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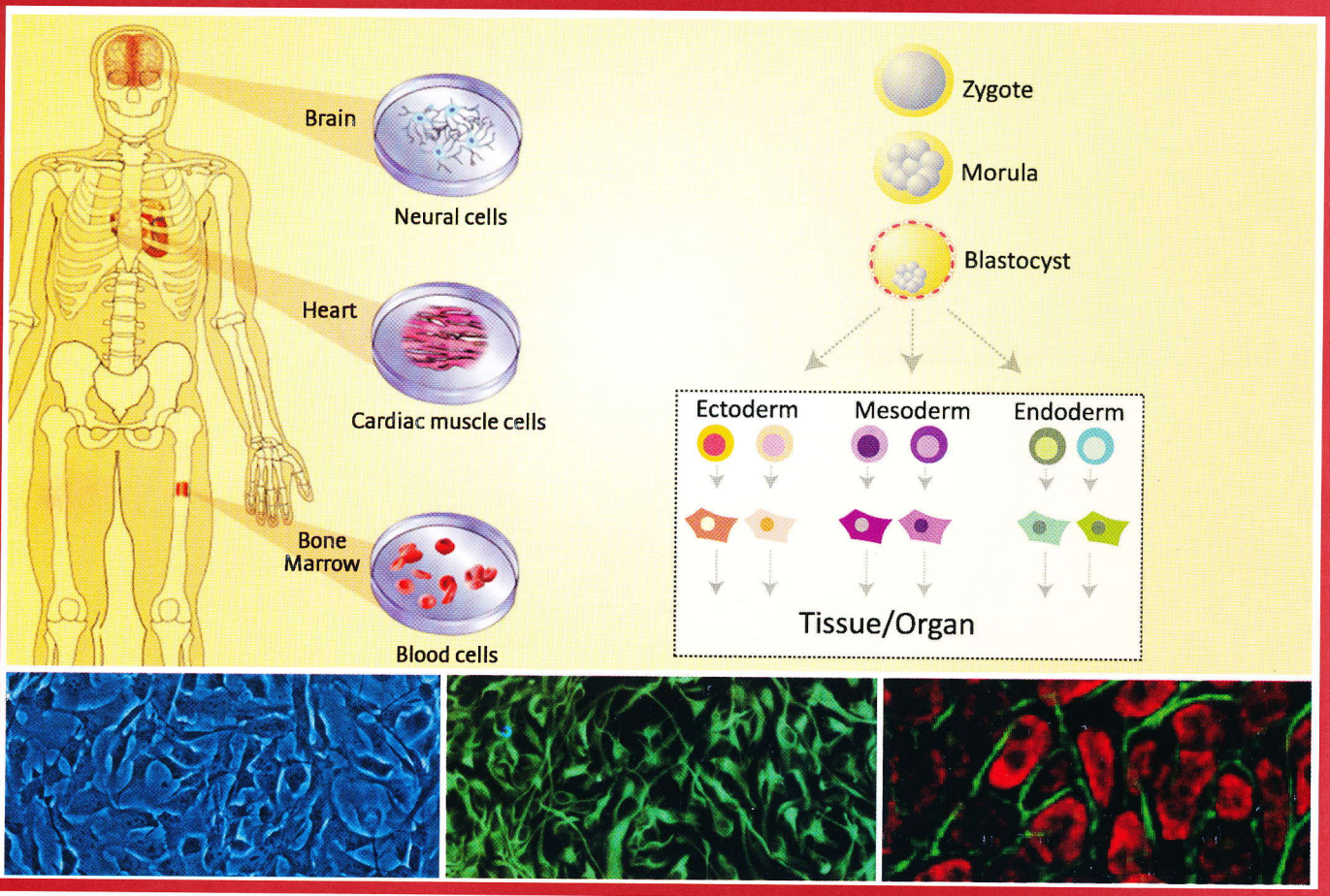

Focus on Stem Cell Proteomics

Editors:
Hana Kovarova, Suresh Jivan Gadher, Bernd Wollscheid

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Editorial

Focus on Stem Cell Proteomics

Advancements in stem cell research over the past decade have sparked incredible interest, imagination and hopes as the possibilities for stem cell applications appear to be endless, and yet unpredictable. On the one hand, there is enormous scientific and medical potential; on the other hand, there are considerable challenges in translating such potential into viable cell-based therapies for addressing conditions such as Alzheimer's disease, stroke, heart diseases, arthritis, blindness, diabetes or spinal cord injury. Independently, the proteomic technologies have progressed over the last decade allowing proteome studies in all areas of biological research and enabling now in principle the comprehensive analysis of stem cell expressed proteins in time and space.

