

# D CADD Adaptation Dynamics



Please write a conclusion for the following subsection of my summarising discussion of my PhD Thesis applying similar latex syntax and my style of writing:

% =====

\unsubsection{\caddadaptationtitle}%

\label{sec:discussion\_caddadaptation}%

As presented in Chapter 1, \MAina cells exhibit rapid upregulation of both adhesion factors and chemoattractants, adapting their \textit{in vitro} \ac{CADD} from homotypic aggregation to colonizing \acp{MSC}. This dynamic behavior includes the loss of adhesion factor expression after cell division, suggesting that myeloma cells can rapidly change their adhesion factor expression in a highly dynamic manner. Given that \INA cells were isolated from an extramedullary site \dashed{the pleura}, such changes likely facilitate colonization of new microenvironments. This section explores the hypothesis that MM cells adapt their \ac{CADD} during each step of dissemination.

% Predicting how and when

% myeloma cells regulate \ac{CADD} could be key to understanding and preventing

% dissemination.

\textbf{\ac{CADD} Adaptation Assumes Distinguishable Niches;} The multistep model proposed by \citete{zeissigTumourDisseminationMultiple2020} posits that myeloma cells acquire regulatory mechanisms specialized for each step of dissemination. The author hypothesizes that the different niches involved in these steps are unique enough to trigger distinct \ac{CADD} adaptations. This requires thorough knowledge of separate niches.

\citete{granataBoneMarrowNiches2022} categorizes the \ac{BM} into sinusoidal, arteriolar, and endosteal niches, each spatially and molecularly distinguishable. The endosteal niche is home to \ac{MSC} and a majority of plasma cells\footnotequote{We suggest that it is reasonable to approach the notion of physical plasma cell survival niches with some skepticism. It is clear that most BM plasma cells rely heavily on access to APRIL or BlyS (66, 70), and it appears that mature plasma cells are relatively stationary (59). However to us, that plasma cells must remain indefinitely in physical survival niches to survive is less obvious.}{wilmoreHereThereAnywhere2017}, and the vascular niches

\dashed{sinusoidal and arteriolar} include endothelial cells \cite{zehentmeierStaticDynamicComponents2014, wilmoreHereThereAnywhere2017}. Other niches encountered during dissemination include peripheral blood, lymph nodes, and extramedullary sites. Comprehensive mapping and characterization of these niches, including their adhesion molecules and soluble factors, is necessary to understand the adhesion requirements for each niche. This is a highly complex task, yet summarizing available information per niche could

provide a powerful basis.

### **Distinct Adhesion Phenotypes Transitioning between Niches:**

Adhesion processes are well-documented in MM progression, particularly within the \ac{BMME} \cite{bouzerdanAdhesionMoleculesMultiple2022}. However, the dynamism of these processes remains unclear. In other cancers, different adhesive phenotypes and transitions, such as those seen in epithelial-mesenchymal transition (EMT), are common \cite{gengDynamicSwitchTwo2014}. For myeloma, EMT-like phenotypes have been described, but a clear association with distinct adhesion behaviors is hindered by the cells maintaining their suspension state \cite{roccaroCXCR4RegulatesExtraMedullary2015, qianSETDB1InducesLenalidomide2023}. This work might be the first to identify adhesive subtypes through functional separation of detachable myeloma cells. As presented earlier, expanding these findings could reveal transitions in adhesive phenotypes during MM dissemination, such as overcoming retention, initiating release, and establishing colonization.

### **Extramedullary Niche:**

\ac{CADD} adaptation predicts a specialized set of adhesion factors for extramedullary niches. A distinct phenotype has been proposed for extramedullary myeloma \footnote{Our analysis concluded that the gain of CD44, loss of CD56, loss of very late antigen-4 (VLA-4), imbalance of the chemokine receptor-4-chemokine ligand-12 (CXCR4-CXCL12) axis, [...] show an increased propensity [...] to leave the bone marrow and hone in extramedullary sites giving rise to more aggressive extramedullary diseases. }{guptaExtramedullaryMultipleMyeloma2022}, characterized by changes in expression of CD44, CD56, VLA-4, and CXCR4 \cite{guptaExtramedullaryMultipleMyeloma2022}. The role of CXCR4 in mediating adhesion factor expression is well established, particularly in extramedullary MM cells \cite{roccaroCXCR4RegulatesExtraMedullary2015, guptaExtramedullaryMultipleMyeloma2022}: Extramedullary myeloma cells overexpress CXCR4, making them more responsive to cues that induce adhesion factor expression, such as CD44/H-CAM.

### **Vascular Niche:**

\ac{CADD} adaptation predicts a specialized set of adhesion factors for endothelial interaction, supporting intravasation and extravasation. Although not assessed in this thesis, the vascular niche is a popular therapeutic target for preventing dissemination \cite{neriTargetingAdhesionMolecules2012}. Key adhesion factors like JAM-A and N-Cadherin have been highlighted as potential targets \cite{solimandoHaltingViciousCycle2020, mrozkTherapeuticTargetingNcadherin2015}. These factors were not differentially expressed between subpopulations isolated in Chapter\,1, suggesting distinct regulatory mechanisms for vascular versus \ac{MSC} interactions.

