ORIGINAL

CAM5.2 immunostaining visualizes hemodynamic-driven ductular-like differentiation in the liver : a practical marker for distinguishing circulatory disturbance–related hyperplastic lesions from hepatocellular tumors

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Abstract : Background and aims : Focal nodular hyperplasia (FNH) is thought to arise from intrahepatic circulatory disturbances, but its distinction from hepatocellular carcinoma (HCC) and hepatocellular adenoma (HCA) remains challenging, especially in lesions with minimal cytological atypia. CAM5.2 is widely available in routine pathology laboratories, yet its diagnostic significance in hepatic lesions is unclear. We investigated whether CAM5.2 immunostaining visualizes hemodynamic-driven phenotypic changes of hepatocytes and whether its spatial pattern is informative. Methods : CAM5.2 immunohistochemical staining was analyzed in surgically resected specimens of FNH, HCA (HNF1α-inactivated and inflammatory subtypes), and HCC. The localization, distribution, and spatial regularity of CAM5.2 expression in hepatocytes and bile duct structures were evaluated and correlated with histological features of vascular remodeling. Results : In FNH, CAM5.2 showed a regular staining pattern confined to nodules and aligned along fibrous septa or abnormal vessels, highlighting ductular structures and adjacent hepatocytes. This pattern was absent in background liver parenchyma. In contrast, hepatocellular tumors showed irregular patterns : HNF1α-inactivated HCA exhibited weak focal positivity, inflammatory HCA diffuse staining, and HCC heterogeneous, patchy, or negative staining. Conclusions : CAM5.2 visualizes hemodynamic-driven, ductular reaction–like phenotypic modulation of hepatocytes. A regular spatial pattern supports circulatory disturbance–related hyperplastic lesions e.g., FNH and aids exclusion of HCC and HCA. J. Med. Invest. 73 : 234-240, February, 2026

Keywords **:** *CAM5.2, Focal nodular hyperplasia, Hepatocellular carcinoma, Circulatory disturbance, Immunohistochemistry*

INTRODUCTION

Focal nodular hyperplasia (FNH) is a representative non-neoplastic hyperplastic lesion of the liver that is widely accepted to arise from intrahepatic circulatory disturbances rather than from true clonal neoplastic proliferation (1-3). In these lesions, abnormal vascular architecture, including arterial hyperperfusion and reduced portal venous flow, leads to localized alterations in hepatic blood supply, resulting in compensatory hyperplasia of hepatocytes and ductular structures (4, 5). Nodular regenerative hyperplasia (NRH), partial nodular transformation (PNT), and related pseudotumorous lesions are considered to belong to the same spectrum of circulatory disturbance–related hyperplastic disorders (6, 7).

In routine surgical pathology practice, the distinction between such hyperplastic lesions and hepatocellular tumors, particularly hepatocellular carcinoma (HCC) and hepatocellular adenoma (HCA), is often challenging. This difficulty is most pronounced in cases showing minimal cytological atypia, equivocal architectural changes, or overlapping vascular features (4, 8). Although immunohistochemical panels including glutamine synthetase (GS), glypican-3, heat shock protein 70 (HSP70), arginase-1, liver fatty acid binding protein (LFABP), C-reactive protein (CRP), and serum amyloid A (SAA) are recommended for differential diagnosis (9), these antibodies are not universally available in all pathology laboratories, especially in regional or community hospital settings.

Cytokeratin CAM5.2 is one of the most widely available antibodies in routine diagnostic pathology. Although CAM5.2 was initially considered an antibody recognizing CK8/18, it is now primarily regarded as an antibody that reacts with CK8 and weakly with CK7 (10). CK8/18 are normally expressed in hepatocytes and bile duct epithelial cells, and CAM5.2 has traditionally been used as a general epithelial marker or as a marker of "ductular differentiation" in hepatic pathology (11). However, the biological significance of CAM5.2 staining in hepatocytes and its diagnostic utility in liver lesions remain ambiguous.

Previous studies have shown that HCC can exhibit variable CAM5.2 staining patterns ranging from diffuse positivity to complete negativity, depending on tumor differentiation and molecular background (12, 13). Likewise, in HCA, CAM5.2 expression varies according to molecular subtype, with inflammatory HCA often showing diffuse positivity and HNF1α-inactivated HCA showing weak or focal staining. These findings indicate that, in neoplastic lesions, CAM5.2 expression is largely governed by tumor-intrinsic molecular alterations rather than by tissue architecture or vascular configuration.

