RESCUE Conference
Stockholm 29 September - 1October 2008
Chairpersons: Clemente Cillo, Basel CH and Ben Bowen, Hayward-CA, USA

Wednesday October 1
9:00 - 12:30 hours

4. Application of existing cell lines/banking related issues
Industrial as well as academic applications: drug discovery, drug testing and drug screening

After a few preliminary remarks, the session was opened by the co-chairmen Ben Bowen (Biolog, Hayward-CA, USA), with the presentation of the Commercial Association Officers presenting at the exhibition stands of the meeting.

In the cell lines: from in-vitro to cellular differentiation

Then the scientific session, chaired by Clemente Cillo (Basel, CH), started with Dave Hay (Edinburgh, UK) talking on the requirement of Wnt3a along hepatocytic differentiation from human embryonic stem cells (hESCs). Wnt3a, one of a closely –related Wnt family, is a secreted ligand for members of the Frizzled family of receptors. These proteins have been implicated in oncogenesis, and in coordinating several developmental processes, including regulation of cell fate and patterning during embryogenesis as well as highly regulated patterns of cell division, self-renewal and differentiation role in hESCs. Though hESCs have been considered as a valuable source of pluripotency primary cells, however, to date their homogeneous cellular differentiation to specific cell types in in-vitro has proven difficult.

In this scenario, Dave Hay exemplified the scope of Wnt3a signalling by highlighting the essential role of Wnt3a is differentially expressed at critical stages of human liver development in vivo as well as in-vitro. He went on to discuss that Wnt3a promotes hepatocyte –like cell (HLC) functionality and facilitates clonal plating of hESCs capable of hepatic differentiation and function. Furthermore, according to the data presented, Wnt3a facilitates in vitro induction of hepatic differentiation in hESCs to produce hapatocytes potentially useful for the clinic.
HSCs (Hematopoietic Stem Cells) were the first identified, and are therefore the most studied, adult stem cell. For several decays, these stem cells have been used in various

clinical settings. Yet our knowledge of how to develop an universal cell line to study the stem-cell differentiation is limited. For example, neuronal-glial pluri-potent stem cells of human embryonic origins can grow as neurospheres in the presence of growth factors. However, human adult neuronal stem cells are difficult to expand under similar condition. It's postulated that glia cells may play an important role to support the expansion, survival and functions of such (precursors) neurons.

In this setting, Una Chen (Giessen, DE) has reported on the characterization of a "tet-on" glia O2A precursor cell line established from the reverse tetracycline-transactivator (rtTA)-SV40 T antigen double transgenic mice, aiming to develop an universal supporting glia cell line. In culture, withdrawal of doxycycline prevents proliferation and the cell line undergoes apoptosis.

Differentiation into type-2-astrocytes and oligodendrocytes can be induced in culture, in the absence of doxycycline, and with epithelial stem cells lines secreting hIL3 or hIL6. In contrast, no maturation into progeny was observed when hCNTF-secreting cell line was used as the co-culture partner under the same conditions. Tet-on glia O2A precursor cells implanted to sites of transacted sciatic nerve of adult mice and kept in the precursor stage by feeding mice with doxycycline containing drinking water are not toxic to the implanted hosts and can enhance the recovery of damaged motor nerves. In this preliminary attempts, they have shown that the cell line have capacity to enhance the repair-generation of damaged adult peripheral neurons when implanted in vivo.

After the coffee break the session, chaired by Ben Bowen, went on with Ian Cotgreave (Astra-Zeneca-Södertälje, SE), Margit Stadler (Eppendorf Biochip-Hamburg, DE), Ben Bowen (Biolog, Hayward-CA, USA).

Transforming progenitors transcription factor into prognosis factors

Several studies focused on the role of developmental pathways [Hedgehog, BMP, Notch, Wnts, and HOX] in tumor biology. As expected from proteins involved with cell identity and proliferation, deregulated HOX gene expression in adult tissues is often correlated with human solid tumors, as it is well described for hematopoietic

malignancies. Clemente Cillo (Basel-CH, Naples-IT) have reported for the first time on the identification of developmentally related HOX transcription factor, HOX A13 (located on chromosome 7), as a new marker of hepatocarcinogenesis.

Selection of hepatocellular carcinomas through HOX A13 hyper-expression allows the transcriptome identification of a specific cell cycle, nuclear pore and severe prognosis HCC phenotypes. Furthermore detection of HOX D13 homeoprotein (located in the HOX cluster on chromosome 2) expression in 79 human cancer phenotypes highlights a prognostic role for HOX D13 protein in pancreas carcinogenesis. HOX A13 and HOX D13 are close related paralogous HOX genes whose deregulation in liver and pancreas carcinogenesis account for a role of paralogous group 13 HOX genes in the potential reversion of a common liver-pancreas progenitor cell gene program.

Stem-cell-related patent issues

The last speakers of the morning session, Marianne Levin and Asa Hellstadius, Professor and doctoral candidate in Private Law (Intellectual Property Law) respectively, (Stockholm, SE), described the ethical considerations and ownership related to the patenting of stem cells. They stated the following:

-Early publication of research may preclude patenting.

-A patent right gives the holder choices and responsibilities: free use, licensing.

-In the patenting of biological material, especially stem cell inventions, a number of hurdles must be passed: ethical considerations (Europe), novelty, inventiveness.

-The situation on hESC patenting is depending on national policies, as well as the European patent office.

-The opposition procedure establishes possibilities for third parties to react towards improper patents.

-There is no exemption for use of inventions in research.

(A detailed report can be found using this link INSERT Levin+Hellstadium+Rescues+2008.pdf" doc here)

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