Looking into the Future

The restoration of the HLA class I mediated antigen presentation in tumor cells is essential. It allows T lymphocytes to recover the recognition and the rejection of tumors. As indicated several times in this book, the concept of "Hard" versus "Soft" molecular HLA lesions has an enormous implication in the escape or rejection of metastatic lesions during immunotherapy. Current immunotherapies can induce HLA class I upregulation and rejection in metastatic lesions with "Reversible/Soft alterations". Different types of traditional and new generation modern immunotherapy protocols are, in fact, inducing the recovery of HLA-I molecules by modifying the tumor microenviroment and stimulating T cell secretion of Th type 1 cytokines, such as interferons. However, tumor cells with "Irreversible/Hard molecular" HLA alterations represent a real threat to the efficacy of cancer immunotherapy and require gene therapy approach for HLA restoration. Hence, we will need to fight "hard lesions" caused by structural genetic lesions produced by DNA point mutations or micro- or macro-deletions affecting the β2 microglobulin gene or the chromosome region that includes the HLA region, as well as the genetic lesions in the interferon activation pathways. It is a long way before these therapies can be implemented in the clinical setting, but the characterization of these HLA class-I alterations in progressing metastatic lesions resistant to immunotherapy will probably speed up the clinical application of this strategy (Fig. 1).

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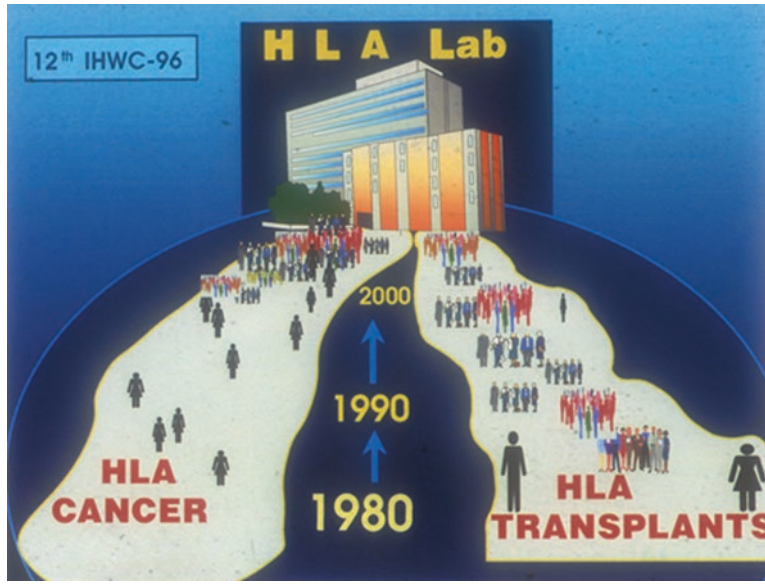

Fig. 1 The relevance of HLA tissue typing in Transplant and Cancer patients. I did this comparison at the 12th International Histocompatibility Workshop and Conference that took place in 1996 in Saint Malo (France) and Paris where the "HLA and Cancer" component was included for the first time. This picture indicates the importance of HLA tissue typing of Cancer patients in our hospitals for the analysis of HLA class I alterations in tumor tissues in order to select a personalized specific treatment as it has been always done for organ transplantation

Concluding Remarks

A Darwinian type of immune selection occurs during tumor development. There are increasing evidences that T lymphocytes are playing a crucial role in recognizing, destroying and rejecting experimental and human tumors. Multiple tumor antigens have been identified that are recognized by T cells as small peptides in the context of the MHC/HLA molecules. At the same time, T cells are selecting HLA-I deficient tumor escape variants that appear in the primary tumor lesion producing at the end a tumor tissue that is composed only of homogeneously HLA-I negative tumor cells. Total or selective losses of HLA class I antigens have been reported in more that 90% of the studied tumours. HLA class I loss is, without any doubt, a major cancer escape mechanism that is frequently observed in tumors originated in different organs. Due to the complexity of the HLA system, different altered tumor phenotypes can be identified in human tumors: HLA I total loss, A,B C locus specific loss, HLA I allelic loss, or HLA haplotype loss. The most important task is to identify and characterize the underlying molecular mechanisms. The new therapies are using antibodies against checkpoint molecules that unblock anti-tumor T lymphocytes. As observed before with "old" immunotherapies, the new generation therapy is also producing "responders", "non responders" and "mixed responders". There are already clear indications that the recurrent and/or progressing metastatic lesions are harbouring "irreversible"molecular alterations that cause a resistance to cytokine-mediated recovery of HLA class I expression. MHC/HLA class I dowregulation should not be seen as an obstacle for T cell based immunotherapy, but as a crucial step in the natural history of tumour development and in the resistance to immunotherapy. There is a long way to go before we undertand why the same treatment produces different responses in different patients , but, without any doubt, MHC/HLA genes and molecules will be playing a leading role in modern cancer immunotherapy in the years to come.

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