Contents

Introduction

To provide a comprehensive background for the following chapters that focus on the interaction of human mesenchymal stromal cells (hMSCs) with multiple myeloma (MM) cells, this

Aims

This project defines these aims:

- Characterize the interaction between myeloma cells and mesenchymal stromal cells
- Develop methods
- Face the challenge of time-dependent cell adhesion through
- Provide tools to analyze multidimensional cell adhesion data

Summarising Discussion

Time-Lapse Microscopy Added Intuition to Exploratory Cell Biology

- When starting this project, dissemination has not been the main topic. - Surprisingly, Time-lapse identified detaching cells - Hence, Time-lapse proved pivotal for this project, shifting the focus onto in vitro dissemination.

Microscopy holds vast amounts of information. Cell movements themselves add a lot more info. Time-lapse video has proven invaluable for exploratory cell biology

the most important key insight on the mechanism of dissemination identified by timelapse was Cell Division - further insights were multiple time measurements

measuring the minimum time for detachments to begin, or the time required for daughter cells to re-attach to the hMSC monolayer. Such mechanistic insights

Other methods like RNAseq and survival analysis did provide molecular and clinical connections, time-lapse microscopy documented cell interactions as-is, but allowed for a deep and intuitive understanding of cryptic molecular data, placing the conclusions into a context that answer key questions about potential and limits of this study, such as the aggregation behavior of INA-6 cells.

Novel Methods of Isolating Adhering Subpopulations

cite all those methods for cell isolation! - Turning around wellplates: Doesn't allow isolation, just quantification - The author did not show all his washing experiments - Washing is very bad (data not shown): Highly dependent on user: position of cell on well bottom (border cells receive less force), position of pipette tip in well (depth, angle and position on bottom) - This motivated us to explore more reproducible methods

It's a challenge: either quantify cell population, or isolate them! - It's better to specialize in one method, than to do both poorly - Well Plate Sandwich Centrifugation is badly suited for quantification, but possible - we switched to developing V-well adhesion assay for quantification - We realized, V-well isolation allows both ultra precise quantification and isolation of small

amounts of cells! - unmatched precision through centrifugation, no washing - But V-well pellets comprise only few cells requiring a lot of technical replicates and an untiring pipetting hand

The Well Plate Sandwich Centrifugation (WPSC) used two different techniques to dissociate MA-INA6 cells from the hMSC monolayer. This had no impact on the ratio of isolated MA-INA6 to nMA-INA6, since nMA-INA6 isolation was performed prior to dissociation using the same protocol consistently. We tried this to test if MACS was really necessary, after all it is costly, time-consuming, introduces an antibody bias and requires cell cold-treatment during antibody: Strong pipetting (*'Wash'*) and repeated Accutase treatment followed by magnetic activated cell sorting (*'MACS'*).

Outlook: High-Value Research Topics for Myeloma Research

As an Outlook, the Author lists research topics arising from this work that have great potential for breakthroughs in myeloma research.

Cell Division as a Mechanism for Dissemination Initiation: The author describes how the detachment of daughter cells from the mother cell after a cycle of hMSC-(re)attachment and proliferation could be a key mechanism in myeloma dissemination. This mechanism was shown in other studies of extravasation. The author sees great potential in this mechanism as a target for future research. It is probably under-researched due to requirement of sophisticated time-lapse equipment, yet the simplicity of detachment through cell division is intriguing through its simplicity. It implies asymmetric cell division. Cancer cells are known to divide asymmetrically, e.g. moving miRNAs to one daughter cell.

Time as a Key Parameter: The area Thermodynamics of started with scientists measuring how long it takes for gases to cool down. The author claims, by measuring the time it takes for cancer cells to detach could lead to breakthroughs in research of myeloma dissemination.

- Cell adhesion is highly time-dependent. - Cell detachment is required for metastasis and dissemination -

key mechanistic insights

measuring the minimum time for detachments to begin, or the time required for daughter cells to re-attach to the hMSC monolayer. Such mechanistic insights

The author recommends high time resolutions, e.g. 1 frame every 15 min, which is a high resolution for common live cell imaging when compared to Purschke et al. (2010). Time-resolution was mostly limited by available disk space. Investing into more hard drives is worth it, since

Lists of Adhesion Gene Associated With Prolonged Patient Survival: The author lists adhesion genes that are associated with prolonged patient survival. These genes are highly

expressed in myeloma samples from patients with longer overall

Semi-Automated Analysis was Required for Establishing Methods

In this work, the development and publication of innovative *in vitro* methodologies (Well Plate Sandwich Centrifugation and V-Well adhesion Assay) necessitated the adoption of semi-automated data analysis tools. These novel methods introduced complexities that span multiple experimental parameters, making the results multidimensional. This demanded precise, efficient and standardized data handling capabilities which were facilitated by tools like `plotastic`.

