To determine the functional role of syndecan-2 in HSCs, Termini et al used lentiviral short hairpin RNAs to knock down syndecan-2 expression in HSCs and showed reduced myeloid repopulation in primary recipients and reduced multilineage repopulation in secondary recipients. Furthermore, syndecan-2 knockdown reduced the fraction of phenotypic HSCs in the G_0 phase and suppressed the expression of Cdkn1c, whereas syndecan-2 overexpression produced the opposite effects. Downregulation of Cdkn1c in combination with downregulation of syndecan-2 did not further reduce HSC quiescence, suggesting that syndecan-2 regulates HSC quiescence through its control of Cdkn1c expression.

Nonetheless, it is worth noting that not all functional HSCs express syndecan-2. The limiting dilution transplantation results from Termini et al indicate that approximately one-third of functional HSCs do not express syndecan-2. Moreover, syndecan-2 expression in HSCs can be turned on and off in vitro, suggesting that syndecan-2 marks 2 interchangeable states of HSCs instead of 2 distinct subtypes of HSCs. However, 8 weeks after transplantation, donor syndecan-2^+CD34$^-$KSL cells gave rise to significantly more syndecan-2^+CD34$^-$KSL cells compared with donor syndecan-2^-CD34$^-$KSL cells. And donor syndecan-2^-CD34$^-$KSL cells rarely produced any syndecan-2^+CD34$^-$KSL cells. Therefore, HSCs do not appear to freely alternate between the syndecan-2 positive and negative states. Further investigation on how HSCs switch between the syndecan-2^+ and syndecan-2^- states can provide more insights into the regulatory mechanism of HSC quiescence.

Syndecan-2 is a member of the syndecan family, consisting of 4 transmembrane heparan sulfate proteoglycans in mammals.[8] Syndecans interact with other cell surface receptors, such as growth factor receptors and integrins, and play key roles in regulating many cellular behaviors and diseases.[8] Inhibition of heparan sulfate synthesis and adding heparan sulfate mimetics can mobilize HSCs,[9,10] suggesting the role of heparan sulfates in the retention of HSCs in their bone marrow niche. Therefore, the discovery of syndecan-2's regulatory role in HSCs may lead to potential applications for improving HSC functions during bone marrow transplantation. Future investigation of syndecan-2 in human HSCs can elucidate its translational potential because syndecan-2 expression is also elevated in human HSCs as reported by Termini et al. However, the authors also showed that bone marrow cells from the syndecan-2 knockout mice exhibited modest decrease in hematopoietic repopulation after bone marrow transplantation. This suggests the existence of a compensatory mechanism that was absent in the acute knockdown of syndecan-2 as demonstrated by Termini et al. The study from Termini et al could lead to future investigations on the translational potential and regulatory mechanism of syndecan-2 in HSCs, which could help improve HSC-based cell and gene therapies.

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LYMPHOID NEOPLASIA

Comment on Mayerhoefer et al, page 240

PET imaging: back in the game for gastric EMZL?

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In this issue of *Blood*, Mayerhoefer et al[1] report the use of a novel PET radiotracer targeting the G-protein–coupled C-X-C chemokine receptor type 4 (CXCR4), for assessment of residual disease in gastric mucosa–associated lymphoid tissue (MALT) lymphoma after first-line *Helicobacter pylori* eradication.

Positron emission tomography-computed tomography (PET-CT), using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has generally been considered to be of little clinical utility for assessing extranodular marginal zone B-cell lymphoma (EMZL),[2] because of globally lower FDG avidity compared with aggressive lymphomas. Specifically, gastric primary MALT lymphoma has shown a low detection rate by FDG PET compared with other localizations, such as primary head-and-neck or bronchial lesions.[3] This difference in detection rates was thought to be related to the thickness of the lesion. Thus, after eradication of *H pylori*, the follow-up is based on findings in pan upper gastrointestinal endoscopy, including multiple biopsy specimens obtained 3 months after treatment to rule out tumor progression with follow-up endoscopies (twice per year for 2 years, then every 12 to 18 months), to monitor the histological regression of the lymphoma.

CXCR4 and its ligand CXCL12 are overexpressed in a variety of tumor types and contribute to tumor growth, angiogenesis, metastasis, and therapeutic resistance. Recently, new imaging probes targeting CXCR4 have been developed for PET imaging, such as pentixafor labeled with gallium-68 (^{68}Ga-pentixafor), thereby enabling noninvasive imaging of CXCR4 expression throughout the whole body. In hematology, most experience with CXCR4-directed PET imaging has been in multiple myeloma[4] and has shown the utility of this tracer. Recently, in patients with newly diagnosed MZL, Duell et al[5] showed that CXCR4-directed imaging detects significantly more MZL localizations, particularly bone marrow infiltration, and affects the Ann Arbor classification, compared with conventional staging, including bone marrow biopsy, endoscopy, and FDG PET-CT.

The present innovative study further supports the use of CXCR4-directed PET imaging in MZL for response assessment. With time-matched gastric biopsy specimens used as the reference standard,[6,7] they found that ^{68}Ga-pentixafor PET accurately identified residual gastric disease in patients with MALT lymphoma with an impressive sensitivity of 95%. However, this high sensitivity is based on an observer-dependent visual assessment of the tracer uptake. Indeed, PET was rated as positive based on the visual increase in gastric uptake relative to the surrounding tissue. Although no false-positive cases were reported in this study, this criterion seems weak in an organ often associated with a slight diffuse physiological uptake and a relatively moderate pathological uptake. The lowest maximal standard unit value of biopsy-proven residual gastric MALT lymphomas in their cohort was 3.3. No blind interobserver reproducibility assessment was performed. Regarding the tumor-to-background ratios, the Deauville scale could be applied to increase the reproducibility in PET reporting between nuclear physicians. In addition, we wonder whether the different subtypes (ulcer, nodular, or gastritis; the subtype was not specified) or the presence of t(11;18)(p21;p21) translocation may have different PET appearances and whether they are associated with different sensitivity in the response. In summary, this study highlights the potential use of CXCR4 PET tracer for noninvasive response assessment in gastric lymphoma, although it warrants further studies to confirm this observation and to harmonize PET positivity criteria. In a broader context, this imaging may be more adaptable than FDG in some specific lymphoma subtypes, such as EMZL, because of the variable FDG avidity, or in central nervous system lymphoma,[8] because of the intense brain physiological uptake. Further studies are warranted to better evaluate the utility of CXCR4-directed PET in diseases where we know that the response assessment criteria based on the Lugano criteria, widely used in aggressive lymphomas, are not perfectly adaptable.

Moreover, it has been shown that dysregulated expression of CXCR4 predicts disease progression in diffuse large B-cell lymphoma, independent of International Prognostic Index score and activated B cell/germinal center B-cell classification. In fact, CXCR4 overexpression impairs rituximab response, with an inverse correlation between the level of CXCR4 surface expression and the degree of rituximab sensitivity.[9] In Burkitt lymphoma and chronic lymphocytic leukemia,[10] the effect of rituximab was enhanced by antagonizing CXCR4. In this way, CXCR4-directed PET imaging should allow the visualization of CXCR4 overexpression through the whole body and thus may be complementary to FDG PET for risk stratification of patients with aggressive lymphoma.

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