In contrast, in non-neoplastic hyperplastic lesions such as

Received for publication January 22, 2026 ; accepted January 28, 2026.

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FNH, CAM5.2 immunostaining has been sporadically reported to highlight ductular reactions and peri-ductular hepatocytes, but the biological and diagnostic implications of its spatial expression pattern have not been systematically analyzed. Importantly, FNH is characterized not only by the presence of ductular reactions but also by a highly organized architecture in which fibrous septa, abnormal vessels, and regenerative hepatocellular plates form a geometrically regular nodular structure (1, 4). This raises the possibility that CAM5.2 expression in FNH and related lesions reflects a hemodynamically induced, spatially ordered phenotypic modulation of hepatocytes rather than a random or tumor-like differentiation process.

Recent experimental and pathological studies have demonstrated that altered hepatic blood flow, shear stress, hypoxia, and oxidative stress activate signaling pathways such as HGF, TGF-β, Notch, and Wnt/β-catenin, which are also involved in ductular reaction and biliary differentiation programs (14-16). Under such conditions, hepatocytes may acquire partial ductular-like phenotypes, including the expression of cytokeratins normally associated with bile duct epithelium. Therefore, CAM5.2 positivity in hyperplastic liver lesions may represent a visual marker of hemodynamic-driven, ductular reaction–like phenotypic modulation of hepatocytes.

Another important but underrecognized issue is that severe circulatory disturbance may lead not only to phenotypic induction but also to tissue extinction, vascular remodeling, and loss of antigenicity. In ischemic or severely remodeled hepatic tissue, immunohistochemical reactivity can be markedly reduced or completely lost, potentially mimicking the staining pattern of poorly differentiated tumors (17, 18). Such phenomena may create diagnostic pitfalls if CAM5.2 negativity is interpreted simplistically as evidence of malignancy.

Based on these considerations, we hypothesized that CAM5.2 immunostaining reflects a distinct biological process in the liver, specifically a hemodynamic "induction phase," during which circulatory disturbance induces ductular reaction–like differentiation of hepatocytes, leading to a highly regular and geometrically organized staining pattern.

The aim of this study was to systematically analyze CAM5.2 expression patterns in FNH, HCA, and HCC and to evaluate its diagnostic utility in distinguishing circulatory disturbance–related hyperplastic lesions from hepatocellular tumors.

MATERIALS AND METHODS

Case selection

This study included a total of 17 hepatic lesions retrieved from the archives of our institution. All cases had been previously diagnosed based on integrated radiological, macroscopic, and histopathological findings, and these diagnoses were regarded as definitive prior to the present study. The study cohort consisted of the following categories :

- Focal nodular hyperplasia (FNH) : 6 cases
- A tumor difficult to distinguish between FNH and hepatocellular adenoma (HCA) : 1 case
- Hepatocellular adenoma (HCA) : 4 cases
  - HNF1α-inactivated HCA : 2 cases
  - Inflammatory HCA : 2 cases
- Hepatocellular carcinoma (HCC) : 6 cases

The diagnosis of each lesion had been established using conventional histological criteria together with clinicoradiological correlation and, when necessary, additional immunohistochemical markers routinely used for hepatocellular tumor classification.

Histological evaluation

All tissue specimens were fixed in 10% neutral-buffered formalin and embedded in paraffin according to standard procedures. Sections of 3–4 μm thickness were prepared and stained with hematoxylin and eosin (H&E) for routine histological evaluation.

For each case, representative sections including both the lesion and the surrounding background liver were selected. Special attention was paid to the following histological features :

- Architectural patterns of the lesion (nodular configuration, trabecular thickness, presence or absence of portal tracts and central veins)
- Cytological atypia and cell density
- Fibrous septa and abnormal vascular structures
- Background liver changes, including features suggestive of circulatory disturbance such as NRH-like architecture, sinusoidal dilatation, and vascular remodeling

Immunohistochemistry for CAM5.2

Immunohistochemical staining for CAM5.2 was performed using an automated immunostaining system (Leica Biosystems, Germany) according to the manufacturer's standard protocol. A commercially available monoclonal antibody against cytokeratin CAM5.2 (Leica Biosystems) was used.

