Utility of CD138/syndecan-1 immunohistochemistry for localization of plasmacytes is tissue-dependent in B6 mice

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Abstract
Objective: Inflammation is present in many diseases and identification of immune cell infiltration is a common assessment. CD138 (syndecan-1) is a recommended immunohistochemical marker for human plasmacytes although it is also expressed in various epithelia and tumors. Similarly, CD138 is a marker for murine plasmacytes, but its tissue immunostaining is not well-defined. Endogenous CD138 expression is an important confounding factor when evaluating plasmocyte infiltration. We studied two plasmocyte markers (CD138 and Kappa light chains) for endogenous immunostaining in five organs and one tumor from B6 mice.

Results: Plasmacytes in Peyer’s patches were positive for CD138 and Kappa markers without endogenous immunostaining. Endogenous CD138 immunostaining was widespread in liver, kidney, lung and a malignant peripheral nerve sheath tumor (MPNST) versus regionalized immunostaining in skin and small intestine wall. Endogenous Kappa immunostaining was absent in all tissues except for plasmacytes. Tissues with widespread endogenous CD138 immunostaining were contrasted by absence of endogenous Kappa immunostaining. Here, plasmacytes would not be distinguished by CD138, but would be obvious by Kappa immunostaining. Our study suggests that utility of immunostaining for plasmacytes by CD138 is tissue dependent in mice. Additionally, Kappa immunostaining may be a useful alternative in mouse tissues with confounding endogenous CD138 immunostaining.

Keywords: B-cells, CD138/syndecan-1, Immunohistochemistry, Kappa light chain, Plasmacytes

Introduction
Inflammation is a pathologic feature in many conditions including but not limited to infectious [1], genetic [2], metabolic [3] and cancer [4, 5] etiologies. Therefore, understanding the contributions of inflammation to disease pathogenesis is a meaningful component of biomedical studies. Several approaches can be used to study inflammation in tissues, each with advantages and limitations [6]. Immunohistochemistry is a common technique that is useful to identify expression of specific markers to localize immune cell infiltration in tissues [7–10]. Immunostaining can be used to determine immune cell location, distribution, activation state, extent of infiltration (qualitative, semi-quantitative, quantitative), and corroborate infiltration with clinical data [6, 7, 11–13].

Plasmacytes (also known as plasma cells) are fully differentiated B cells able to synthesize and secrete immunoglobulins [14]. Plasmacytes are defined by the expression of several protein markers in mice and humans [15], but the value of these individual markers for study can be technique dependent. For instance, CD138 (syndecan-1) is recommended as an immunohistochemical tissue marker specific for plasmacytes in humans and mice [10,
CD138 is member of the syndecan family that are characterized by three structural components: extracellular, transmembrane and intracellular domains [18]. The transmembrane configuration of CD138 reflects its importance in cell-to-cell and matrix-to-cell interactions. In human tissues, CD138 immunostaining is seen in plasmacytes and several epithelial tissues, and is increasingly recognized in several types of human cancer [18, 19]. In mouse tissues, CD138 immunostaining is seen in plasmacytes, but published images of these are often constrained to tissues devoid of epithelium (e.g., lymphoid tissues) [16, 17]. In contrast to humans, endogenous CD138 expression is healthy mouse organs or even in cancers (except plasmacyte cancers) are not defined by immunostaining studies [10, 16, 17].

The diagnostic ability to detect specific cellular staining ( histochemical or immunohistochemistry) is limited by the extent and intensity of endogenous immunostaining in the experimental tissues [20–22]. Ideally, target immune cells expressing the marker should have strong specific immunostaining while the adjacent off-target cells should lack immunostaining. These staining differences provide the contrast needed for successful tissue studies using morphology, scoring or digital analysis [23].

In this study, we conducted two parallel investigations. First, CD138 expression was evaluated by immunostaining to define endogenous cellular/tissue localization in select healthy mouse organs. We also had access to a malignant peripheral nerve sheath tumor (MPNST) and this cancer tissue was also evaluated. In the second investigation, serial tissue sections were immunostained for a different plasmacyte marker, Kappa light chains (Kappa). We then compared the extent of endogenous immunostaining for each marker to determine how it might impact detection of plasmacytes.

