Presidential Sessions

Presidential Session II

Sunday 25 September 2011, 12:20−14:40

G1 Hamilton Fairley Award

New therapeutic avenues in lung cancer based on disturbances in PI3K and RAS pathways

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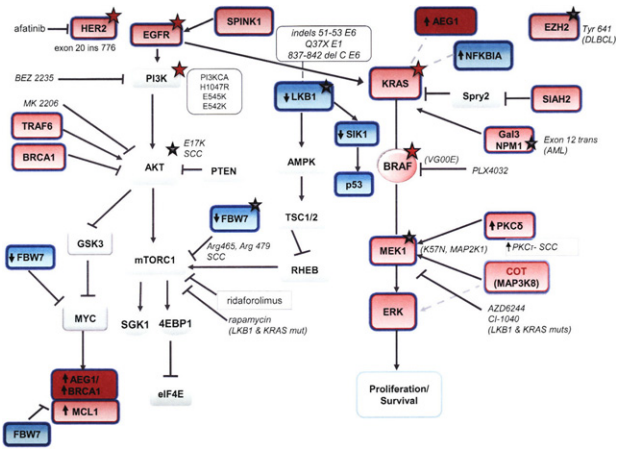
The vast majority of tumors, including lung cancer, have several alterations in the PI3K and RAS pathways, as well as in p53. The new challenge in providing better treatment for patients lies in understanding the relationship between different genetic abnormalities that can serve both as prognostic markers and as the basis for novel therapeutic intervention. For example, we have observed that AEG-1 and BRCA1 mRNA expression significantly influences progression-free survival (PFS), either in metastatic non-small-cell lung cancer (NSCLC) patients with or without EGFR mutations. BRCA1 mRNA expression was also an independent prognostic marker in erlotinib-treated EGFR mutated NSCLC patients, with significant differences in the length of PFS according to BRCA1 levels: median PFS was 27 months in patients with low BRCA1 mRNA expression [1]. Moreover, a significantly better PFS was obtained in those patients who had elevated expression of NFKBIA (a gatekeeper of the EGFR pathway and the inhibitor of NFκB activation) [2].

FBW7 is an important tumor suppressor gene that degrades mTORC1 and the loss of FBW7 could be a potential biomarker for treatment with mTOR pathway inhibitors [3]. FBW7 also inhibits the pro-survival protein MCL1 which is a crucial regulator of apoptosis triggered by antitubulin drugs. It has been suggested that profiling FBW7 and MCL1 status of tumors in terms of protein levels, messenger RNA levels and genetic status could be useful for predicting patient response to antitubulin drugs [4,5]. Intriguingly, in a systematic characterisation of somatic mutations in cancer genomes, a high frequency of FBW7 was observed in squamous cell lung cancer. However, in the report no details of the type of EGFR mutations are given [6]. Hotspot mutations have been described in FBW7 that occur in high frequencies, 30%, in cholangiocarcinomas and also in T-ALL [7]. Therefore, it is of great interest to examine FBW7 status, including mRNA expression.

EZH2, an oncogene which activates NFκB and RAS, was closely correlated with BRCA1 expression in a series of 60 metastatic NSCLC patients, but with no correlation between levels of EZH2 and K-ras mutations. EZH2 mutations (Try641) have been reported in follicular and diffuse large B-cell lymphomas [8].



BRAF mutations have been identified in NSCLC, more frequently in women (9%), and only V600E had prognostic significance in a series of 1000 lung cancers screened (Marchetti et al., in press). In addition, MEK1 mutations have been described at low frequencies [9], which could be susceptible to treatment with selective inhibitors [10]. MAP3K8 (the gene encoding COT) is a MAPK pathway agonist that drives resistance to RAF inhibition in BRAF (V600E) cell lines [11]. Other downstream components that can influence clinical behavior of tumors with K-ras mutations is the recently described model for PKCδ regulation of apoptosis and survival in K-ras dependent NSCLC [12]. Overexpression of PKCδ promotes tumor progression in pancreatic cancer [13].

Therefore, in tumors with K-ras mutations, many genetic modifiers can be relevant in delivering prognostic information and for predicting response to selective inhibitors, including MEK inhibitors [10] or mTOR inhibitors. Interestingly, overexpression of the atypical PKCι confers poor prognosis in early NSCLC and is amplified in squamous cell lung cancer [14]. LKB1/STK11 is also one of the most frequently mutated tumor suppressor genes in NSCLC [15].

References

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Presidential Session III

Monday 26 September 2011, 12:15−14:25

G2 ECCO Clinical Research Award

Adjuvant Systemic Treatment for Women with Breast Cancer: The Future of Clinical Trials

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Adjuvant systemic therapies have been studied for several decades in randomized clinical trials. Historically, prognosis (primarily nodal status) and age (as surrogate for menopausal status) were the main features that defined eligibility of patients for specific trials. Evidence regarding the importance of steroid hormone receptors and HER2 overexpression/amplification for determining appropriate treatments required consideration of these two additional features for study eligibility. Within the past decade the heterogeneity of breast cancer was further highlighted with the recognition of biological subtypes based on gene expression. Recently, intrinsic biological subtype nomenclature was recommended to provide a ‘short-hand’ for specific clinico-pathological classification to be applied in clinical practice and trial design. The following subtypes were defined: “Luminal A”, “Luminal B HER2-negative”, “Luminal B HER2-positive”,