As these two distinct fields – 'proteomics' and 'stem cell biology' evolve; diverging rather than converging progression has been observed. At the juncture of this dilemma lies the fact that hurdles in stem cell research are immense and proteomics may be able to help resolve some of the difficulties as well as reveal proteins critical to stem cell differentiation, maintenance and specific lineage determination. Such a merger of stem cell research and proteomic expertise seems essential and could be very productive possibly leading to a solution. Currently, opportunities for experts from proteomic and stem cell fields to meet are limited and the distinct lack of communication and exchange of ideas is apparent. This is even more evident when scientific journals are examined, highlighting that crucial scientific finding may be missed or key technologies or methodologies may remain un-optimised, thus preventing synergistic progress which may lead to much awaited medical breakthroughs. More importantly, effective data evaluation and correlation across several laboratories or research institutions currently engaged in application of proteomics into stem cell research would offer tremendous potential toward perhaps the most important expected application of human stem cells – generation of cells and tissues that could be used for cell-based regenerative and reparative therapies of diseases that plague mankind.

Collaboration between the two specialities can also be extremely beneficial as judged by the current trend where financially driven biotechnology companies have started to collaborate for mutual benefits and end-point results. An example of one such collaboration is the use of stem cell transplantation technology and proteomics expertise to identify proteins expressed in brain during repair following the grafting of neural stem cells. Proteomics has already helped identify markers in the blood to diagnose stroke, while stem cell experts have observed functional recovery in animal models of the disease following transplantation with neural stem cells. The combined approaches may enable the discovery of new therapies or targets related to this condition.

Since our understanding of many of the basic cellular processes underlying stem cell self-renewal, maintenance and differentiation are still very limited, it is essential that we expand our knowledge and understanding at protein level if stem cell research is to reach its full potential. Currently, there is a growing need in stem cell biology for methodologies and technologies that may help unravel the mysteries of self-renewal and differentiation. Proteomic workflows have already enabled the characterisation of surface and intracellular proteins of cultured cells as well as understanding 'cell–cell' or 'cell–matrix' interactions plus the study of proteins secreted by cells. Characterisation of stem cell proteins with a view to defining subset of stem cells or identifying differentiation specific proteins as a benchmark for intermediate or terminal steps in stem cell differentiation has already begun for primary cells as well as cell lines. Although the proteomic interrogation of stem cells is still in its infancy mainly due to technological limitations in combination with limited availability of stem cell samples, it is already feasible to generate relative quantitative stem cell protein maps of sub-compartments and to derive partial functional protein interaction networks. Since proteomic studies are able to detect such protein–protein

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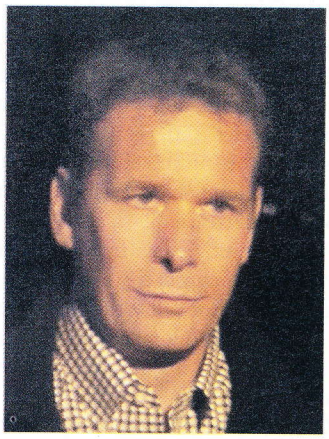

Bernd Wollscheid

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interactions as well as post-translational modifications, novel sophisticated proteomic technologies at the disposal of stem cell researchers may help pave the way for a better understanding of stem cell functionalities at the protein level. More importantly, proteomic technologies have evolved due to needs rather than routine and proteomics can help to overcome confusion, raise cautionary alerts or shed new light on caveats of stem cell biology or indeed, explain inconsistencies.

