Research Highlights

Highlights from the latest articles in personalized medicine

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Molecular dissection of cancers – another piece in the puzzle to better assess, and treat, disease using biomarkers that correlate with disease type and stage

Evaluation of: McDonnell TJ, Chari NS, Cho-Vega JH *et al.*: Biomarker expression patterns that correlate with high grade features in treatment naive, organ-confined prostate cancer. *BMC Medical Genomics* 1, 1 (2008).
– Felix Frueh

The study by McDonnell *et al.* [1] is one of the most recent forays into the use of biomarkers for better assessment of disease state in cancer. Ultimately, we believe, these approaches will help us to improve making treatment choices, for example, by distinguishing aggressive from nonaggressive forms of cancer, as the authors point out in their paper. McDonnell *et al.* focused on prostate cancer and take the current clinical characterization of the cancer (Gleason score) as a standard to compare cancers with equal Gleason scores using tissue microarrays (TMA) to measure a set of nine cell death and cell-cycle regulatory proteins. TMA is a relatively new technology (the first review article appeared in 2001 [2]) with high potential for clinical application: it enables asking many more questions compared with conventional techniques (e.g., traditional histopathology) using significantly less tissue. Parallel analysis of

large sets of biomarkers has become possible, and the presence or absence of a series of qualified disease-characterizing markers can provide us with information on tumor type, disease progression, response to therapy and so on. McDonnell *et al.* report that the use of four markers (bcl-xL, Fas, bax and p21) 'provide potentially important information predictive of clinically aggressive behavior'. They further suggest that 'the findings indicate that tumors of equivalent Gleason grade, although morphologically similar, have varying patterns of biomarker expression that correlate with the Gleason score of the tumor'. If indeed these findings can be replicated, preferentially in a prospective study, this approach could become a key measure prior to making a treatment decision in prostate cancer.

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Genetic polymorphisms influencing drug responsiveness in Crohn's disease

Evaluation of: Matsukura H, Ikeda S, Yoshimura N, Takazoe M, Muramatsu M: Genetic polymorphisms of tumor necrosis factor receptor superfamily 1A and 1B affect responses to infliximab in Japanese patients with Crohn's disease. *Aliment Pharmacol. Ther.* 27, 765–770 (2008).

– Amalia Issa

Crohn's disease (CD), a chronic inflammatory bowel disease, is common in Western nations [1], and in more recent decades has become increasingly common in Japan [2]. The antitumor necrosis factor α (TNF- α) monoclonal antibody, infliximab (IFX), has been demonstrated to result in remission, with sustained benefit in some 30–40% of patients with CD [3,4]. There is evidence that this selective responsiveness of CD patients to IFX is owing to interindividual drug availability associated with the TNF receptor super family [5–6]. Matsukura *et al.* [7] examined whether SNPs of the TNF receptor super family 1A (TNFRSF 1A) and the TNF receptor super family 1B (TNFRSF 1B) might be associated with interindividual drug variability that might account for differences observed in IFX responsiveness in a cohort of Japanese CD patients. The authors recruited 81 CD patients who were IFX-naïve to

participate in the study. Patients were administered either one dose of IFX (5 mg/kg) or three consecutive doses of IFX, depending upon whether patients had inflammatory or fistulizing CD. Therapeutic efficacy of IFX was assessed 4 weeks following drug administration, using the Harvey-Bradshaw index (HBI), a standard approach to evaluating clinical activity of Crohn's. Based upon the HBI, patients were *a priori* classified as either IFX treatment responders ($n = 48$) or IFX nonresponders ($n = 32$), and genotyped for TNFRSF 1A and TNFRSF 1B polymorphisms that had been shown to be associated with susceptibility to CD and responsiveness to IFX in prior studies. Of the five polymorphisms tested for, a significant ($p = 0.04$) association was observed only between the TNFRSF 1A, rs767455 allele and the efficacy of IFX. Logistic regression analysis revealed that the rs767455 was significantly associated with a reduced effect of IFX (OR = 0.26; 95% CI: 0.08–0.91). The results presented in this paper suggest that variation in TNF receptor genotypes may be associated with interindividual variability of IFX in Japanese Crohn's disease patients. However, more studies are required, as this pharmacogenomic study was carried out in a relatively small cohort of patients, and therefore vulnerable to type 1 errors and likely not sufficiently powered to effectively exclude genetic variants.