**Main text**

**Methods**

Mouse tissues were acquired from archival tissue repositories (Comparative Pathology Laboratory, University of Iowa) that originated from studies approved by University of Iowa Animal Care and Use Committee following published guidelines for animal care and use. Use of archival tissue repositories avoided the need for live mice to be studied. Organs (lungs, intestine, liver, kidney and skin) from male and female (3/sex) mice were studied. Inclusion criteria for mice included: adult (sexually mature over ~8 weeks of age) and record of wildtype “B6” strain. Additionally, tissue blocks from a mouse with a malignant peripheral nerve sheath tumor was identified. The mouse had been treated with anti-tumor drugs [Palbociclib (100 mg/kg) and Mirdametinib (1 mg/kg), daily oral gavage] for 15 days prior to harvest. The tumor was induced by CRISPR/Cas9 editing of Nf1, Ink4a and Arf genes in the sciatic nerve of a wild-type C57BL/6 mouse, as describe [24–26].

All tissues were formalin-fixed and paraffin-embedded. Tissues sectioned (~4 µm) onto glass slides and hydrated through a series of progressive xylenes and ethanol baths. Immunohistochemistry of markers was optimized for detection of plasmacytes in lymph node. CD138/syndecan-1 was performed as previously described [27]. Briefly, heat-induced antigen retrieval (Tris buffer pH 9.0, 125 °C × 5 min) was performed followed by a series of tissue blocks [3% hydrogen peroxide × 8 min, avidin/biotin blocking kit (#SP-2001, Vector Laboratories), and Rodent Block M kit (Biocare Medical)]. Primary antibody (1:3000 × 1 h, rat anti-mouse monoclonal, clone 281-2, Cat#553712, BD Pharmingen Company) was applied followed by secondary antibody [biotinylated rabbit anti-rat IgG, (Vector Laboratories BA-4001)] and ABC kit (PK-6100, Vectastain Elite ABC kit). For Kappa light chains (Kappa), antigen retrieval (Tris buffer pH 9.0, 125 °C × 5 min) was performed followed by a series of tissue blocks (3% hydrogen peroxide × 8 min and 10% goat serum × 30 min). Primary antibody against Kappa (1:400 × 1 h, rabbit monoclonal, clone RM103, #SAB5600201, Sigma Aldrich) was applied followed by Envision-Plus HRP Rabbit kit (Agilent). For both markers, dianinobenzidine (DAB, brown color) was applied as the chromogen, tissues were counter-stained with Harris hematoxylin (blue color) and cover slipped.

For each type of mouse tissue, immunostaining for the two markers were examined by a boarded veterinary pathologist in a post-examination masked manner [28]. Tissues were qualitatively evaluated [23] using tissue morphology to identify immunostain localization by each marker. Immunostaining intensity was defined as negative (lacking obvious stain); + (weak brown stain); or ++ (moderate to strong stain i.e. partially to fully obscuring detection of the counterstain). These results were summarily reported as representative of the groups, but if any differences were noted, these were reported in more detail. Representative images were collected (BX53 microscope, DP73 digital camera and CellSens Dimen- 
sion Software, Olympus).

**Results**

In the small intestine, Peyer’s patches are secondary lymphoid organs that appear along the serosal border [29]. The Peyer’s patches were initially examined for CD138 and Kappa immunostaining. Both markers immunostained plasmacyte aggregates within and adjacent to germinal centers (Fig. 1a, b; Table 1), while the lymphoid tissue was negative. Plasmacytes are also commonly localized to the lamina propria of small intestinal villi
Here, plasmacytes were strongly stained by CD138 and Kappa (Fig. 1c, d). Intestinal epithelium showed regional variability of CD138 immunostaining that was consistently stronger in the crypt than in the villus enterocytes (Fig. 1c). Kappa immunostaining of the small intestine epithelium was negative (Fig. 1d).