Briefly, paraffin sections were deparaffinized and rehydrated, followed by heat-induced antigen retrieval. Endogenous peroxidase activity was blocked prior to incubation with the primary antibody. Antibody binding was visualized using a polymer-based detection system with 3,3′-diaminobenzidine (DAB) as the chromogen, and sections were counterstained with hematoxylin. Appropriate positive and negative controls were included in each staining run.

Evaluation of CAM5.2 staining patterns

CAM5.2 immunoreactivity was assessed independently in both the lesion and the surrounding non-lesional liver tissue. The following parameters were evaluated :

1. Cellular localization
   - Membranous and/or cytoplasmic staining of hepatocytes
   - Staining of bile duct epithelium and ductular structures
2. Distribution pattern
   - Nodular or lesion-confined
   - Diffuse
   - Patchy
   - Completely negative
3. Spatial regularity
   - Regular, geometrically organized staining aligned with fibrous septa or abnormal vascular structures
   - Irregular, random, or disorganized staining without spatial correlation
4. Staining intensity
   - Negative
   - Weak
   - Moderate
   - Strong

In FNH, particular attention was paid to whether CAM5.2-positive hepatocytes were arranged in a regular pattern along fibrous bands or abnormal vascular structures. In hepatocellular tumors, the presence or absence of spatial regularity was specifically evaluated.

Definition of CAM5.2 expression patterns

Based on preliminary observations, CAM5.2 staining patterns were conceptually categorized as follows :

- Regular (hemodynamic) pattern :

A geometrically ordered arrangement of CAM5.2-positive hepatocytes and ductular structures confined to nodules or aligned

along fibrous septa and abnormal vascular channels, interpreted as reflecting hemodynamic-driven phenotypic modulation.

・Irregular (neoplastic) pattern :

Diffuse, patchy, heterogeneous, or absent staining without spatial organization, interpreted as reflecting tumor-intrinsic differentiation status rather than hemodynamic influence.

Ethical considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional review board of our institution. Because this was a retrospective study using archived pathological specimens, the requirement for informed consent was waived (approval number : ToCMS No.4635).

RESULTS

CAM5.2 expression in focal nodular hyperplasia (FNH)

All six cases of FNH demonstrated a characteristic and highly reproducible CAM5.2 staining pattern (Figure 1). Immunoreactivity was strictly confined within the nodules and was absent in the surrounding background liver parenchyma, except for normal bile duct epithelium.

Within the nodules, CAM5.2 strongly highlighted ductular structures embedded in fibrous septa and showed membranous to cytoplasmic positivity in hepatocytes located immediately adjacent to these ductular reactions. Importantly, CAM5.2-positive hepatocytes were arranged in a geometrically regular pattern, aligned along fibrous bands and abnormal vascular structures. This configuration produced a distinctive "map-like" or "architectural" staining pattern that closely reflected the underlying vascular and stromal framework of the lesion.

The intensity of staining was generally moderate to strong, and the pattern was sharply demarcated at the interface between the lesion and the background liver, in which hepatocytes were consistently negative. This regular and lesion-restricted pattern was observed in all six FNH cases without exception.

We also performed Cytokeratin 7 (CK7) staining (Figure 2), but CK7 was positive only in the small bile ducts, and the "map-like" or "architectural" staining pattern was not detected.

CAM5.2 expression in the tumor difficult to distinguish between FNH and HCA

The single lesion that had been difficult to classify between FNH and HCA on conventional histology showed a CAM5.2 staining pattern identical to that observed in typical FNH. CAM5.2-positive hepatocytes and ductular structures were arranged in a regular and geometrically organized manner within the lesion, whereas the surrounding liver parenchyma lacked hepatocellular staining.

Based on this staining pattern, the lesion was reinterpreted as being more consistent with a circulatory disturbance–related hyperplastic lesion rather than a hepatocellular neoplasm.

CAM5.2 expression in hepatocellular adenoma (HCA)

Distinct CAM5.2 staining patterns were observed according to the molecular subtype of HCA (Figure 3).

HNF1α-inactivated HCA (2 cases)

Both cases showed only weak and focal CAM5.2 positivity in hepatocytes. The staining lacked spatial organization and was not associated with fibrous septa, abnormal vascular structures, or ductular reactions. No geometrical or nodular regularity was observed. The surrounding liver parenchyma was negative, except for bile duct epithelium.