Inherent Multidimensionality of Adhesion Studies: Cell adhesion studies often involve multiple independent parameters, posing significant analytical challenges. Two critical dimensions are particularly notable: *'Subpopulation'* and *'Time'*. Analyzing cell adhesion often involves isolation of adherent and non-adherent subpopulations, effectively introducing *'Subpopulation'* as a vital dimension in the dataset (Dziadowicz et al., 2022). This study specifically categorized cells into three levels of MSC-interaction: CM-INA6, nMA-INA6, and MA-INA6. Furthermore, the dynamic nature of cell adhesion processes is profoundly influenced by the factor *'Time'*, making it a crucial experimental parameter for investigation (Rebl et al., 2010; McKay et al., 1997; Bolado-Carrancio et al., 2020). This work includes extensive time-lapse microscopy experiments utilizing a high time resolution (1 frame every 15 min), similar to those time resolutions used by Purschke et al. (2010). This precision was required for key mechanistic insights on hMSC-INA-6 interaction dynamics. These included identifying rolling movements of nMA-INA6 daughter cells around MA-INA6 mother cells, measuring the minimum time for INA-6 detachments to begin, and measuring the time required for daughter cells to re-attach to the hMSC monolayer, etc. Next to mechanistic insights, adhesion time played a crucial methodological role in this study as well: During the V-Well adhesion experiments, we did not know initially how long INA-6 cells required to form strong adhesion with hMSCs before pelleting nMA-INA6, but required a timepoint with hour precision to capture detachments after cell division that was accelerated through prior cell cycle synchronization at M-Phase.

The extensive facetting features of `seaborn` and `plotastic` were essential for visualizing these multidimensional datasets, allowing for quick exploration of the data (Waskom, 2021).

Further Contributions and Remedies to Multidimensional Complexity: In addition to *'Subpopulation'* and *'Time'*, this study faced additional layers of complexity that were managed through semi-automated analysis.

Experiments typically involved at least three biological replicates and corresponding technical replicates. Although replicates were not treated as independent variables – instead serving for displaying variance – they can add substantially to the data management workload. In this

work, semi-automation nullified the manual burdens of handling replicates: `pandas` was used to automate aggregation of technical replicates into means after removing technical outliers thorugh z-score thresholding, while the jupyter notebook format allowed for reviewing filtered data for specific data losses. The removal of technical noise was especially relevant for qPCR data, where low gene expression can lead to sudden increase in Ct value (non-detects). In fact, the decision to remove or impute non-detects is under active discussion, however, available algorithms are hard to understand for non bioinformaticians, but also do not separate biological from technical variance, which is considered bad practice by Motulsky (2018) (McCall et al., 2014; Sherina, 2020). Semi-automation also nullified the burden of handling biological replicates: The automatic aggregation of datapoints during plotting is a key feature of `seaborn`, on which `plotastic` was built. Without such automation, calculating means and standard deviations for simple barplots would have required extensive manual computation in *Microsoft Excel*, or tedious plot configurations in *Graphpad Prism* due to limited facetting functionality of multiple variable tables (*GraphPad Prism 10 User Guide*, 2024).

Replicates can expand datasets as this factor comprises a lot of levels. Similarly, the factor *'Gene'* multiplied the dataset by a total of 30 genes when validating RNAseq data with RT-qPCR. With three subpopulations, one timepoint, eleven biological replicates, and three technical replicates, the qPCR dataset used in this study grew to 2970 datapoints to be statistically analyzed and visualized. This is a manageable size for manual analysis, but the effort involved illustrates the definition of semi-big data.

Methodological variability also introduced additional dimensions: The Well Plate Sandwich Centrifugation (WPSC) used two different techniques to dissociate MA-INA6 cells from the hMSC monolayer: Strong pipetting (*'Wash'*) and repeated Accutase treatment followed by magnetic activated cell sorting (*'MACS'*). These variations, recorded as the factor *'method'*, further complicated the dataset. Although this distinction is not discussed in this work – rather pooled into one group –, this showcases how protocol changes can add dimensions to the dataset that are not necessarily relevant for the biological question but essential for method optimizations and validation.