In the liver, CD138 immunostaining was prominent in a sinusoidal pattern that has been reported in humans as localization to the basolateral surface of hepatocytes [31] (Fig. 1e; Table 1). Additionally, CD138 immunostaining was mild in cytoplasm of hepatocytes and moderate in bile duct epithelium. Kappa immunostaining was negative (Fig. 1f).
In the kidney (Fig. 1g–j; Table 1), CD138 immunostaining was widespread in tubules/ducts with stronger staining in the cortex compared to the medulla and papilla. In the renal pelvis, CD138 immunostaining was localized to the lining urothelium (Fig. 1g). Glomeruli had CD138 immunostaining localized to Bowman’s capsule with scattered cells staining in all glomeruli (Fig. 1i). Kappa immunostaining (Fig. 1h, j) was completely negative in two of six animals (Fig. 1h), but in four of the six animals Kappa immunostaining was localized to a few cells in multifocal glomeruli (Fig. 1j). Plasmacytes have been observed in glomeruli as part of chronic kidney diseases [32]. Discrete plasmacyte aggregates were seen by Kappa immunostaining but were obscured by endogenous CD138 immunostaining.

In the skin, CD138 immunostaining was seen in epidermis and follicular epithelium/adnexa (Fig. 1k; Table 1). Kappa immunostaining was consistently negative (Fig. 1l).

In the lung, CD138 immunostaining was localized to airway surface epithelium as well as alveolar epithelia (type 2 cells > type 1 cells) (Fig. 2a; Table 1). Kappa immunostaining was consistently negative (Fig. 2b).

In a murine MPNST, plasmacyte markers were evaluated (Fig. 2c, d; Table 1). CD138 immunostaining had widespread localization to most cancer cells, obscuring any plasmacytes (Fig. 2c). In contrast, Kappa immunostaining was consistently negative in cancer cells and this allowed for discrete detection of small plasmacyte aggregates within the tumor (Fig. 2d).

**Discussion**

We evaluated CD138 immunostaining in healthy mouse tissues to determine normal endogenous expression and whether it could possibly confound evaluation for CD138+ plasmacytes. We found that endogenous CD138 immunostaining was tissue dependent in mice. Lymphoid tissues of the Peyer’s patches lacked immunostaining, making the identification and specific localization of CD138+ plasmacytes straightforward. The contrast between positive and negative immunostaining tissue explains why CD138 is useful for plasmacyte detection in lymphoid tissues in humans and mice [10, 17, 33, 34]. For CD138, kidney, liver, lung and even a MPNST tumor had widespread immunostaining, while skin and small intestine had more regionalized epithelial staining. Our findings suggest that widespread endogenous CD138 immunostaining in experimental tissues and tumors could limit the diagnostic analysis for CD138+ plasmacytes [20]. Wide expression of CD138 in

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**Table 1** CD138 and Kappa immunostaining patterns in various tissues

| Organ/tissue        | CD138                                                                 | Kappa                                                                 |
|---------------------|------------------------------------------------------------------------|-----------------------------------------------------------------------|
| Small intestine     | Peyer’s patches (+++) Lamina propria of villi (+++)                    | Peyer’s patches (+++) Lamina propria of villi (+++)                    |
| Plasmacytes         | Enteroctyes (crypts > surface) (Neg to +++)                           |                                                                       |
| Enterocytes         |                                                                         |                                                                       |
| Liver               | Sinusoidal pattern/basolateral hepatocytes (+++)                      | (Neg)                                                                |
| Hepatocytes         | Hepatocyte cytoplasm (+)                                              | (Neg)                                                                |
| Bile duct           | Biliary epithelium (+++)                                             | (Neg)                                                                |
| Kidney              | Bowman’s capsule (+) Cellular immunostaining common (+++)            | Cellular immunostaining rare to scattered, detected in only 4 of 6 animals (++/++) |
| Glomeruli           |                                                                         |                                                                       |
| Tubules/ducts       | Cortex > medulla (++/++)                                              | (Neg)                                                                |
| Pelvis              | Urothelium (+++)                                                     | (Neg)                                                                |
| Skin                |                                                                         |                                                                       |
| Epidermis           | (+++)                                                                 | (Neg)                                                                |
| Follicles/adnexa    | Follicular epithelium (+++)                                           | (Neg)                                                                |
| Sebaceous glands    |                                                                        |                                                                       |
| Lung                |                                                                         |                                                                       |
| Airways             | Surface epithelium (+++)                                             | (Neg)                                                                |
| Alveolar epithelium | Type 2 cells (+++)                                                   | (Neg)                                                                |
|                     | Type 1 cell (+)                                                       |                                                                       |

