Mechanisms and biomarkers of acquired resistance to targeted cancer therapies

No abstract received.  No conflict of interest information specified.

Mutations and acquired resistance in colorectal cancer

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It is now evident that colorectal cancers (CRC) indistinguishable by light microscopy are actually distinct diseases requiring unique therapeutic approaches. Tissue and liquid biopsies can be used to define CRC molecular subtypes and to monitor response and resistance to therapy. Using these approaches, CRC patients were found to respond selectively to targeted agents interfering with oncogenic nodes of the EGFR signaling pathway. Notably, the patient-specific responses can be recapitulated and paralleled in cellular and mouse clinical proles (CRC-avatars). The inevitable development of acquired resistance to inhibitors of the EGFR signaling pathway presently limits further clinical advances. Strategies to prevent or overcome resistance are therefore essential to design the next generation of molecule-driven clinical trials for CRC patients. No conflict of interest.

Pooled Paper: JAK2/STAT5 inhibition circumvents resistance to PI3K/mTOR blockade: A rationale for co-targeting these pathways in metastatic breast cancer

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Background: Hyperactive PI3K/mTOR signaling is prevalent in the majority of human malignancies and its inhibition exhibits potent antitumor activity in a wide spectrum of solid cancers. Unfortunately, single-agent targeted cancer therapy is usually short-lived and thwarted by different resistance mechanisms.

Material and Methods: We used a combination of in vitro and in vivo models of luminal and triple-negative breast cancer and a battery of biochemical, cell biological, tumorigenesis and metastasis assays.

Results: We discovered a JAK2/STAT5-evoked positive feedback loop that causes adaptive resistance to dual PI3K/mTOR inhibition. Mechanistically, PI3K/mTOR inhibition increased IRS1-dependent activation of JAK2/STAT5. Genetic or pharmacological inhibition of JAK2 abrogated this vicious feedback loop. Combined PI3K/mTOR and JAK2 inhibition synergistically reduced cancer cell viability in vitro as well as tumor growth in vivo, and decreased tumor seeding and metastasis due to its impact on the IL-8 receptor CXCR1+ tumor-initiating subpopulation of cells. We further found that combined PI3K/mTOR and JAK2 inhibition increased event-free as a well as overall survival of tumor-bearing animals.

Conclusion: This study reveals a new link between growth factor signaling, JAK2/STAT activation, cytokine secretion and metastasis. Our results provide a rationale for combined targeting of the PI3K/mTOR and JAK2/STAT5 pathways in triple-negative breast cancer, a particularly aggressive and currently incurable disease. Conflict of interest: Ownership: RA, VR, MM and TR are Novartis employees.

In vivo RNAi screening for novel therapeutic cancer targets

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Melanoma is the most aggressive type of skin cancer and its incidence is steadily increasing. Melanomas tend to spread rapidly, which is associated with a grim prognosis. Until recently, most advanced stage melanomas were refractory to the available therapeutic options, but there are recent developments offering better perspectives. For example, new therapeutic approaches have become available, which target genetic vulnerabilities within the melanomas. A primary example of such a dependency is the common BRAFV600E mutation, which is essential for proliferation and survival of melanoma cells. In the clinic, the mutant BRAF oncogene product can be targeted by specific inhibitors, including vemurafenib, which cause unprecedented melanoma regression. However, relapse eventually occurs around six months due to a variety of resistance mechanisms, both MAP kinase-dependent and -independent. Therefore, in spite of these new perspectives, there is a dire need to identify additional targets amenable to therapeutic intervention, to be used in combination with vemurafenib or other specific inhibitors to overcome or prevent drug resistance and improve durable responses. To achieve this, we set out to identify melanoma factors that are required for proliferation and survival specifically in an in vivo setting. Thus, we performed negative selection RNAi screens parallel in vitro and in vivo and focused on the hits, making them an ideal candidate for preventive therapy as well as for the corresponding cells in culture. The results from these screens will be discussed.

Conflict of interest: Other substantive relationships: CSO of MetaCurix.

Symposium Mechanisms of Drug Resistance

Sunday 6 July 2014 10:45–12:30

Symposium Cancer Prevention

Sunday 6 July 2014 10:45–12:30

Progress in breast cancer prevention

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Two drugs, tamoxifen and raloxifene, are licensed for preventive therapy in the United States. Both have been shown to reduce incidence by approximately 40%, but in a head-to-head comparison tamoxifen was about 25% more effective. However as these drugs are now off patent there seems to be no direct way for them to be licensed for prevention in Europe, although NICE has now recommended their use for high risk women in the UK, and they can be prescribed off label. More recently two other selective oestrogen receptor modifiers (SERMs), lasofoxifene and arzoxifene have been investigated in large prevention trials. Both appear to be at least as effective as tamoxifen in breast cancer risk reduction, but lasofoxifene also showed large reductions in heart disease and fracture rates, making it an ideal candidate for preventive therapy. All of these drugs have recently been evaluated with extended follow up in an individual patient overview where a 55% reduction in ER positive cancer in the five years of active treatment was seen, but also a 42% reduction in the next 5 years, as a result of ‘carryover’ benefits after treatment cessation. No reduction in ER negative tumours has occurred, and in fact a marginally increased (14%, P = 0.09) incidence was seen. Newer approaches are looking at the role of aromatase inhibitors, where substantial reductions in contralateral tumours have been seen when they were used as adjuvant treatments for early breast cancer. Two prevention trials in high risk women without breast cancer have been conducted. The MAP3 trial evaluated exemestane and a 65% reduction in invasive tumours after a relatively short 30 months median follow up was seen. More recently the IBIS 2 trial using anastrozole has completed analysis of 3846 women with a median follow up of 5 years. Briefly a 53% reduction in all breast cancer was seen, with a larger reduction in ER positive invasive breast cancer. Fracture rates were not significantly increased, due in part to bone mineral density scans at baseline, and monitoring of those who were found to be osteoporotic or osteopenic with treatment as necessary. Musculoskeletal and vasomotor symptoms were increased but only by about 10%, but rates were very high in the placebo arm, indicating that most of the reported symptoms in uncontrolled situations are not drug related. As both of these classes of drugs (SERMs and AIs) have important side effects, it is important for women taking them to monitor their risk. Other substantive relationships: Corporate-sponsored research: AstraZeneca.

Conflict of interest: Corporate-sponsored research: AstraZeneca.

Worldwide prevention of cervical cancer

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Most HPV vaccination programmes target adolescent girls and young women. This will have little effect on overall cancer rates for several decades, as most of the 8 million women who will develop cervical cancer over the next 20 years have already been infected with HPV. The majority of HPV infections disappear...