Tentative steps to highlight the benefits of joint approaches in stem cell and proteomics research were taken at a conference organised in Hinxton, Cambridge, UK in March the 22nd–23rd 2009 entitled, "Perspectives in Stem Cell Proteomics". With this promising progress in mind and to facilitate interactions between specialists in proteomics and stem cell biology, we have embarked on a new initiative of putting together a Focus Issue on Stem Cell Proteomics to highlight some of the commonalities as well as diversities of proteome biology of stem cell research. This issue covers contemporary and emerging areas in stem cell research by publication of review, research papers presenting novel findings or hypotheses based on original data, as well as technical brief. The scope related to stem cell proteomics is broad and includes topics in stem cell biology covering basic and regulatory aspects of embryonic and adult stem cells, induced pluripotent stem cells, specific lineages, biotechnology, translational studies into disease models, as well as diseases such as cancer where stem cell-specific behaviour play a key role. We have but touched just a few of the above in this issue. Original articles in this issue are expected to provide novel insights based on latest research data and which discuss emerging issues and controversies. One key aim is that studies outlined and their cross referencing may help accelerate studies in the field, by providing practical protocols and techniques of use for both novice and established investigator.

Proteomic technologies have progressed over the last decade allowing proteome studies in all areas of biological research and enabling now in principle the comprehensive analysis of stem cell-expressed proteins in time and space.

The overview by Rebekah Gundry et al. presents an interesting and important perspective on the role of proteomics in stem cell research. A very thorough list of large-scale proteomics experiments is presented, giving a good view of global studies to this point. The authors have also taken great care in discussing the criteria for pluripotency and provide a detailed analysis of the current view of the pluripotent cell proteome. Importantly, they highlight the heterogeneity which, besides the practical implications, represents significant challenges to interpreting proteomic data. Certainly, there is one area – the cell surface subproteome that would especially benefit from enhanced research efforts.

Proteomic technologies have the potential of playing a critical role in revolutionising stem cell research. Multiple signalling pathways have been suggested as a prerequisite for the maintenance of undifferentiated hESCs despite the fact that the underlying molecular mechanisms induced by these pathways remain poorly understood. The results of the study by Zoumaro-Djayoon et al. emphasised that FGF-2 plays a key role in signalling pathway controlling the maintenance of undifferentiated hESCs through the phosphorylation of: (i) FGFRs and other RTKs which in-turn activate proteins belonging to different downstream signalling pathways, such as ERK, Wnt and PI3K/AKT, (ii) cytoskeleton associated proteins, and (iii) pluripotency-associated proteins and transcription regulators. Such data may serve as a resource for future investigations into stem cell maintenance.

Data from Farina et al. provide the first secretome profiles of mESC during cardiac and neural differentiation and identify new potential mediators of stem cell microenvironment during targeted differentiation where as Hughes et al. highlight the growth of hESCs and illustrates the utility of employing complementary protein fractionation methods for the analysis of complex extracellular matrix samples in order to elucidate components essential for hESC maintenance.

An interesting paper by Maltman et al. describes a top-down label-free LC-MALDI-TOF/TOF quantification approach to screen the very-low-molecular-weight proteome, the peptidome of neural progenitor cells and derivative populations to identify potential neural stem/progenitor cell biomarkers. Interestingly, the findings demonstrate proteomic complexity which underlies the limitations of major intermediate filament proteins and which has been long established as neural markers.

Clinical conditions to which we have currently no answers or a cure such as Alzheimer's disease, Parkinson's disease and senile dementia, could benefit from new insights at the protein

level. One such interesting study includes that by Chaerkady et al. They have looked at the oligodendrocytes and have managed to identify several novel potential markers and putative proteins associated with oligodendrocyte lineage cells. Such proteins within the oligodendrocyte lineage are potential candidate markers for novel therapies for diseases with demyelinating process.

Cancer stem cell-related research is an emerging field and looked upon with excitement and expectations for causative and curative outcomes. The study by Dai et al. provides interesting information regarding the influence of γ-secretase inhibitor treatment on glycosylation pattern in glioblastoma multiforms. Better understanding of such processes may certainly lead to an improved understanding of drug mechanism and drugs utilised in the treatment of the disease.