Inflammatory HCA (2 cases)

In contrast, both inflammatory HCA cases exhibited diffuse and relatively strong CAM5.2 positivity throughout the tumor. However, despite the diffuse staining, the pattern was entirely disorganized and lacked any geometrical regularity. CAM5.2 expression was not confined to periductular areas and did not align with stromal or vascular architecture.

These findings indicate that CAM5.2 expression in HCA is determined by tumor subtype–specific biological properties rather than by hemodynamic or architectural factors.

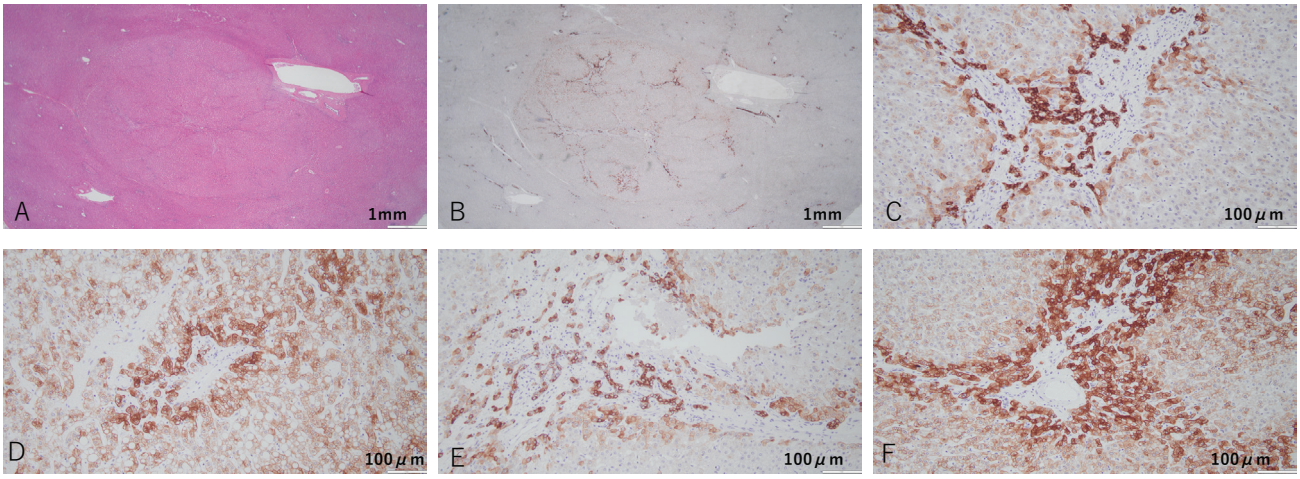

Figure 1. Regular CAM5.2 expression pattern in focal nodular hyperplasia (FNH).
(A) H&E staining shows a well-demarcated nodular lesion with fibrous septa and abnormal vascular structures.
(B) Low-power view of CAM5.2 immunostaining demonstrates positivity confined within the nodule, highlighting ductular structures and surrounding hepatocytes.
(C) High-power view shows strong CAM5.2 positivity in ductular structures and surrounding hepatocytes.
(D–F) High-power views show membranous to cytoplasmic CAM5.2 positivity in hepatocytes arranged in a geometrically ordered pattern along fibrous septa and abnormal vessels.
The surrounding background liver parenchyma is negative except for bile duct epithelium.

CAM5.2 expression in hepatocellular carcinoma (HCC)

The six cases of HCC showed highly heterogeneous CAM5.2 staining patterns (Figure 3) :

- Three cases demonstrated diffuse positivity throughout the tumor.
- Two cases showed patchy or heterogeneous staining, with irregularly distributed positive and negative areas.
- One case was completely negative for CAM5.2.

In none of the HCC cases did CAM5.2 expression show spatial regularity, nodular confinement, or alignment with fibrous septa or vascular structures. The staining patterns were random and disorganized, reflecting tumor-intrinsic heterogeneity rather than a structured response to tissue architecture.

These results clearly contrast with the orderly CAM5.2 expression observed in FNH.

DISCUSSION

FNH, NRH, and related hyperplastic lesions are widely accepted as manifestations of intrahepatic circulatory disturbances rather than true neoplastic processes (1-3, 5, 6). Abnormal vascular architecture, including arterial hyperperfusion, reduced portal venous inflow, and uneven sinusoidal perfusion, plays a central role in their pathogenesis (1, 4, 5). These hemodynamic alterations induce localized hepatocellular hyperplasia and ductular reactions, resulting in the characteristic nodular or regenerative patterns observed histologically (1, 2, 6). Our study demonstrates that CAM5.2 immunostaining visualizes this hemodynamic-driven tissue response in a highly reproducible and geometrically ordered fashion.

