REVISTA MÉDICA
VALDECILLA

Cancer genomics paves the way to targeted therapy.

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Palabras clave:

Genómica del Cáncer, Terapia dirigida.

Keywords:

Cancer Genomics, Targeted Therapy.

Resumen:
La lucha contra el cáncer es aún un desafío mayor, con cerca de 14 millones de nuevos casos de cáncer al año y más de 8 millones de muertes anuales atribuidas al cáncer. Con la ayuda de múltiples servicios clínicos del HUMV y otras Instituciones, trabajamos para demostrar la hipótesis de que análisis integrados de genómica y secuenciación dirigida de alta profundidad en especímenes quirúrgicos de rutina puede generar datos firmes y relevantes sobre la complejidad molecular, composición subclonal, índice mutacional, firmas mutacionales y mutaciones precisas en genes con implicaciones terapéuticas; así generando una herramienta diagnóstica robusta que permita predecir sensibilidad a terapias específicas. In este proyecto, hemos podido demostrar que los estudios genómicos del cáncer demuestran dianas útiles para la intervención terapéutica y que la combinación de múltiples terapias inactivando rutas oncogénicas convergentes representa una opción plausible para pacientes con cáncer avanzado.

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. With the collaboration of multiple clinical services at the HUMV and other clinical institutions, we are working to demonstrate the hypothesis that genomics integrative analysis and high-depth targeted mutational analysis in routine cancer 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 cancer genome studies do demonstrate actionable targets, and that the combination of multiple therapies targeting convergent pathways represent a plausible option for advanced cancer patients.

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Cancer challenges

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[1].

Progresses in cancer therapy are strictly dependent on the acquisition of new data on cancer molecular complexity and the integration of these molecular data into the clinicopathological background of the patients. Medical and academical institutions along the world are trying to elaborate a cancer taxonomy that responds to these challenges. 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, thus providing targets for therapy and predictive and prognostic markers for patient stratification.

Although the elaboration of this cancer taxonomy is a task for multiple clinical specialities and academic researchers, pathologists play a central role in the integration of clinical and molecular data and the definition of clinicopathological entities.

The explosion of cancer genomics

Moore's Law is a computing term that originated around 1970; the simplified version of this law states that overall processing power for computers will double every two years. Consequently the cost of tumour sequencing has decreased at the same speed, this making possible that cancer genome analysis is becoming a routine clinical tool. This has expanded dramatically the armamentarium of tools for cancer diagnosis and has made possible the development of ambitious international projects, like the International Cancer Genome Consortium (ICGC), organized to coordinate a large number of research projects that have the common aim of elucidating comprehensively the genomic changes present in multiple forms of cancers that contribute to the burden of disease throughout the world [2].

The primary goals of the ICGC were to generate comprehensive catalogues of genomic abnormalities (somatic mutations, abnormal expression of genes, epigenetic modifications) in tumours from 50 different cancer types and/or subtypes which are of clinical and societal importance across the globe, making these data available to the research community as rapidly as possible, and with minimal restrictions, to accelerate research into the causes and control of cancer.

Currently, the ICGC has received commitments from funding organizations in Asia, Australia, Europe, North America and South America for 88 project teams in 17 jurisdictions to study over 25,000 tumor genomes. Projects that are currently funded are examining tumors affecting: the biliary tract, bladder, blood, bone, brain, breast, cervix, colon, eye, head and neck, kidney, liver, lung, nasopharynx, oral cavity, ovary, pancreas, prostate, rectum, skin, soft tissues, stomach, thyroid and uterus. Results of these projects have been published in the major scientific journals (https://icgc.org).

Use of genomics in cancer diagnosis. Development of tools in genomics and informatics made possible to apply NGS for clinical diagnosis

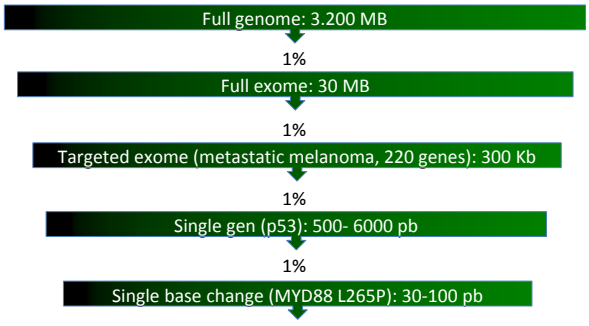

Figure 1: Complexity of cancer genomes can now be revealed through the use of Next Generation Sequencing technologies. Thus, now cancer exomes or targeted mutational analysis can be performed at a low cost and reasonable speed.

First results of the cancer genomics projects

New fascinating data is being quickly produced as a result of this and associated projects. Some of the more striking new data and concept emerged from this project are:

- **Cancer is a multigenic disorder,** with more than 1000 mutated genes and 0-700 mutated genes per case[3]. 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[4]. Thus, COSMIC, the Catalogue Of Somatic Mutations In Cancer (http://cancer.sanger.ac.uk), the world's most comprehensive resource for exploring the impact of somatic mutations in human cancer, described in the latest release (v70; Aug 2014) 2 002 811 coding point mutations in over one million tumor samples and across most human genes[4].

- **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[5] 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[6] and others.

- There is a high degree of **intratumoral heterogeneity,** much higher than initially expected[7]. Thus, single-cell sequencing or high-depth sequencing shows that tumours contain multiple subclones that compete for survival[8]. 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**[9]. 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[10]. 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[9]. Thus, the presence of a subclonal driver mutation maybe an independent risk factor for rapid disease progression[11], and indeed the presence of very mimor 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[12].

- 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[13].

- 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 indice 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 lung cancers shapes response to anti-PD-1 therapy[14].

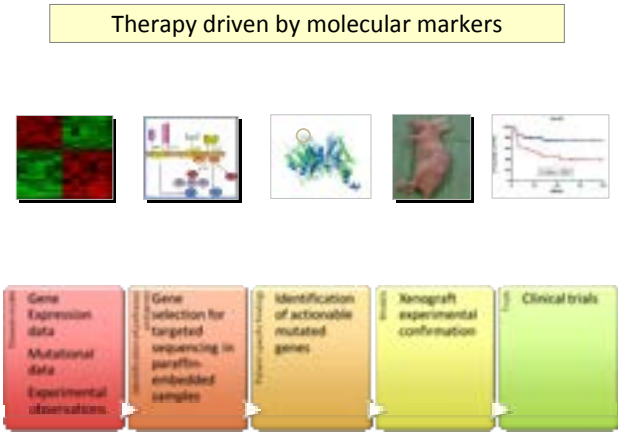

Figure 2: Cancer genomics project steps:

A. Identification of a disease model following the integration of Gene expression, mutation and experimental data allow selecting a suitable opportunity for research.
B. Identification of pathways and genes to be analysed in routine specimens
C. The study of precise tumour sample demonstrate actionable mutated genes, tumour specific targetable signatures or genes
D. In vivo experiments performed in immunosuppressed mice (PDXs) allow to test specific drug and drug combinations
E. These results open the opportunity for clinical trials where to evaluate the clinical application

Therapy driven by molecular integrative analysis, the purpose of the Cancer Genomics Group

In this context, with the invaluable collaboration of the Oncology, Haematology, 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 cancer 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 cancer genomes do contain actionable targets, and that the combination of multiple therapies targeting convergent pathways represent a plausible option for advanced cancer patients[15-22].

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