Seminario CIPF

Lymphoma precision medicine

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Abstract: Cancer is still a mayor challenge with something more than 14M new cases per year in the world and more of 8M patients dying yearly because of cancer (http://globocan.iarc.fr/Pages/fact_sheets_population.aspx). progresses in cancer therapy are strictly dependent on the new data on cancer molecular complexity. Cancer taxonomy is the systems that allow assigning treatment based on the combined analysis of morphology, immunophenotype and molecular features of the disease. Final objective of this approach is a precise definition of clinicopathological entities leading to the identification of underlying molecular alterations, targets for therapy and predictive and prognostic markers for patient stratification.

Some of the more striking new data and concept emerged from the current projects are:

- Cancer is a multigenic disorder, with more than 1000 mutated genes and 0-700 mutated genes per case. Thus, the idea that mutation in a limited number of genes could be responsible for common cancer types has now being replaced by the evidence that a large majority of cancer samples contain from dozens to hundreds of mutations in multiples genes; as a corollary to this the census of cancer genes is increasing up to several hundreds.

- Entities defined on a clinicopathological basis show an unexpected degree of molecular heterogeneity. As an example, in breast cancer driver mutations have been found in at least 40 cancer genes and 73 different combinations of mutated cancer genes were identified alter genomic analysis

- Analysis of different tumour types have shown that basically each tumour sample contains a unique combination of mutated genes, such as been shown for Squamous cell Lung Cancer and others.

- There is a high degree of intratumoral heterogeneity, much higher than initially expected. Thus, single-cell sequencing or high-depth sequencing shows that tumours contain multiple subclones that compete for survival. This increased Intratumor heterogeneity can lead to underestimation of the tumour genomics landscape obtained from single tumour-biopsy samples or serum DNA analysis, and present key challenges to personalized-medicine and biomarker development.

- Additionally, intratumoral heterogeneity is in the basis of the therapeutic failure through Darwinian selection. Thus sequential analysis of tumour samples or serum DNA demonstrates that tumours dynamically evolve along the time, acquiring or losing some of the genetic events that may dictate response to targeted therapy. Pressure
for this Darwinian change may be partially the result of therapy contributing to change the equilibrium different subclones. Thus, studies in AML and other tumours demonstrate that relapse is associated with the appearance of new mutations and clonal evolution, which is partially shaped by the initial chemotherapy that the patients receive to establish and maintain remissions. Thus, the presence of a subclonal driver mutation maybe an independent risk factor for rapid disease progression, and indeed the presence of very minor subclones at the diagnosis of the disease have been demonstrated to be an important driver of the subsequent disease course in CLL cases carrying p53 mutations.

- Genetic mutations are, nevertheless, not the unique cause of cancer. Thus, studies in pediatric tumors, such as ependymoma, have extremely low mutation rate, with none significant recurrent somatic single nucleotide variants, associated with a CpG island methylator phenotype, thus suggesting that genetic modifiers should be the therapeutic candidates for this malignancy.

- New hope has been brought to the field by the finding that immune checkpoint inhibitors, which unleash a patient’s own T cells to kill tumors, may induce durable remissions in tumours resistant to multiple lines of therapy. Interestingly, higher mutational rates in tumours has been shown to predict a favourable response to these checkpoint inhibitors, thus suggesting that the genomic landscape of aggressive cancer shapes response to anti-PD-1 therapy.

T-cell lymphoma, therapy driven by molecular integrative analysis, the purpose of the Lymphoma Group at the Fundación Jiménez Díaz.

In this context, with the invaluable collaboration of the Oncology, Haematology, Dermatology, Pathology and other clinical services, we are developing a project following the hypothesis that genomics integrative analysis and high-depth targeted mutational analysis in routine T-cell lymphoma specimens may generate consistent, relevant data informing about molecular complexity, subclonal composition, mutational rate, mutational signatures and precise mutations in genes with therapeutic implications; thus generating a robust, solid, diagnostic tool that may allow to predict the sensitivity to specific therapies. In this project we have been able to demonstrate that T-cell lymphoma contain actionable mutated genes in the MAPK, JAK/STAT, NFAT, NFKB, and chromatin modification pathways, and that the combination of multiple therapies targeting convergent pathways represent a plausible option for advanced T-cell lymphoma patients.