In all FNH cases examined, CAM5.2 expression was strictly confined within the nodules and arranged in a regular pattern along fibrous septa and abnormal vascular structures. This

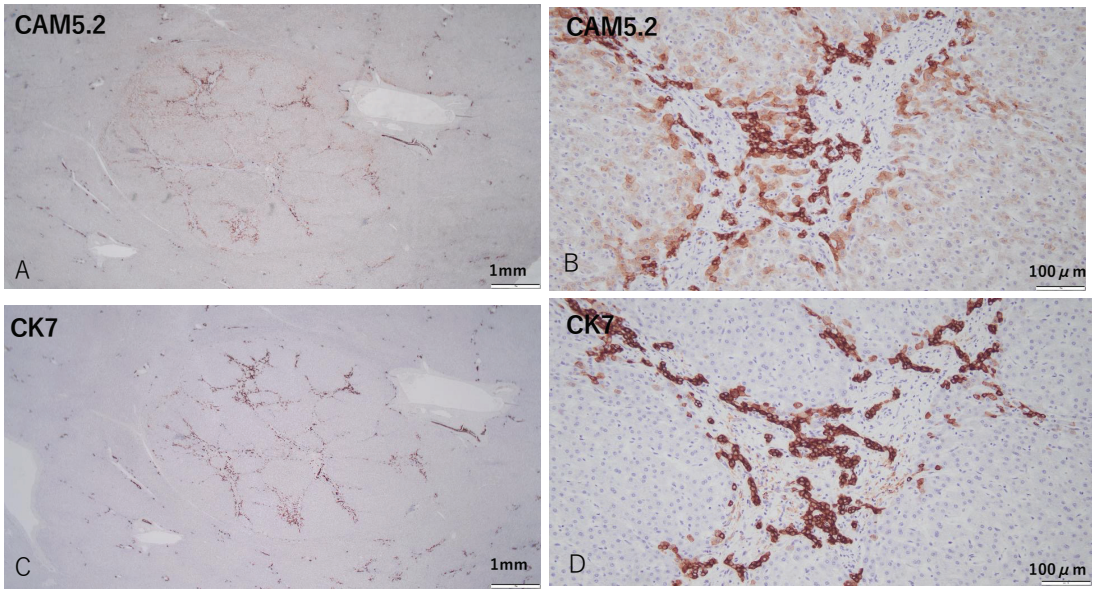

Figure 2. Comparison of Staining between CK7 and CAM5.2 in focal nodular hyperplasia (FNH)
(A) Low-power view of CAM5.2 immunostaining.
(B) High-power view of CAM5.2 immunostaining.
(C) Low-power view of CK7 immunostaining does not show a distinctive architectural staining pattern, unlike CAM5.2.
(D) High-power view of CK7 immunostaining shows positivity mainly in proliferating bile ductules, with much weaker staining in the surrounding hepatocytes, unlike CAM5.2.

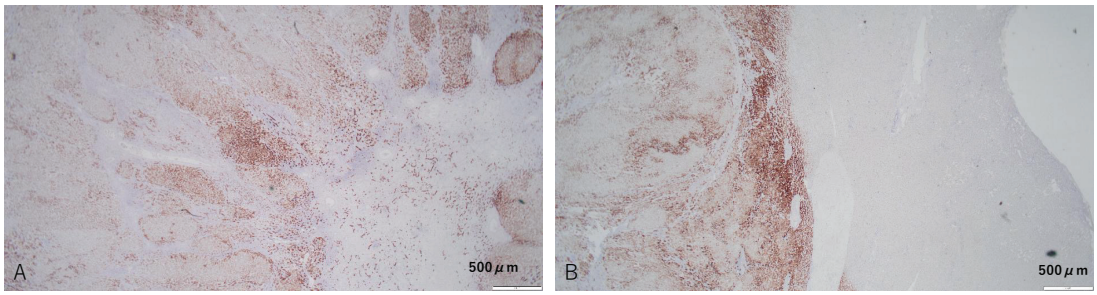

Figure 3. CAM5.2 expression in the tumor difficult to distinguish between FNH and HCA
(A), (B) Low-power view of CAM5.2 immunostaining. CAM5.2 immunostaining demonstrates positivity confined to the nodule, highlighting ductular structures and the surrounding hepatocytes, mimicking the staining pattern seen in FNH