### **Circulating MM:**

An adaptive \ac{CADD} would predict that circulating MM cells lose adhesion factors. Studies confirm that \dashed{compared to BM-resident cells} circulating \ac{MM} cells exhibit reduced expression of multiple adhesion factors, including  $\alpha4\beta1$  and CD138/Syndecan-1 \cite{paivaDetailedCharacterizationMultiple2013, paivaCompetitionClonalPlasma2011, akhmetzyanovaDynamicCD138Surface2020}. Evidence suggests that a dynamic loss of CD138/Syndecan-1 and gain of JAM-C causes intravasation, circulation, and dissemination of MM cells \cite{akhmetzyanovaDynamicCD138Surface2020, brandtJunctionalAdhesionMolecule2022}. This thesis also shows that \nMAina cells, after emerging as daughter cells from \MAina, not only lose adhesion factor expression but also exhibit increased survival during IL-6 deprivation, potentially aiding survival in circulation.

### \textbf{\textit{Intermediary Conclusion:} Evidence for Adhesion Phenotypes Lacks Functional Characterization and Proof of Phenotypic Transitions:}

The concept of \ac{CADD} adaptation is supported by the existence of distinct BM niches and the identification of separable adhesion phenotypes. However, most transitions between these phenotypes during dissemination are unexplored. Functional characterization of adhesive phenotypes and their transitions could provide a robust framework for understanding dissemination as a multistep process, reinforcing the dynamic adhesion hypothetical framework. Mapping adhesive properties for each involved niche could aid this endeavor.

### \textbf{\textit{Implications for Therapy:}}

Adhesion molecules have been targeted for therapy for over a decade \cite{nairChapterSixEmerging2012, neriTargetingAdhesionMolecules2012}. Especially inhibiting adhesion molecules involved in interaction with the endothelium effectively reduces tumor burden in mouse models \cite{asosinghUniquePathwayHoming2001a, mrozkTherapeuticTargetingNcadherin2015}. A deeper understanding of how myeloma cells regulate \ac{CADD} could be key to predicting and preventing dissemination. \ac{CADD} adaptation suggests that different adhesion factors should be either antagonized or agonized depending on their role. For instance, adhesion factors involved in intravasation and extravasation should be antagonized, while those facilitating BM retention should be agonized\,\textendash\autoref{tab:1} provides a list of potential retention targets.

### \textbf{\textit{Considerations for Further Research:}}

This has huge implications for studying adhesion factors in MM \textit{in vitro}. Given that some factors are not present in MM cells, but are potentially rapidly expressed with the right signal. Hence, further studies focusing on adhesion factor expression \textit{in vitro} should provide one specific microenvironmental context, and not generalize to all available niches.

- Separate between initial adhesion and upregulated adhesion factors. INA already adhere within the first hour, further upregulating adhesion factors after 24h. One could perform a WPSC assay after 30 minutes of adhesion, separating INA-6 cells that adhere quickly from those that don't, and subsequent RNAseq would identify the adhesion factors required for initial adhesion. This way, one could differentiate between initial colonization. Assuming that an initial adhesion is essential for subsequent colonization processes, the identification of initial adhesion factors could be crucial for predicting colonization potential of different niches.

Studying adhesion factors in MM *in vitro* requires considering the specific microenvironmental context. Some adhesion factors are not present in MM cells but can be rapidly expressed with appropriate signals. Also, further studies should differentiate between initial adhesion and upregulated adhesion factors. For example, performing a WPSC assay after 30 minutes of adhesion could separate INA-6 cells based on initial adhesion capability, with RNAseq of INA identifying initial adhesion factors. This differentiation could be crucial for predicting colonization potential across niches, as initial adhesion is likely essential for subsequent growth in BM or extramedullary environments.



Here's a conclusion for the discussed subsection, applying the LaTeX syntax and adhering to the style of writing as in the provided example:

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**Concluding Remarks:** The exploration of CADD adaptation across various niches reveals a complex interplay between myeloma cells and their environments, characterized by a dynamic regulation of adhesion factors. The evidence presented supports the hypothesis that myeloma cells modify their adhesion phenotype in response to the unique demands of each microenvironment they encounter during dissemination. This adaptive capability suggests that targeting these specific adhesion mechanisms could offer a promising strategy for therapeutic intervention, particularly in preventing the colonization of new niches. The distinctions between the adhesion phenotypes among the niches—vascular, bone marrow, and extramedullary—underscore the necessity for a targeted approach in therapy, which could involve modulation of specific adhesion factors to either promote retention or prevent dissemination.

Despite these insights, the current understanding of the functional roles and transitions of these adhesion phenotypes during myeloma progression remains incomplete. Future research should focus on delineating these roles more clearly by functional assays and real-time imaging to capture the dynamic changes in adhesion factor expression during cell transition between niches. Such studies will be crucial for validating the CADD adaptation model and for identifying potential therapeutic targets that could disrupt the dissemination process at various stages.

**Future Directions:** It is imperative to further characterize these adhesion factors in a controlled *in vitro* environment, where specific microenvironmental contexts are simulated. This approach will allow for a more nuanced understanding of how adhesion factors are upregulated and their role in niche-specific colonization. By integrating detailed molecular and cellular analyses, such as single-cell RNA sequencing and proteomics, researchers can identify critical adhesion factors that facilitate the initial colonization processes. This knowledge could then inform the development of interventions aimed at either enhancing or inhibiting these factors, thereby providing a more strategic approach to the management and treatment of multiple myeloma.

This conclusion integrates the key themes discussed in the section and aligns with the scientific and formal tone appropriate for a PhD thesis discussion. It also suggests future research directions, maintaining coherence with the broader themes of niche-specific adaptation and therapeutic targeting.



That is perfect, thank you!



You're welcome! I'm glad you found it perfect. If you need any more help with your thesis or anything else, feel free to ask. Good luck with your writing!

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