FEATURES

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Teratomas and Pluripotent Stem Cells: Clinical Implications

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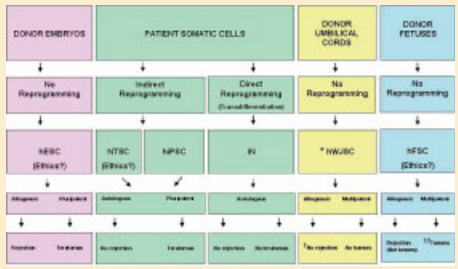
Although basic research on pluripotent hESCs, hiPSCs and NTSCs has been aggressive their clinical application has been slow. One of the major clinical problems of pluripotency is the induction of teratoma formation from left-over rogue undifferentiated pluripotent cells residing in the differentiated cell population. To date several studies have shown that even a few such undifferentiated cells can induce teratomas in immunodeficient animals. The laboratory methods used thus far that attempted to eliminate these rogue undifferentiated cells have been the use of cytotoxic antibodies, pluripotent apoptotic agents, cell-suicide induction, removal of the SSEA-labeled cells using FAC/MAC sorting, density gradients, prolonged differentiation *in vitro* to encourage the rogue cells to complete their differentiation, and delivery of the differentiated cells after encapsulation. However, none of these methods have been adequately tested and safety has not been confirmed in large controlled animal or human studies. While such studies are in progress Fong et al explored the therapeutic potential of stem cells from other embryonic sources such as the human umbilical cord Wharton's jelly. The authors show that these hWJSCs are multipotent, hypoimmunogenic and do not induce teratomas in animal models. They propose that hWJSCs may be a useful adjunct stem cell source for cell based therapies and cord blood banking.



Targeting Chromosomal Instability in Breast Cancer

Rebecca Burrell, Nicolai Juul, Stephen Johnston, Jorge Reis-Filho, Zoltan Szallasi, and Charles Swanton

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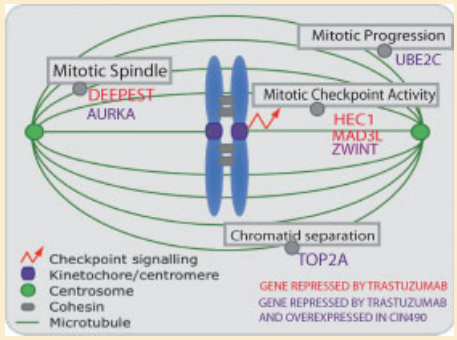
Intrinsic and acquired drug resistance represent a major obstacle to the successful treatment of cancer. Tumour heterogeneity and chromosomal instability (CIN) are likely to be important determinants of drug sensitivity, for example, CIN is associated with taxane resistance but exhibits relative sensitivity to platinum based therapies in ovarian cancer. A meta-analysis of patients with HER2 positive breast cancer suggests there is considerable heterogeneity in tumour CIN status between patients. Burrell et al propose a model examining the effect of the distribution of CIN in HER2+ breast cancer in determining the response profiles seen in clinical trials for this patient group. Evidence indicates that HER2 inhibitors may target CIN cells, consistent with evidence that HER2 signalling may be associated with chromosomal instability. Given the relationship between CIN and resistance to taxanes, together with data demonstrating that EGFR/HER2 blockade may reverse CIN in cancer cell models, a biological rationale is presented that may explain the additive benefit witnessed in clinical trials with the combination of taxanes and HER2 receptor blockade in HER2+ breast cancer. This model suggests that the distribution of tumour CIN status should be considered when designing combinatorial therapeutic regimens and when interpreting clinical trial data.



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Cancer Cell Invasiveness

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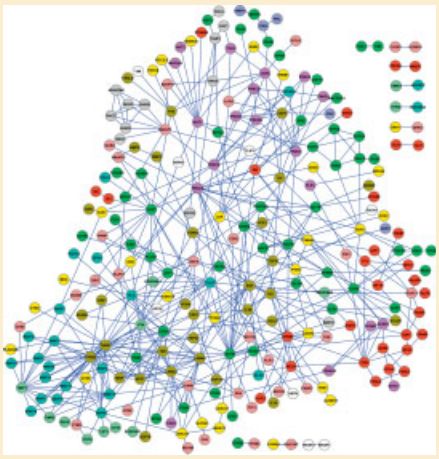

Invasion is an essential step for cancer metastasis. Much is unknown about the mechanism of invasion in different cancers and the signaling pathways that regulate it. Identification of cancer invasiveness signaling networks is needed for targeted therapies of cancers, including combination and personalized therapies. There is a substantial gap between the many proteins and microRNAs that modulate cell invasiveness in different cancer cells and the few signaling pathways experimentally verified to control cancer invasiveness. Kan et al. have brought together these various proteins and RNAs because there was no publication that filled this important gap. They have noted 589 proteins, 28 microRNAs and one long non-coding RNA that modulate invasiveness in different cancer cells. Intriguingly, 44 proteins stimulate invasiveness in some cancer cells, but suppress it in other cancer cells. Virtually all of the proteins that show experimentally verified activation or inhibition effects on, or binding interactions with, each other are linked together in a single network, in a "hub-and-spoke" architecture. When viewed together, the data reveal trends toward anticipated future results and show gaps in what is known about cancer invasiveness signaling.

Optimizing Stem Cell Culture

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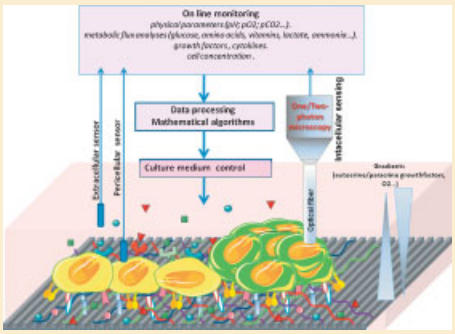

A fundamental problem in stem cell culture is the control of stem cell fate. Stem cells always balance between self-renewal and differentiation. Accumulative evidence demonstrates that stem cell fate in culture is not only controlled by the composition of the medium but is also governed by the atmosphere, the culture substrate, and cell-cell interactions. In addition to growth factors or cytokines, oxygen is now considered as a major soluble factor. The importance of rigidity, stiffness, and geometry of cell culture substrate leads one to consider mechanotransduction as a major determinant of cell signaling. Optimized, well-defined stem cell culture conditions are critical both for basic research and for stem cell-based therapies. This requires the development of new sensor and monitoring devices acting at the pericellular and intracellular levels. One or two-photon fiber microscopy techniques could be explored for pO_2 sensing using exogeneous or endogeneous fluorophores in the cytoplasm. The optimization of stem cell culture conditions is a driving force for the development of new technological devices, which may have broader basic and clinical repercussions for stem cell-based therapies.