Lymphoid neoplasms are a paradigm for the analysis of cancer pathogenesis

Lymphoma study represents a useful model whose study has deepened our knowledge of cancer mechanisms [1,2]. This has been possible due to:

- a significant accumulation of information concerning characteristic cytogenetic changes in specific tumour types, such as those involving c-myc, bcl2, cyclin D1, bcl6, API2, ALK, and others
- studies about the relationship between viral products and other molecular alterations (EBV, HHV8, HTLV-I)
- transfer of knowledge about cytogenetic and molecular alterations to diagnosis and progression (translocations involving Bcl2, Cyclin D1, c-myc, p53 mutations)
- availability of new therapeutic tools, such as monoclonal antibodies, kinase inhibitors, proteasome inhibitors, etc.
- existence of multicentre clinical trials aimed at evaluating the clinical and prognostic implications of lymphoid biological variability, and at the indications for new drugs.

Additionally, lymphoma research contributes critically to the elucidation of the influence of ageing, infection, immune surveillance and other genetic and environmental factors on the increased incidence of lymphoma reported in most western countries. At the same time, lymphoma research has allowed information from basic research to be applied within the fields of diagnosis (molecular markers) and therapy. As such, it is a paradigm of the integration between basic and applied research.

Lymphoma therapy needs identification of rational targets and new drugs

Lymphoid neoplasms are a heterogeneous group of lymphoproliferative malignancies with differing patterns of behaviour and responses to treatment [1,2]. Nevertheless, most of the current lymphoma therapy is still based on cytotoxic drugs or monoclonal antibodies directed against cell surface lymphocyte markers. In a significant proportion of cases, standard treatments fail to cure a percentage of patients or lead to side effects with significant morbidity. The main bottleneck for improving on this situation is likely constituted by the limited knowledge of the molecular mechanisms underlying lymphomagenesis, and the lack of the integration of the knowledge so far generated. Data generated by high-throughput and functional studies have not yet led to the development and clinical application of new rational drugs, but are nevertheless suggesting multiple new targets for treatment.

New high-throughput technologies offer opportunities for identification of targets and functional analysis of lymphoma pathways

The effort for revealing B-cell lymphoma pathogenesis has shown that an integrated analysis including data obtained at DNA (aCGH, mutational studies), RNA (transcriptomics, miRNAs), epigenetic (chip on chip, methylation patterns) and phosphoproteomic levels, paired with functional analysis, may open new opportunities for revealing the intricacies of lymphoma pathogenesis and identify essential genes and pathways [3,4,5].

For the first time, an integrated analysis of DNA mutation and copy numbers, transcriptome and miRNA profiles is now achievable in a series of standardized lymphoma cases[5]. This analysis is being additionally complemented with interference assays aimed to reveal the role of individual genes in specific pathways such as B-cell receptor signalling cascade or apoptosis. Developments on the bioinformatics tools also allow the recognition of signatures associated with sensitivity to specific drugs or inhibition of specific pathways, as has been shown for the connectivity maps developed by T. Golub and colleagues[4].

Research strategies are aimed at matching the individual variability of patients and cancer mechanisms with variability- adjusted therapies [4], through the identification of:

- early diagnosis for screening populations at risk
- predictive and prognostic markers that could allow us to:
  - assign individual treatments
  - stratify patients according to risk
- new therapeutic targets.

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