Cancer Stem Cells and Intrinsic Disorder

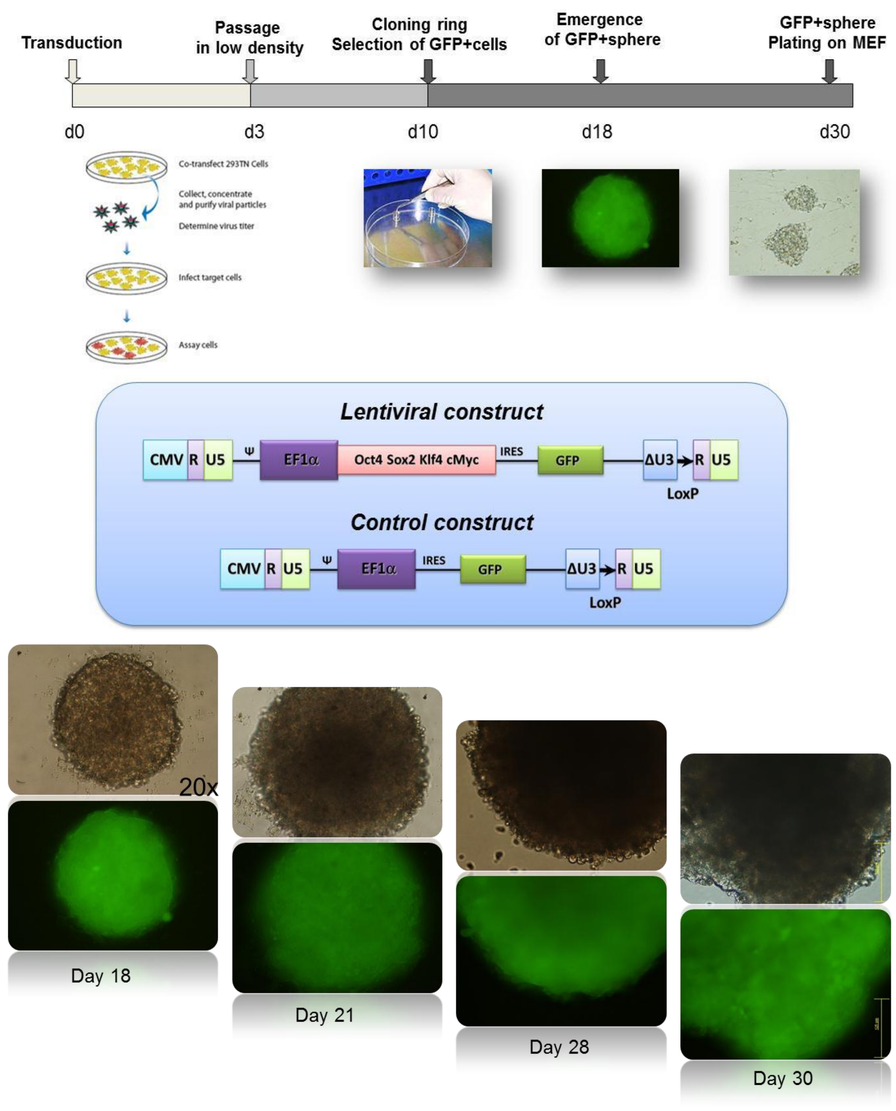
Hadas Raveh-Amit[1], Virag Vas[2], Sara Berzsenyi[1], Sara Santos-Franco[2], Andras Dinnyes[1,2]

[1]Biotalentum Ltd, [2]Molecular Animal Biotechnology Laboratory, Szent Istvan University, Godollo, Hungary

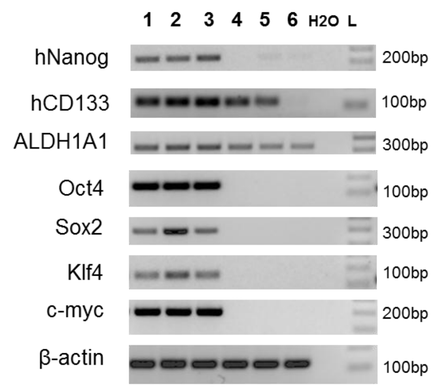
Abstract

Cancer stem cells (CSCs), a small fraction of tumor cells with the capacity of both self-renewal and unlimited slow proliferation, are often resistant to chemotherapy and radiation and thus considered to be responsible for continuously supplying new cancer cells. Since in vivo detection of CSCs remains challenging, in vitro models are highly desired. Here, we generated a CSC model (termed cancer stem-like cells; CSLCs), by stably expressing the four pluripotent transcription factors, Oct4, Sox2, Klf-4, and C-myc, in lung adenocarcinoma cancer cells and maintaining the cells in chemically defined media. CSLCs exhibited spheroid structures, altered gene expression and drug resistance in accordance to CSCs characteristics. Next, we aimed to gain mechanistic insights as to the signaling regulatory pathways leading to cancer stem cells properties. Our bioinformatics analysis shows that the reprogramming factors and most of the CSC-associated proteins are enriched in intrinsically disordered proteins, i.e. proteins that have no single well-defined tertiary structure in their native, functional state. Comprehensive analysis revealed that the disordered properties of these proteins may result in their altered function, potentially contributing to cancer development and potentially opens a new avenue in cancer research and drug screening.

