ASSESSING INTERACTION NETWORKS WITHIN INDUCED PLURIPOTENT STEM CELL EXPANSION BIOPROCESSING TO ELUCIDATE COMPLEXITIES OF CELLULAR PHENOTYPE AND DEVELOP ADVANCED PROCESS CONTROL STRATEGIES

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Insights into intracellular regulation of pluripotent phenotype and response to environmental stimuli have revealed complex interaction networks consolidating the nexus of gene expression, epigenetic regulation, metabolic pathway activity, cell cycle dynamics, and structural organization. The subtleties of this network are further complicated by activity introduced through induction of pluripotency from somatic phenotypes, including increased population heterogeneity, age-related genetic aberrations, abnormal epigenetic marks, changes to regulation of cell cycle, and metabolic differences. The environmental niche plays a critical role in regulating the cell population. Mechanical forces, population organization, growth factors, inhibitors, and nutrients within the niche heavily influence regulation of phenotype. Within the context of the bioprocess, inadequate control over the intersection of these dynamics within a batch and over successive passages translates to abnormal and heterogeneous phenotypes, clonal dominance activity, immunogenic potential, tumorigenic advantage, and altered functional characteristics in the downstream therapeutic cell product. Recent studies by our group have elucidated unique metabolic pathway activity of human iPSCs cultured in dynamic suspension under varied oxygenation conditions. The results show distinct metabolic trajectories between conditions, coupled with significant differences in proliferation, aggregate morphology, and nutrient consumption. Coupled with process data, investigation of metabolism shows important interplay between cell activity and the dynamic state of the in vitro process environment. Our datasets provide compelling evidence to suggest manipulation of pluripotent phenotype through alteration of process conditions. Integration of additional omics platforms will aid in building models to describe the interplay between modulation of process conditions and cellular response, guiding advanced process control and intervention.

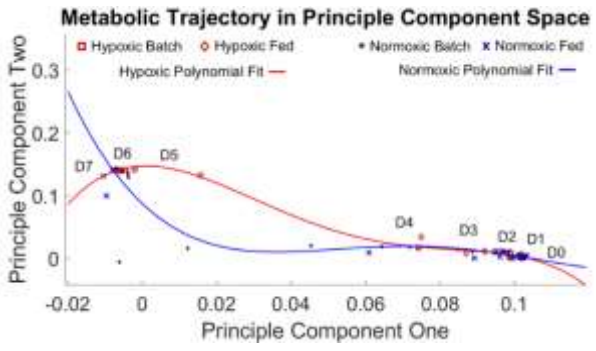

Figure 1 – Computational modeling of distinct metabolic trajectories in iPSC populations as a result of oxygen availability.

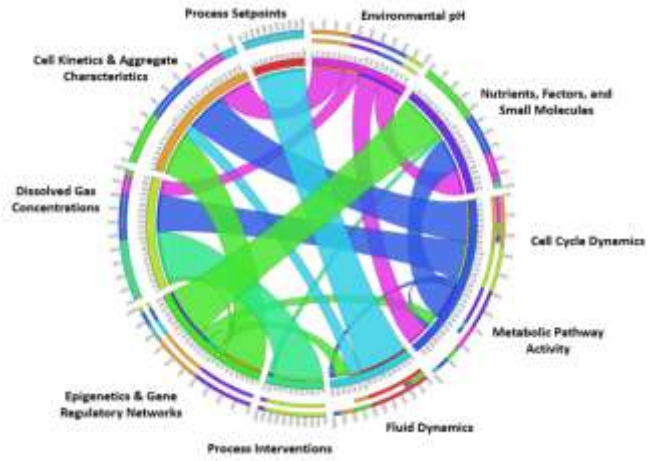

Figure 2 – Interaction network encompassing bioprocess parameters and intracellular dynamics.