finding is consistent with the well-organized stromal and vascular framework of FNH described in previous pathological studies (1, 4, 19). While CAM5.2 has traditionally been regarded as a general epithelial or ductular marker (10, 11), our data indicate that its spatial distribution pattern, rather than mere positivity or negativity, is diagnostically informative. The regular arrangement of CAM5.2-positive hepatocytes and ductular structures appears to reflect a coordinated, non-neoplastic tissue response to altered blood flow.

The biological basis of this phenomenon can be interpreted in the context of ductular reaction. Experimental and pathological studies have shown that altered hepatic blood flow, shear stress, hypoxia, and oxidative stress activate signaling pathways such as HGF, TGF-β, Notch, and Wnt/β-catenin, which are critically involved in biliary differentiation and progenitor cell activation (14-16). Under such conditions, hepatocytes may acquire partial biliary or ductular phenotypes, including expression of cytokeratins typically associated with bile duct epithelium. CAM5.2 positivity in FNH therefore represents a phenotypic modulation of hepatocytes toward a ductular reaction–like state, driven by hemodynamic stress rather than by genetic or neoplastic transformation.

Importantly, the spatial regularity of CAM5.2 expression observed in FNH sharply contrasts with its behavior in hepatocellular tumors. In our series, HCC exhibited highly heterogeneous staining patterns, including diffuse positivity, patchy distribution, and complete negativity, none of which showed architectural regularity. This observation is consistent with previous reports demonstrating that CAM5.2 expression in HCC depends on tumor differentiation, molecular background, and cytoskeletal remodeling rather than on tissue architecture (12, 13). Similarly, in HCA, CAM5.2 expression was subtype dependent : weak and focal in HNF1α-inactivated HCA and diffuse in inflammatory HCA, in agreement with earlier molecular and immunophenotypic classifications (9, 20). These results confirm that, in neoplastic lesions, CAM5.2 expression is governed primarily by tumor-intrinsic molecular programs rather than by hemodynamic factors.

From a diagnostic standpoint, the present study emphasizes that CAM5.2 is not a tumor marker in the liver. Instead, it functions as a visual indicator of hemodynamic-driven, ductular reaction–like phenotypic modulation of hepatocytes. A regular, geometrically ordered CAM5.2 pattern strongly supports a diagnosis of circulatory disturbance–related hyperplastic lesions such as FNH and helps exclude HCC and HCA, particularly in cases with minimal cytological atypia (12, 21-24).

In normal hepatocytes, CK8/18 exist as stable structural components deep within the cytoskeleton as intermediate filaments

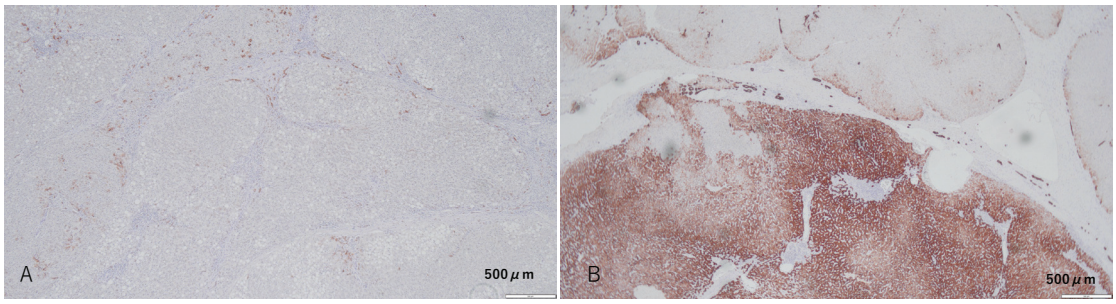

Figure 4. Distinct CAM5.2 expression patterns in hepatocellular adenoma (HCA).
(A) HNF1α-inactivated HCA shows weak and focal CAM5.2 positivity in hepatocytes without spatial organization.
(B) Inflammatory HCA shows diffuse and strong CAM5.2 positivity throughout the tumor ; however, the staining pattern lacks geometrical regularity and is not aligned with stromal or vascular architecture.
These findings indicate that CAM5.2 expression in HCA is determined by tumor subtype–specific molecular characteristics rather than by hemodynamic or architectural factors.