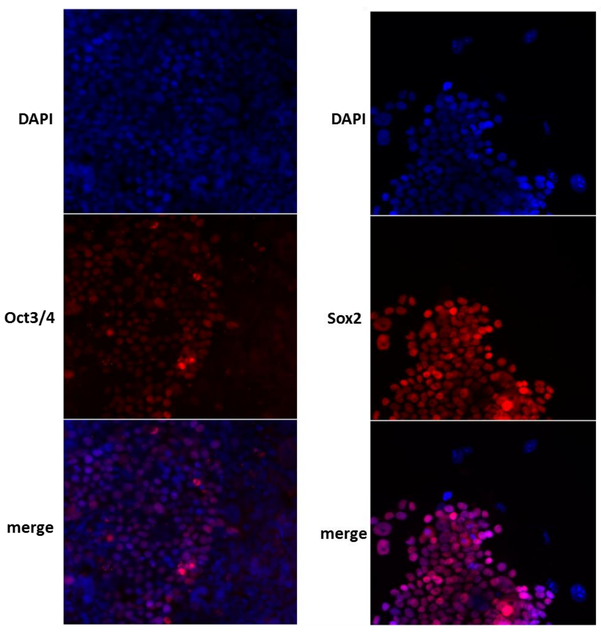
Transduction of the four OSKM Yamanaka factors in lung cancer cells



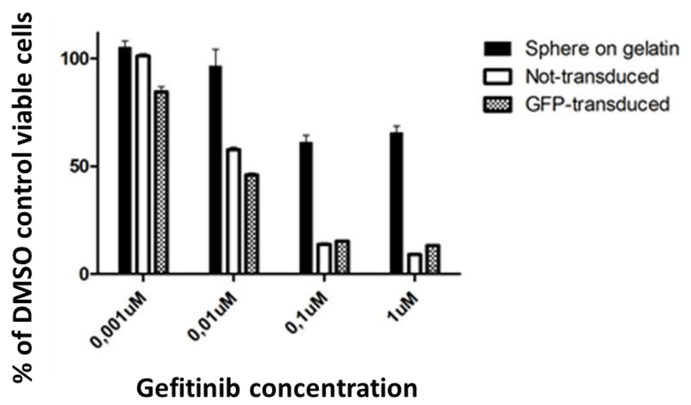
The OSKM-transduced lung cancer cells express the exogenous mouse pluripotent factors, endogenous human pluripotent factors and cancer stem cell markers

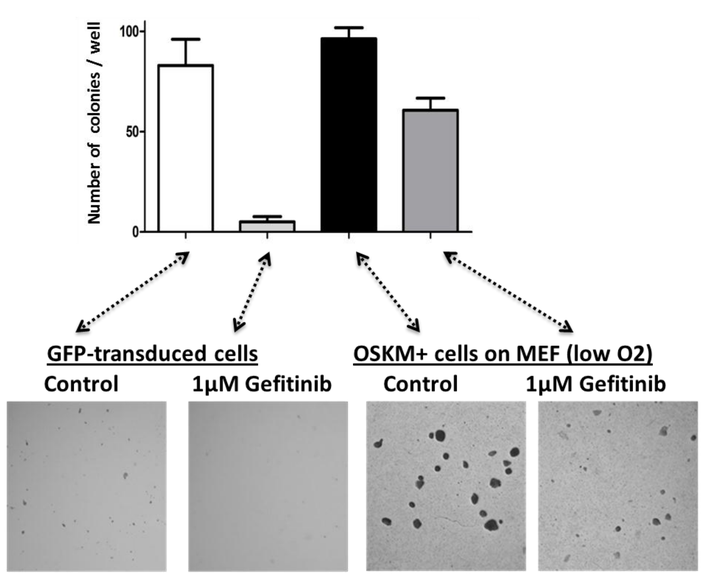


1: OSKM Sphere clone on MEF low O2
2: OSKM Sphere clone on gelatin low O2
3:OSKM Sphere clone on MEF normal O2
4: Not-transduced HCC827 cells on low
5: GFP-transduced HCC827 cells on low O2
6: HCC827 parental cell on normal O2
7: H2O
L: ladder

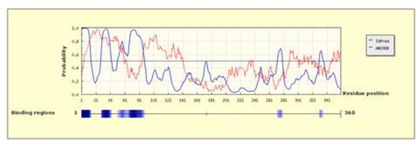


The OSKM-transduced lung cancer cells are more resistant to Gefitinib-induced cell death than the parental cancer cell line

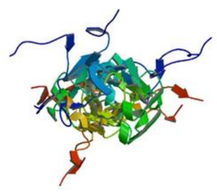




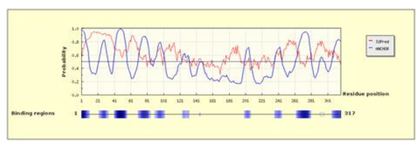
The Yamanaka factors contain intrinsically disordered regions (IDRs) in functional domains



Oct-4

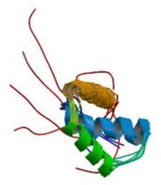


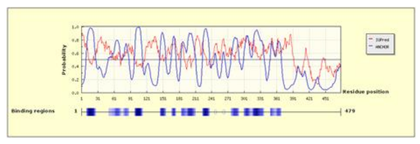
Solution structure of Oct4 pou-homeodomain



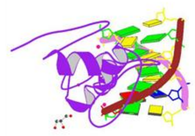
Sox-2

Solution structure of the HMG box DNA-binding domain of human stem cell transcription factor Sox2

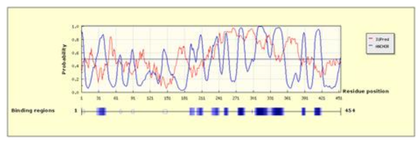




Klf-4

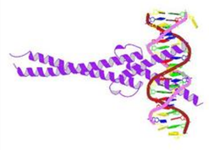


Crystal structure of the zinc finger domain of Klf-4 bound to its DNA target



C-myc

Crystal structure of Myc-Max recognizing DNA



Acknowledgments

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