1

Results

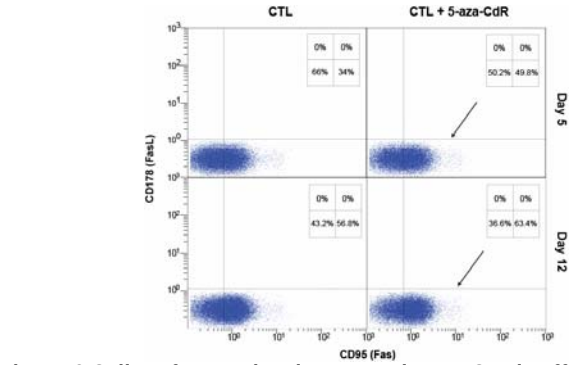
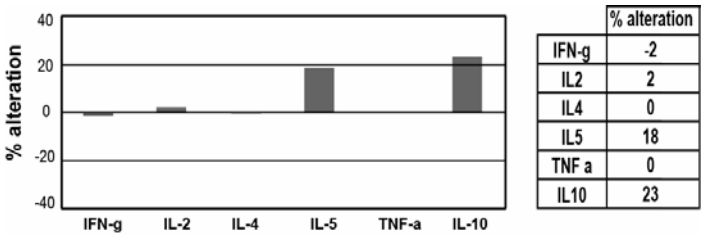


Figure 2 Cell surface molecule expression on CTL is affected by 5-aza-CdR. CD95 was the only cell surface molecule that altered its expression on CTL after culture with 5-aza-CdR (47% increase). This effect did not seem to remain after drug removal (10% increase). No other significant changes were evident amongst other molecules studied (CD8, CD25, CD27, CD28, CD57, CD62L, CD69, CD122, CD127, CCR7).



	% alteration
IFN-g	-2
IL2	2
IL4	0
IL5	18
TNF a	0
IL10	23

Figure 3 Culture with 5-aza-CdR alters cytokine secretion. CTL cultured in the presence of drug and specific peptide stimulation, appear to increase their levels of IL-5 and IL-10

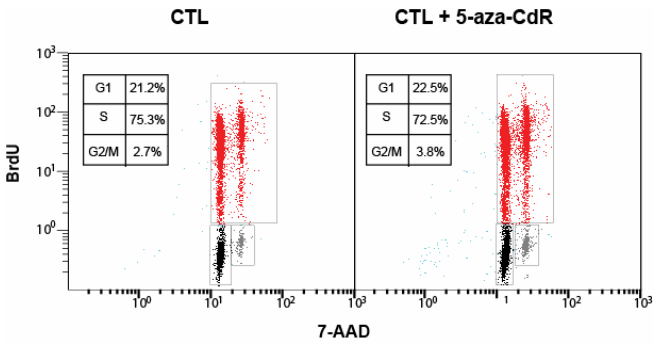
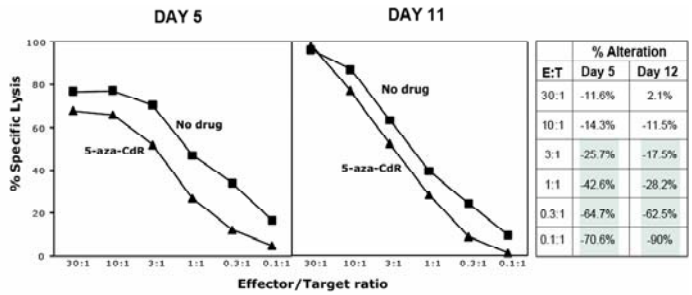


Figure 4 Cell cycle analysis. CTL cultured in the presence of subtoxic doses of 5-aza-CdR, are not affected in terms of their viability or their cell cycle kinetics

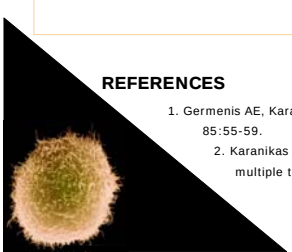


E:T	% Alteration Day 5	% Alteration Day 12
30:1	-11.6%	2.1%
10:1	-14.3%	-11.5%
3:1	-25.7%	-17.5%
1:1	-42.6%	-28.2%
0.3:1	-64.7%	-62.5%
0.1:1	-70.6%	-90%

Figure 5 Culture with 5-aza-CdR severely affects CTL lytic ability. function. Tumor-specific CTL clones cultured in the presence of 5-aza-CdR, exhibit a severely compromised response to targets expressing the tumor peptides (71% reduction). This response is maintained after removal of the drug (90% reduction).

Conclusion

Our intriguing findings address the anti-tumor immune responses from an entirely novel perspective, introducing epigenetics of the immune system and the CD8+ T cell in particular, as the key player in carcinogenesis. Exploiting further our results could provide improved attempts towards clinically effective cancer immunotherapy.



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1. Germenis AE, Karanikas V. Immunoepigenetics: the unseen side of cancer immunoediting. Immunol Cell Biol 2007; 85:55-59.
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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