Best of EHA

A. Bosly

The six best abstracts submitted at the European Hematology Association (EHA), 17th Meeting, 2012, Amsterdam were selected for the presidential symposium. Two of them were related to the whole exome analysis: one in T-acute lymphoblastic leukaemia (T-ALL) and one in multiple myeloma (MM).

(Belg J Hematol 2012;3:112-113)

T-ALL

T-ALL is caused by accumulation of somatic mutations. In order to gain insight in the spectrum of mutations present in adult and pediatric T-ALL, K. De Keersmacker et al from Leuven (Belgium) performed a whole exome sequencing on 36 paired diagnosis/remission T-ALL patients plus eighteen diagnosis only and on seventeen T-ALL cell lines. Thirty-five out of 389 mutated genes were selected because they are recurrently mutated. Eight out of 35 expressed the X chromosome explaining the male predominance in T-ALL. Ten genes are known as oncogene or tumour suppressor genes in T-ALL. Twenty-five are potentially novel oncogenic in T-ALL with function in signal transduction transcriptional or epigenetic regulation.

In seven T-ALL cases (13%) exhibited mutations in genes implicated in ribosomes. Mutation of RPL10 gene was identified in 8,4% of pediatric T-ALL and causes ribosome defect. (# O0567).

MM

N. Bolli et al. from Cambridge (U.K), by the analysis of whole exome explore clonal architecture and genomic evolution in multiple myeloma (MM) by analysis CD138 purified BM cells in 67 patients. They confirmed mutations in previously identified genes KRAS in 25% of cases, BRAF 13%, NRAS 13%, FAM46C 9%, TP53 9%, CCND1 1%.

In same patients BRAF mutation co-occurred with KRAS. Several genes unreported in MM were reported. In 97% of patients, at least two subclones were identified in the diagnosis suggesting that MM is a heterogeneous disease. During evolution some mutations were reported NRAS, TP53 loss.

Lessons from these analyses are:

- A comprehensive list of variants (some unreported).
- MM is heterogeneous at diagnosis and
- genetic changes occurred during evolution.

Clinical importance of this work in the future will be to identify at diagnosis clones likely to be resistant to a given treatment and to assess treatment efficacy post-induction. (# 00571)

T cell dysfunction

G. Ramsay from Barts Cancer Institute (London) explored T cell dysfunction in chronic lymphocytic leukaemia (CLL). T cell from CLL have a profound deregulation of functions. Tumour molecules expressed on B-CLL cells could mediate T cell dysfunction.

High expression of some of these molecules (B7 related) CD200, CD274 and CD276 and CD270 were linked to poor prognosis, and antibodies against these molecules restore T cell synapse in vitro. Lenalidomide blocks tumour cell induced T cell synapse dysfunction by inducing down regulation of these molecules.

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In vivo, lenalidomide increases cytolytic activity and monoclonal anti B7 antibodies could be also useful. This paper is just published in Blood 2012. (# 00568)

AML

A. van der Reijden from Nijmegen (The Netherlands) explores the mechanism of action in acute myeloblatic leukaemia (AML) with t(8;21).

In more than 10% of patients with AML, t(8:21) is present and resulted in a fusion AML1-ETO genes.

AML1 is a subunit of CBF (transcription factor) and ETO is a transcription co-repressor. AML1-ETO contributes to leukaemia by altered gene expression.

GFI1 is a repressing gene to GFI but AML1-ETO inhibits GFI1 repressive function.

Mice experiences demonstrate that GFI1/AML1-ETO is responsible for the development of leukaemia and thus GFI1 is a potential therapeutic target. (# 0569).

FA

R. Ceccaldi et al. from St-Louis, Paris (France) presented hematopoietic stem cell function in Fanconi anaemia (FA). FA is characterised by a progressive bone marrow failure and has a strong susceptibility to develop MDS and AML.

CD34+ counts and CFU counts were low in bone marrow from FA patients (91 pts) in comparison with healthy donors.

Hematopoietic stem cells from FA have a strong activation of p53 and p21 leading to a decrease of cell cycle arrest favouring apoptosis and senescence p53 inhibits HSC in vivo.

By interest p53 response is also involved in Blackfan-Diamond anaemia related to ribosomal abnormality and also involved in dyskeratosis congenital with telomeric abnormalities unifying downstream signaling mechanism. (# 00570)

TTP

F. Callewaert et al. from Ablynx Zwijnaarde (Belgium) tested the efficacity and safety of Nanobody ALX-0681 in the prevention and treatment of acute early episodes of acquired thrombotic thrombocytopenic purpura (TTP) in baboons.

TTP is a rare and life threatening disorder characterised by the neutralization of ADAMTS13 activity to process large von Willebrand (vW) factor multimers leading to platelet aggregation. ALX-0681 is a therapeutic nanobody (variable part of antibody) to inhibit interaction between ULvWF and the platelet receptor GP1b-IX-V and is a new attractive potential therapeutic agent. Pre-clinical in vivo model in baboons demonstrates activity and safety. Now Phase II study in men is ongoing. (# 0572)