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Lapatinib monotherapy in inflammatory breast cancer: the story unfolds

Evaluation of: Johnston S, Trudeau M, Kaufman B *et al.*: Phase II study of predictive biomarker profiles for response targeting human epidermal growth factor receptor 2 (Her-2) in advanced inflammatory breast cancer with lapatinib monotherapy. *J. Clin. Oncol.* 26(7), 1066–1072 (2008).
– Eleni Andreopoulou & Massimo Cristofanilli

Inflammatory breast cancer (IBC) remains the most aggressive and enigmatic form of invasive breast cancer. Several molecular abnormalities are possibly implicated with its aggressive phenotype and dismal prognosis. Among the conventional biomarkers associated with IBC are ER and PR negativity, EGFR and HER-2, MIB1, E-cadherin over-expression, MUC1 cytoplasmic staining

and p53 mutations. Utilization of novel targeted therapies towards elucidating the signaling pathway and identification of molecular pharmacodynamic markers predictive of drug response has now become a goal of modern therapy as oncologists seek a more rationale approach to treatment.

Human epidermal growth factor receptor 2 (HER2) has a central role in

the formation of active HER complexes since it is the preferred dimeric partner with the other HER family receptors. Lapatinib represents a successful example of small molecule dual specific TK domain inhibitor against ERB1 and ERB2 as an alternate strategy for HER-signaling disruption in addition to HER2 inhibitors.

The article by Johnston *et al.* in the *Journal of Clinical Oncology* provides a biologic insight into predictive biomarker profiles for response, targeting HER2 in IBC with lapatinib monotherapy. A total of 45 heavily pretreated patients with histologically confirmed locally advanced or metastatic IBC that was refractory to or recurred after anthracycline-based chemotherapy in the adjuvant or metastatic setting were enrolled, with 30 patients assigned to cohort A (Her2/neu⁺, EGFR⁺ or EGFR⁻) and 15 patients assigned to Cohort B (Her2/neu⁻, EGFR⁺). A total of 50% of the patients in cohort A and 7% in cohort B had received prior trastuzumab. Patients received lapatinib 1500 mg/day and a panel of protein biomarkers was evaluated by immunohistochemistry (IHC) in fresh tumor biopsies collected within 7 days of lapatinib initiation.

Overall response rate within HER2 positive IBC was 50% (2 CR and 13 PR), with median progression-free survival (PFS) of 14 weeks. There was a 4–8% response rate to lapatinib monotherapy in a similar population of heavily pretreated HER2-positive non-IBC breast cancers [1]. By contrast, only 1% of the patients who were HER2-negative, EGFR-positive achieved response with a PFS of 4 weeks, leading to closure of enrolment in cohort B. These results are consistent with preclinical data in breast cancer cell lines in which HER2 overexpression, not EGFR, is predictive of response to lapatinib [2].

The lack of clinical activity of selective EGFR tyrosine kinases inhibitors as monotherapy in breast cancer further indicates HER2 as having a more prom-

inent role in regulating inflammatory breast cancer cell growth and survival compared with EGFR, which has been supported by a Phase II trial of neoadjuvant lapatinib monotherapy followed by lapatinib/paclitaxel in chemotherapy-naïve IBC patients. Of the 30 patients with HER2⁺ disease, 30% achieved a clinical response with the initial lapatinib monotherapy, while none of the five patients with HER2⁻/EGFR⁺ disease achieved a response [3]. Ongoing clinical trials are examining lapatinib alone or in combination with pazopanib in patients with IBC [4,5].

As expected, RhoC and E-cadherin overexpression were seen in tumors from both cohorts, while p-HER-3 expression and lack of p53 expression were associated with response to lapatinib ($p < 0.05$). Coexpression of p-HER-2 and p-HER-3 predicted response to lapatinib, suggesting that HER2/HER3 heterodimers might be important in the biology of IBC. Moreover, the increased expression of the ErbB2/ ErbB4 ligand, heregulin, further implicates an autocrine and paracrine loop whereby HRG binds HER3 promoting downstream survival signaling through HER2/HER3 heterodimers. The authors emphasized that these results suggest that the presence of pHER3 in HER2⁺ IBC identifies tumors whose outcome is more likely to be dependent on HER2–HER3 heterodimeric signaling. Additionally, Bcl-2 and β -catenin expression were not associated with response to lapatinib and PTEN deficiency and expression of IGF-1R were not associated with resistance to lapatinib.

This article focuses on understanding molecular characteristics of IBC to help us develop clinically relevant diagnostic tools, identification of markers unique to IBC and novel therapeutic approaches. As the changing management paradigm focuses on treatment individualization involving modulation of deregulated critical biochemical pathways, the implications of these data warrant further study with contemporary technology.

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Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.