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LETTER TO THE EDITOR

Cancer testis antigens and melanoma stem cells: new promises for therapeutic intervention

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To the Editor

We read with great interest the paper by Gedye et al. [1] reporting that clonogenic $CD133^+$ melanoma cells, with stem cell-like behaviour, express cancer testis antigens (CTA) and are effectively recognized by CTA-specific cytotoxic T lymphocytes. Based on their findings, the authors agreeably concluded that immune targeting of CTA, expressed on melanoma stem cells (MSC), may represent a promising therapeutic option for the treatment of melanoma patients.

We had previously drawn similar conclusions utilizing the first-described model of human MSC, represented by a clonogenic population of $CD20^+$-enriched melanoma cells, able to propagate as non-adherent (NA) spheres when cultured in growth medium for human embryonic stem cells [2]. Indeed, we found a highly homogeneous expression of a panel of CTA in NA cells, which overlapped with that of the more differentiated, $CD20^-$, adherent counterpart [3].

In line with Gedye's results on $CD133^+$ melanoma cells [1], the frequent expression of CTA that we found in NA MSC bears highly relevant implications from the clinical viewpoint. In fact, their consistent expression identified within investigated MSC warrants their reliable targeting by CTA-based immunotherapy; additionally, the concomitant expression of several CTA we found offers multiple molecular targets to multivalent CTA-based vaccines, possibly avoiding the emergence of CTA-negative clones in the course of treatment [3]. The ultimate phenotypic profile identifying MSC has not been established yet; however, the concordant identification of CTA in two distinct models of MSC strongly supports the notion that immunological targeting of MSC via CTA should represent an optimal therapeutic strategy to achieve their complete eradication within the tumor mass. This aspect is crucial for the development of more effective therapeutic options for the treatment of melanoma, since MSC have been reported to be resistant to conventional chemo- and radio-therapy [4], and several large clinical trials are actively investigating the therapeutic efficacy of CTA-based immunotherapies in different cancer indications and stages of disease [5].

Aiming to investigate the transcriptional regulatory mechanism(s) of CTA in MSC, we also demonstrated that the CTA profile of MSC is most likely susceptible to epigenetic modelling, as shown by the striking correlation found between promoter methylation status and gene expression of the CTA MAGE-A3 and NY-ESO-1 in NA MSC ([3] and unpublished data). The epigenetic regulation of the CTA phenotype in MSC foresees that DNA hypomethylating drugs, such as 5-aza-2′-deoxycytidine (5-AZA-CdR), can be effectively utilized to induce and/or upregulate CTA expression by CTA-negative or -weakly positive MSC, thus potentiating their constitutive immunogenicity and/or their recognition by CTA-specific T cells. This achievement will be most likely driven by hypomethylation of CTA promoters by 5-AZA-CdR, rather than by the selection of CTA-positive chemoresistant MSC, as suggested by Gedye et al.

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Supporting this notion, the key role of DNA methylation in regulating presence and levels of CTA expression in melanoma cells is well acknowledged, and also the ability of 5-AZA-CdR to persistently induce or upregulate CTA expression in neoplastic cells, both in vitro and in vivo, has been exhaustively demonstrated to depend on its DNA hypomethylating activity [6].

In conclusion, the available data on CTA, along with the recently described susceptibility of $CD133^+$ MSC to natural killer cell-mediated recognition and lysis [7], strongly support the clinical potential of immunotherapeutic approaches in eradicating MSC. Along this line is the potential of 5-AZA-CdR to implement novel combined chemo-immunotherapeutic approaches for the most effective immunologic targeting of melanoma cells with stem cell-like characteristics, as well as of melanoma cells with a more differentiated phenotype.

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