Agility During Establishment of V-Well Assay

The concept of agility in laboratory research, inspired by the Agile Manifesto's principle of *"Responding to change over following a plan"* (*Manifesto for Agile Software Development*, 2001), is increasingly relevant in biomedical research (West, 2018). This adaptive approach was particularly crucial during the development of the V-Well adhesion assay in this study. Semi-automation using python significantly enhanced this agility, allowing rapid statistical testing and visualization of data, which would have taken considerably longer if done manually. This capability enabled real-time adjustments to the experimental technique during live microscopy

sessions, integrating raw data tables directly into Python scripts for immediate analysis. Such an agile and adaptive work environment, facilitated by python tools and `seaborn`, proved invaluable for refining the *in vitro* methods being developed. Additionally, the simplicity offered by `seaborn` for complex data plotting, such as the cell cycle profiling shown in Appendix A.1: Fig. 3, which required minimal code to produce a detailed series of 24 histograms, underscores the utility of semi-automation in enhancing laboratory efficiency. While this work does not quantify the full benefits of semi-automation, the author's experiences suggest significant potential impacts on the speed and adaptability of method development in biomedical research.

Quick Exploration and (Re-)Analysis using `plotastic` The development of new methodologies for studying myeloma dissemination necessitated frequent adjustments in data presentation, making `plotastic` an essential tool for rapid visualization and iterative analysis. The ability to swiftly rearrange data visualizations – adjusting factors represented on the x-axis or altering color codes – is crucial, especially when exploring novel research methodologies. `plotastic` enhances `seaborn`'s existing functionalities with features like the `.switch()` method, simplifying the exploration of different plot structures through switching factors through `seaborn`'s facetting parameters (`hue`, `row`, `col`, etc.). Its `multiplots` feature is particularly valuable, enabling the automation of multiple `seaborn` functions to maintain consistent plotting formats throughout the publication, a critical requirement for many journals.

Re-analysis processes, often cumbersome with traditional software like *GraphPad Prism*, are streamlined with `plotastic`. It facilitates the rapid reconfiguration of plots and statistical annotations without the need to manually redo the analysis pipeline—this adaptability was pivotal during the peer review of Kuric et al. (2024), where adjustments were necessary for Chapter 1 Fig. 4 and 5. This capability underscores `plotastic`'s role in enhancing the reproducibility and flexibility of data analysis, addressing a long-standing issue in the field where the complexity of data often discourages the application of sophisticated analytical techniques (Bustin, 2014). `plotastic`'s simplicity and efficiency in handling semi-big data exemplify its necessity and effectiveness in modern biomedical research, providing a clear example of how automation can transform the analysis landscape.

Intermediate Conclusion: Together, adhesion studies, especially combined with methodologies that further add dimensions (Cell Cycle profiling), explode experimental complexity, which require sophisticated tools for high requirements posed by multidimensionality.

These requirements were facilitated by `seaborn` for quick processing of intermediate results during method optimizations and by `plotastic` for designing publication-grade analyses and figures. Developing `plotastic` was mostly a necessity that arose from late-stage data processing (statistics, and publication figures), filling `seaborn`'s shortcomings, but also ensured standards for consistent plot formatting and statistical analysis. The author lays emphasis on `plotastic`

as an infrastructure for quick and confident re-structuring of publication figures that include statistical annotations, especially during his peer-review process.

Challenges of Integrating `plotastic` into Biomedicine

Although `plotastic` is designed for the overall scientific community and has passed peer-review, time will tell if the single author's vision of an optimized automated statistical workflow can be extrapolated to biomedicine. The author's himself continues to use `plotastic` in future projects that require visualizing single datapoints and statistical rigor.

For biomedicine overall, the author sees the greatest challenge in adopting `plotastic` since it is a tool based on a command line interface (CLI), whereas the majority of biologists prefer graphical user interfaces (GUI). The author argues that a CLI can perform everything that a GUI can, but better, faster, and more efficiently, provided that one is willing to undergo the switch, which can be intimidating. However, many python tools already provide extremely easy commands (e.g. `seaborn`), and `plotastic` further lowers the barrier to entry. The author also argues that ChatGPT is a strong argument to switch to CLI, since large language models are highly compatible with text, which is the main format of CLIs. This allows for understanding context, providing code drafts, identifying errors, adding and changing analyses, autocompletion of repetitive commands, follow-up questions and many more.

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Appendices

A Supplementary Data & Methods

A.1 Figures

A.2 Tables

A.3 Materials & Methods

B Documentation of plotastic