There is no doubt that the stem cell niche which comprises stem cells, stromal cells, soluble factors, extracellular matrix constituents and vascular networks is extremely important regulatory environment. Ji et al. report the extracellular (secretome) and adherent plasma membrane proteomes of basal and mammary stem cell luminal progenitor and mature luminal cell lines using GeLC-MS/MS-based proteomic profiling. The study revealed a distinct switch in components modulating Wnt and ephrin signalling, and integrin-mediated interactions among the three cell subpopulations.

An enhanced chemically defined SILAC culture system for quantitative proteomics study of hESCs was the focus of study by Wang et al. The authors described a new chemically defined SILAC-medium and a novel protocol allowing significantly higher hESCs yield. Hence, such a system could provides a new platform that can be readily adapted by laboratories for further comprehensive quantitative analysis of stem cells as well as induced human pluripotent stem cells.

Recent breakthroughs in the field of stem cell research such as the finding that cells may be reprogrammed to a pluripotent state by bringing in a few stem cell-specific transcription factors and newer approaches seen here may help all researchers significantly. New data sets regarding cellular protein changes, surfaceome, secretome, as well as phosphorylation dynamics in differentiating pluripotent cells including knowledge of the intricate cross-talk between signalling pathways in pluripotent stem cell differentiation may help future exploitation in therapeutic settings for the benefit of mankind. It is evident that a happy marriage or merger of proteomics and stem cell research is certainly the way forward if we are to reap the benefits of recent advances in stem cell research.

We hope you find this collection of articles beneficial and stimulating and we would like to emphasise that this issue is the outcome of excellent contribution from many authors and extraordinary efforts of selected reviewers who dedicated their time and expertise to scrutinise and quality control the submitted manuscripts. Our sincere thanks go to all of them for their invaluable input – without which this 'first ever' issue of 'Focus on Stem Cell Proteomics' would not have been conceived.

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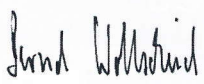

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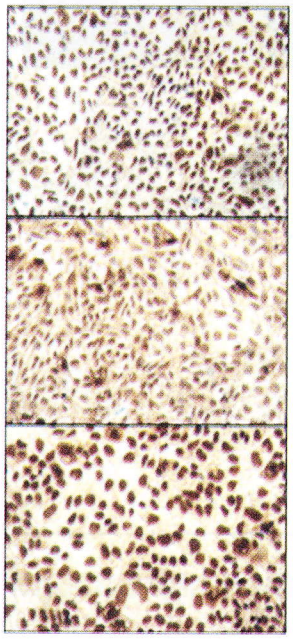

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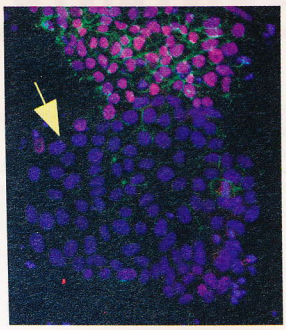

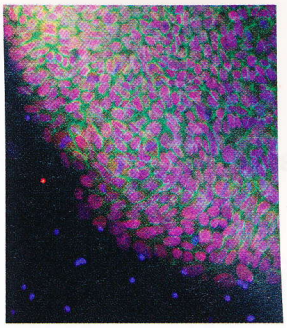

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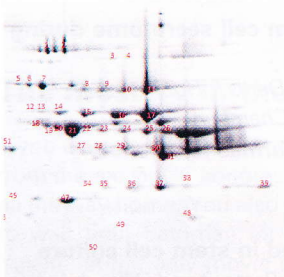

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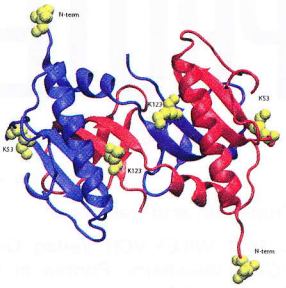

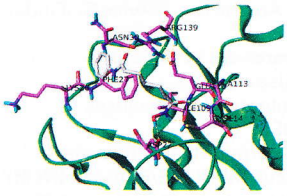

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