(Staining intensity) = Neg negative; + weak; ++ moderate to strong
nonhematopoietic murine tissues was reported in one study, but immunostaining had not been evaluated [35]. Surprisingly, many studies for localization of CD138+ plasmacytes in mouse tissues don’t mention observed endogenous CD138 expression in epithelial cells [36]. Conversely, mouse studies investigating epithelial expression of CD138 often fail to mention potential for infiltrative plasmacyte immunostaining to affect tissue analysis [37–41]. Several of these same epithelial-focused studies exclusively use “syndecan-1” but avoid use of “CD138” terminology; the reverse bias in terminology use is also common in plasmacyte studies. Inconsistent use of marker terminology can confuse researchers reading the published literature. These results suggest more consistency in marker terminology along with transparent discussion of expected to observed tissue distribution by markers should be included in immunohistochemical studies.

A second aim of this study was to evaluate Kappa as an alternative plasmacyte marker in serial sections of the same mouse tissues. Kappa light chains are components of antibodies produced by B cells/plasmacytes and may play a role in immunity and self-tolerance [42, 43]. We found that endogenous immunohistochemical expression in mouse tissues was broadly negative except for observation of Kappa+ cells morphologically consistent with plasmacytes in tissues. Interestingly, kidney and MPNST tissues provided clear examples of how widespread endogenous expression could negatively affect detection of plasmacytes. In a different example, the small intestine had discreet plasmacyte immunostaining for both markers in the lamina propria of villi, as expected in the normal intestine. Since endogenous immunostaining of the villus epithelium did not overtly affect identification of the plasmacytes—CD138 could feasibly be used in some types of studies on tissues (small intestine, skin) with regional endogenous expression.

Our study identifies several considerations for researchers studying plasmacytes (or other immune cells) by immunohistochemistry in tissues. (1) Investigational tissues should be evaluated for endogenous expression of candidate markers. If the endogenous expression is sufficiently low or localized—then use of that marker for plasmacyte localization may be feasible. (2) If the endogenous tissue expression of the candidate marker is sufficient to affect plasmacyte detection or analysis then
alternative approaches such as a different marker or dual labeling might be needed. (3) If endogenous expression is detected in study tissues, it should be acknowledged for transparency and reproducibility in other studies. (4) Awareness of endogenous tissue expression could have important implications for other techniques too, such as immunofluorescence and whole tissue expression studies. These techniques often rely on assumptions of marker specificity and they lack the ability for secondary quality checks using morphologic corroboration that is available in immunohistochemistry studies from fixed sections. (5) Lastly, this study can help mitigate gaps in the literature about CD138 immunostaining and guide scientists to make more efficient choices regarding their study designs and use of resources (fiscal, labor and reagents).

Limitations
This study is not without potential limitations. First, we studied select tissues from mice on a B6 background to provide useful examples of staining patterns, but we cannot assume that our results will necessarily be applicable to other tissues or other murine strains or substrains. Second, we focused primarily on healthy tissues, so we cannot rule out that diseased tissues with inflammation or remodeling changes might display differences in cellular localization or intensity using the markers we studied. Lastly, we studied one cancer type—a MPNST that showed widespread immunostaining of tumor cells for CD138. While we cannot make definitive statements about CD138 immunostaining in other mouse cancers, its presence in several human cancers (carcinomas and sarcomas) [18, 19] could suggest CD138 expression in cancers could confound mouse plasmacyte detection and localization.

Abbreviations
ABC: Avidin biotin complex; DAB: Diaminobenzidine; HRP: Horseradish peroxidase; MPNST: Malignant peripheral nerve sheath tumor.

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Author contributions
DM and DQ developed the conceptual ideas and all authors contributed to planning the experimental design. JAG, TB, CK, JK and RD, identified/secured appropriate studies and tissues for inclusion. ML, AA, and SV optimized, and performed the histotechnology and immunohistochemistry procedures. DM, ML, and JAG optimized and performed analysis of digital images and immunostain scoring. All authors contributed to the drafting/revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All tissues were collected from a repository of archival paraffin-embedded tissue blocks that originated in studies approved by the University of Iowa Animal Care and Use Committee and that followed appropriate federal guidelines on animal studies.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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