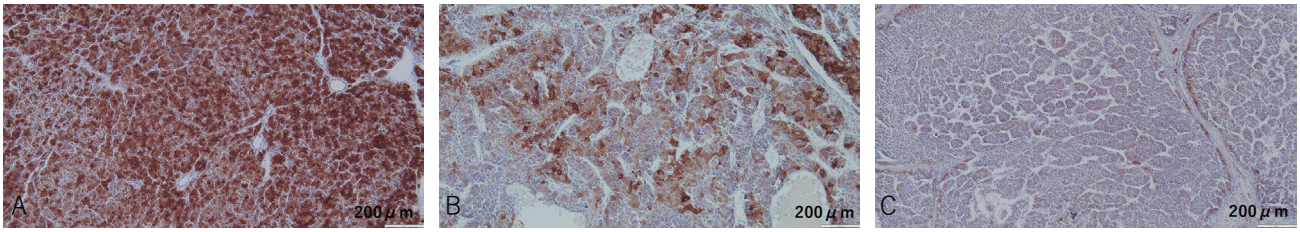

Figure 5. Heterogeneous CAM5.2 expression patterns in hepatocellular carcinoma (HCC).
Representative examples of HCC showing (A) diffuse positivity, (B) patchy and heterogeneous staining, and (C) complete absence of CAM5.2 immunoreactivity.
None of these patterns demonstrate spatial regularity or alignment with fibrous septa or vascular structures, reflecting tumor-intrinsic heterogeneity rather than an organized hemodynamic response.
(D) High-power view of the tumor-like area shows complete absence of CAM5.2 staining in both hepatocytes and bile duct epithelium.
This biphasic pattern supports the coexistence of an *induction phase* and an *extinction/remodeling phase* in circulatory disturbance–related lesions.

(13, 14, 25). In this state, antibodies have difficulty accessing epitopes, often resulting in weak staining or negativity with CAM5.2. Conversely, under conditions such as regeneration, degeneration, tumorigenesis, cholestasis, or ischemic stress, keratins undergo reorganization, solubilization, and redistribution. This facilitates antibody binding, leading to CAM5.2 positivity. Thus, CAM5.2 strongly reflects the "stress state of hepatocytes" rather than merely their "presence." Furthermore, CAM5.2 was originally developed for the detection of adenocarcinomas, epithelial tumors, and undifferentiated carcinomas. Therefore, it stains proliferating cells more effectively, particularly those with a restructured cytoskeleton and unstable cellular architecture. Cells with a highly differentiated and extremely stable cytoskeleton, such as normal hepatocytes, are not the intended primary targets.

This is of particular importance because many pathology laboratories lack access to the full spectrum of immunohistochemical panels recommended for hepatocellular tumor classification, including GS, glypican-3, HSP70, LFABP, CRP, and SAA (20, 23). In contrast, CAM5.2 is almost universally available in routine diagnostic pathology, requires no special reagents or platforms, and can be readily incorporated into standard immunohistochemical workflows. Moreover, its interpretation relies not on complex molecular subtyping but on straightforward recognition of spatial staining patterns, making it a practical, robust, and highly cost-effective adjunct marker, particularly in resource-limited or community hospital settings.

The limitations of this study include its retrospective nature and the relatively small number of cases. However, the striking contrast between regular and irregular CAM5.2 patterns across lesion categories, together with the internal control provided by the biphasic staining within a single liver, strongly supports the validity of our conclusions.

In summary, our study demonstrates that CAM5.2 immunostaining visualizes two fundamentally different biological processes in the liver :

(1) a hemodynamic induction process producing spatially ordered, ductular reaction–like phenotypic changes in hepatocytes in FNH ; and

(2) tumor-intrinsic differentiation programs producing irregular and disorganized expression in HCA and HCC.

Recognition of these distinct patterns provides a powerful and practical tool for distinguishing circulatory disturbance–related hyperplastic lesions from hepatocellular tumors and for avoiding overdiagnosis of malignancy in daily diagnostic practice.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by the 2025 Research Grant for Promoting Women in Science under the MEXT Initiative for Building a Diverse Research Environment (Female Leader Development Program), the 2025 Tokushima University President's Discretionary Fund (K. Tsuneyama), and the Kobayashi Foundation (M. Shimizu and W. Shao).

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