

Immunity in Medicine

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Cancer therapy breakthroughs

Lung cancer is the leading cause of cancer related deaths worldwide. Recently tyrosine kinase inhibitor therapy with imatinib (Gleevec) has already revolutionized the treatment of chronic myelogenous leukemia and other tumours with activating mutation in these kinases. Inhibitor of Epidermal Growth Factor Receptor (EGFR) tyrosine kinase, Gefitinib (Iressa) was approved in Japan and USA for treatment of non-small cell lung carcinoma (NSCLC), the rationale being the overexpression of EGFR in lung carcinoma tissue compared to adjacent normal tissue. Clinical trials however, revealed high variability in drug response. Two Boston groups^{1,2} independently screened EGFR gene for mutations in NSCLC tumors. They discovered mutations in exons 18 through 21 which were either, small, in-frame deletions or amino acid substitutions clustered around the tyrosine kinase domain of EGFR. The surrounding normal tissue did not possess the mutations, proving that they were somatic in origin. Additionally, these mutations were only present in gefitinib responsive patients, being most frequent in adenocarcinomas. In vitro culture studies showed that the cell line harboring mutations in the EGFR gene was 50 times more sensitive to gefitinib than other cell lines.

The identification of EGFR mutations in a subset of NSCLC and the association between these mutations and gefitinib sensitivity demonstrate that alteration in protein structure and not only the expression levels, render tumors sensitive to particular drugs.

Cetuximab is a monoclonal antibody against the EGFR. It has been shown that combination therapy of advanced colorectal cancer with cetuximab and irinotecan causes disease regression in approximately 22 percent of patients. Vascular endothelial growth factor (VEGF) is an important regulator of angiogenesis. Bevacizumab is a monoclonal antibody against VEGF. A small clinical trial involving patients who had received no previous therapy for advanced colorectal cancer showed that the addition of bevacizumab to fluorouracil and leucovorin increased the response rate from 17 percent to 40 percent. This phase 3 trial³ was initiated when the addition of irinotecan to fluorouracil and leucovorin (IFL) had just been shown to prolong survival in patients with metastatic colorectal cancer and was considered the new standard first-line therapy for this disease. The results showed that the addition of bevacizumab to IFL was associated with increases in the median overall survival (20.3 months vs. 15.6 months); median duration of progression-free survival (10.6 months vs. 6.2 months); response rate (44.8 percent vs. 34.8 percent); and the median duration of response (10.4 months vs. 7.1 months). Hypertension was noted as the only side-effect of bevacizumab combination therapy. The results of this phase 3 study³ provide support for the use of antiangiogenic agents in the treatment of cancer.

1. Paez JG et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004 Jun; 304(5676):1497-500.

2. Lynch TJ et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004 May 20;350(21):2129-39.

3. Hurwitz H et al. Bevacizumab plus irinotecan, fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335-2342.

Vaccine against Hepatitis C

A potential vaccine against HCV is presented in a thesis from Karolinska Institute, Sweden. HCV is a major cause of chronic liver disease affecting 170 million people worldwide. Antiviral therapy with interferon alpha and ribavirin is used quite effectively but about 60% patients become chronic HCV carriers. HCV infection has a high rate of viral persistence, thought to be mediated through its high genetic variability. This severely compromises vaccine development. Two regions of HCV are genetically stable – the core and the NS3 protein, a non-structural protein with protease and helicase properties. Previous attempts at vaccine

development against these proteins have resulted in poor immunological responses. Frelin and colleagues¹ noted that when NS4A, a cofactor of NS3 was included in the protein complex used for immunization of mice, there was a more rapid and increased antibody response. The T-cell (predominantly TH1) mediated response was similarly boosted. Finally the authors evaluated the transdermal delivery of this immunogen using the gene gun approach which has already been validated in humans and demonstrated that the NS3/4A complex was able to immunize adequately.

1. Frelin L et al. Low dose and gene gun immunization with a hepatitis C virus nonstructural (NS)3 DNA-based vaccine containing NS4A inhibit NS3/4A-expressing tumors in vivo. *Gene Ther.* 2003 Apr;10(8):686-99.

2. Lars Frelin, lars.frelin@labmed.ki.se

Parasite coat uncovers links in Asthma

The target population for the survey was all medical Asthma is thought to result from an exaggerated TH2 airway inflammation. Striking similarities exist between the TH2 responses in asthma and in antiparasitic immune reactions. Thus it is believed that TH2 inflammation evolved to deal with parasites and that allergy and atopic asthma arise when these immunological responses are poorly controlled, independent of parasitic infection. Chitin is the second most abundant polysaccharide in nature and is found in fungal cell walls and in exoskeletons of crustaceans and sheaths of nematodes. Degrading enzymes called chitinases keep chitin concentration in check. Recently acid mammalian chitinase (AMCase) group of enzymes of unknown function have been described in humans. Zhu et al.¹ investigated the role of AMCase in TH2 mediated inflammation in mice and showed that AMCase expression was increased in lung epithelial cells and macrophages after challenge with an aeroallergen. Subsequent experiments demonstrated that this response was stimulated by TH2 cells and did not occur in the absence of IL-13. Marked decrease in inflammation occurred when mice were treated with chitinase inhibitor, allosamidin. These findings add to our understanding of the pathogenesis of asthma in a number of ways – first, the genetic expression ability of chitinases could be an important determinant in an individual's susceptibility to asthma and atopy; second AMCase has an optimum pH of 2.3 which resolves with steroid therapy and thus the beneficial effects of steroids in asthma may be in part mediated through decreasing bioactivity of AMCase; thirdly, AMCase is a potential therapeutic target for asthma and related disorders.

1. Zhu et al. Acidic mammalian chitinase in asthmatic Th2 inflammation and IL-13 pathway activation. *Science.* 2004 Jun 11;304(5677):1678-82.

Tuberculosis and Typhoid survival strategies

Pathogenicity of mycobacteria and salmonella is tightly linked to intracellular survival, but some species of these organisms have evolved strategies to survive intracellularly and avoid degradation. Walburger et al.¹ found that a kinase, called protein kinase G (PknG) is secreted by pathogenic mycobacteria into macrophage phagosomes which inhibited phagosome-lysosome fusion preventing degradation of invading microbes. They also discovered an inhibitor of PknG which has the potential of being used as an anti-tuberculous drug. Hernandez et al.², discovered that a phosphatase, called SopB, is secreted into the host cells by Salmonella and plays a crucial role in the formation of spacious phagosomes. These large vesicles provide a favourable environment where Salmonella can reside and establish its replicative niche. Deletion of the gene for SopB resulted in the virtual absence of large phagosomes and a significantly decreased Salmonella survival.

1. Walburger A et al. Protein kinase G from pathogenic mycobacteria promotes survival within macrophages. *Science.* 2004 Jun 18;304(5678):1800-4.

2. Hernandez LD et al. Salmonella modulates vesicular traffic by altering phosphoinositide metabolism. *Science.* 2004 Jun 18;304(5678):1805-7.