05 July 2008 13:30 - 14:30

Muhlbock Lecture

1
Identification of stem cells in small intestine and colon by a single marker gene Lgr5

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The intestinal epithelium is the most rapidly self-renewing tissue in adult mammals. Current models state that 4-6 crypt stem cells reside at the +4 position immediately above the Paneth cells in the small intestine; colon stem cells remain undefined. Lgr5/Gpr49 was selected from a panel of intestinal Wnt target genes for its restricted crypt expression. Two knock-in alleles revealed exclusive expression of Lgr5 in cycling, columnar cells at the crypt base. In addition, Lgr5 was expressed in rare cells in several other tissues. Using an inducible Cre knock-in allele and the Rosa26-LacZ reporter strain, lineage tracing experiments were performed in adult mice. The $Lgr5^{+ve}$ crypt base columnar cell (CBC) generated all epithelial lineages over a 60-day period, implying that it represents the stem cell of the small intestine and colon. The expression pattern of Lgr5 suggests that it marks stem cells in multiple adult tissues and cancers.

05 July 2008 15:00 - 17:00

SYMPOSIUM

Receptor signalling

2
Computational simulation of the EGF receptor system

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The Epidermal Growth Factor (EGF) family of receptors and ligands consists of four receptors and eleven ligands. The Neuregulin sub-group of ligands can be made in over thirty different forms due to alternative splicing. This complex system has evolved to process multiple inputs and produce an array of outputs which ultimately regulate some of the most important behaviours of cells including cell replication, differentiation, motility and survival.

Numerous reports have demonstrated that these factors are expressed at altered levels in cancer cells and they are now well established targets for different types of signal transduction inhibitor drugs. We have developed a computer simulation of the system using object orientated modelling in which the levels of the different receptors and ligands can be selected and the system run to equilibrium.

We have determined the level of expression of the four receptors and eleven ligands in 100 cases of breast cancer using immunohistochemical staining. We are inputting this information into the program to simulate the entire system. The output enables us to determine the level of activity of each receptor type in each case. This tool may aid in the future in selecting the correct choice of signal transduction inhibitor drug for individual patients making them more effective and economic to use.

3
The EGF receptor signalling system

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Growth factors and their transmembrane receptors contribute to all steps of tumor progression, from the initial phase of clonal expansion, through angiogenesis and metastasis. Hence, the information relay system involved in growth factor signalling provides potential site for signal interception and tumor inhibition. A relevant example comprises the epidermal growth factor (EGF) and the respective receptor tyrosine kinase, namely ErbB-1/EGFR, which belongs to a prototype signalling module that drives carcinoma development. The extended module includes two autonomous receptor, EGFR and ErbB-4, and two non-autonomous receptors, namely: a ligand-less oncogenic receptor, HER2/ErbB-2, and a kinase-dead receptor (ErbB-3). This signalling module is richly involved in human cancer and already serves as a target for several cancer drugs. Due to inherent complexity and a large amount of experimental data, we propose a systems approach to understanding ErbB signaling. EGF - to - ErbB signaling is envisioned as a bow-tie configured, evolvable network, sharing modularity, redundancy and control circuits with robust biological and engineered systems. Our work concentrates on system controls, a plethora of negative feedback loops, which include E3 ubiquitin ligases, receptor endocytosis and newly transcribed genes. Because network fragility is an inevitable tradeoff of robustness, systems level understanding is expected to identify therapeutic opportunities for targeting aberrant activation of the network in human pathologies. Specific examples include anti-receptor antibodies such as Trastuzumab and kinase inhibitors, such as Lapatinib. Mechanisms underlying response to drugs and evolvement of secondary resistance will be discussed.

4
The EGF receptor system as a target for therapy

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The epidermal growth factor receptor (EGFR) and its ligands that belong to the EGF family of peptides are involved in the pathogenesis of different types of carcinoma. These proteins form a complex system that regulates the proliferation and the survival of cancer cells and that represents a suitable target for novel therapeutic approaches. Two main classes of anti-EGFR agents are in advanced clinical development: monoclonal antibodies (MoAb) that compete with ligands in binding to the extracellular domain of the EGFR, and tyrosine kinase inhibitors (TKI), which bind and inactivate the EGFR TK domain. The anti-EGFR MoAbs cetuximab and panitumumab have been approved for treatment of metastatic colorectal cancer (mCRC). Cetuximab has been shown to improve the activity of irinotecan-based chemotherapy in EGFR-positive irinotecan-resistant or –refractory mCRC patients. Panitumumab was found to improve the survival of mCRC patients as compared with best supportive care. The EGFR-TKI erlotinib has been approved for 2nd and 3rd line treatment of advanced or metastastic non-small-cell lung cancer (NSCLC) following the results of the BR.21 study that showed a survival advantage for patients treated with erlotinib as compared with placebo. More recently, the TKI gefitinib was found to be non-inferior to docetaxel in the treatment of advanced NSCLC. The EGFR-TKIs failed to increase the efficacy of standard chemotherapy in the first line treatment of NSCLC. The major drawback in the clinical development of anti-EGFR agents is the lack of predictive markers. No correlation between the levels of expression of EGFR and response to anti-EGFR agents was found in both CRC and NSCLC. The response rate to EGFR-TKIs is higher in NSCLC patients carrying mutations of the EGFR TK domain. However, patients that do not carry such mutations can also benefit of treatment with EGFR-TKIs. Contrasting results on the role of EGFR gene amplification in determining the sensitivity to EGFR targeting agents have been reported. Recent findings suggest that both CRC and NSCLC patients carrying a mutated KRAS do not benefit from treatment with anti-EGFR agents. In this regard, panitumumab has been approved for treatment of mCRC patients that carry a wild type KRAS gene. In conclusion, anti-EGFR drugs have shown promising activity in different tumor types. However, biological markers to select patients that can benefit of treatment with anti-EGFR agents are definitely needed.

5
Mechanisms of resistance to EGFR inhibitors

No abstract received.

05 July 2008 15:00 - 17:00

SYMPOSIUM

Gene expression and cancer

6
Non-coding RNA and chromatin remodeling: intergenic transcripts regulate the epigenetic state of rRNA genes

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Epigenetic control mechanisms silence half of the ribosomal RNA genes (rDNA) in eukaryotes. This silencing is brought about by NoRC, a SNF2h-containing remodeling complex, that recruits chromatin modifying activities