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Biological significance and translational challenges of circPICALM RNA and its encoded protein circPICALM-219aa in cholangiocarcinoma

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COMMENTARY

Circular RNAs (circRNAs) are an emerging field in cancer research. These covalently closed RNA molecules lack conventional 5' and 3' ends, which contributes to their relative stability. Many circRNAs show tissue- or context-specific expression[1]. Beyond their established capacity to interact with microRNAs and RNA-binding proteins, selected circRNAs can also be translated into functional peptides or proteins with potential roles in tumor biology[2,3].

Li *et al.* recently reported that circPICALM is overexpressed in intrahepatic cholangiocarcinoma (iCCA) and described an N^6-methyladenosine (m^{6}A)-regulated translational program through which circPICALM encodes a 219-amino-acid protein, circPICALM-219aa. Their data link this protein to sustained IL-6/JAK/STAT3 signaling and metastatic behavior in iCCA[4].

In the cohort studied by Li *et al.*, higher tumor circPICALM RNA expression was associated with vascular invasion, lymph-node metastasis, early recurrence, and poorer overall survival[4]. Mechanistically, the authors report that YTHDC1- and METTL3-dependent m^{6}A modification promotes circPICALM biogenesis, whereas DDX3 facilitates internal ribosome entry site (IRES)-dependent translation of circPICALM-219aa[4]. The translated protein acts as a competitive scaffold that interferes with the inhibitory SOCS3-STAT3 interaction, thereby sustaining IL-6/JAK/STAT3 signaling. Functional experiments in the source study support a metastasis-promoting role for circPICALM-219aa in the models examined[4].

An important next question is whether this pathway is broadly relevant across iCCA or concentrated in particular molecular or etiological subgroups. iCCA is biologically heterogeneous, and it will be informative to determine whether circPICALM expression and circPICALM-219aa activity differ between inflammation-associated

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tumors and genetically defined subsets, including *FGFR2*-rearranged or *IDH1*-mutant tumors. Such analyses could clarify whether circPICALM marks a general metastatic program or a context-dependent phenotype[5].

Several limitations of the current evidence should also be considered. The clinical associations were derived from a single-center cohort and require independent, preferably multicenter, external validation. Protein-level conclusions depend on the specificity and reproducibility of the custom antibody used to detect circPICALM-219aa and should therefore be confirmed. In addition, experimental metastasis models cannot fully reproduce the natural history, stromal complexity, and immune context of human iCCA.

From a clinical perspective, tumor circPICALM RNA is a candidate prognostic biomarker in iCCA, given its association with vascular invasion, metastasis, and early recurrence. Its potential value in postoperative risk stratification requires further validation, particularly regarding its prognostic relevance beyond established clinicopathological factors. Moreover, the detection of circPICALM RNA in blood or bile could offer opportunities for non-invasive monitoring. However, its presence in these compartments, diagnostic performance, and added value compared with established biomarkers such as carbohydrate antigen 19-9 (CA19-9) remain to be investigated.

The immunological consequences of circPICALM-219aa expression also remain largely unexplored. STAT3 is a common signaling node in inflammation-associated cancers. Future studies should define the relative contribution of circPICALM-219aa to STAT3 activation compared with other inflammatory and oncogenic inputs present in iCCA[6]. Persistent STAT3 activation is widely recognized as a master regulator of tumor immune suppression, orchestrating the recruitment and functional polarization of multiple immune cell populations while dampening anti-tumor immunity[6]. Consequently, the biological impact of circPICALM-219aa is likely to extend beyond tumor cells themselves. Future studies employing immunocompetent or humanized models, together with spatial transcriptomics and single-cell immune profiling, will be necessary to determine whether circPICALM-219aa also remodels the immune microenvironment and contributes to resistance against immunotherapy[7].

The peptide could represent a candidate junction-derived neoepitope with potential tumor selectivity. Its absence from conventional PICALM does not establish tumor specificity. Expression in normal tissue, human leukocyte antigen (HLA) presentation, T-cell recognition, cross-reactivity with normal peptides or tissues, and safety all require experimental evaluation before immunotherapeutic applications can be considered. Nevertheless, circRNA-derived proteins might be a good candidate for vaccination approaches, targeted protein degradation or T-cell receptor engineering, since many traditional oncogenes have limited treatment specificity due to their considerable similarity to normal proteins.

Selective targeting of circPICALM or circPICALM-219aa would require efficient intracellular delivery and sufficient selectivity to avoid perturbing linear PICALM. Intratumoral heterogeneity may limit target coverage, and adaptive or acquired resistance could emerge if tumors maintain STAT3 signaling through alternative cytokine or oncogenic pathways. Moreover, circPICALM-219aa is a small intracellular protein whose reported function depends on protein-protein interactions, a class of targets that can be pharmacologically challenging. Additionally, its downstream IL-6/JAK/STAT3 pathway has proven challenging to target therapeutically[8].

Nevertheless, emerging approaches, including targeted protein degradation, peptide-based inhibitors, and back-splice-junction-specific antisense oligonucleotides, may offer new therapeutic opportunities.

Overall, the identification of circPICALM-219aa as a metastasis-promoting protein highlights the oncogenic potential of the traditionally considered non-coding transcriptome. The clinical associations support further investigation of circPICALM RNA as a prognostic biomarker, whereas the protein provides a mechanistic basis for exploring therapeutic and immunological hypotheses. Neither molecule is ready for diagnostic or therapeutic use, but circRNA and circRNA-derived proteins represent an additional layer of tumor biology that may yield prognostic biomarkers, immunological targets, or druggable dependencies once their expression, specificity, and clinical relevance have been independently validated. Further research may uncover additional circRNA-derived proteins with biological and therapeutic relevance.

DECLARATIONS

Authors' contributions

Conceptualization: Heinrich B, Greten TF
Literature review: Heinrich B
Writing - original draft: Heinrich B
Critical review: Greten TF
Writing - review and editing: Heinrich B, Greten TF
Both authors read and approved the final manuscript.

Availability of data and materials

Not applicable.

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During the preparation of this manuscript, the AI tool ChatGPT (GPT-6 Sol, released 2026-09-22) was used to assist with language editing, preparation of responses to reviewer comments, and the formulation of proposed revisions to clarify the interpretation of published evidence. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. Both authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

Both authors declared that there are no conflicts of interest. The contribution of the NIH author is considered a work of the United States Government. The findings and conclusions presented in this paper are those of the authors and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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