FAP-Targeted Nanoparticle-based Imaging in Cancer: A Systematic Review

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ABSTRACT

Background: Fibroblast Activation Protein (FAP)-targeted nanoparticles (NPs) are designed to accumulate in cancerous stroma. These NPs hold promise for imaging applications in cancer therapy.

Objective: This systematic review aimed to comprehensively explore the use of FAP-targeting NPs for cancer diagnosis through different imaging modalities.

Material and Methods: This systematic review followed the framework proposed by O'Malley and Arksey. Peer-reviewed studies were searched in the Scopus, Science Direct, PubMed, and Google Scholar databases. Eligible studies were selected, and data were extracted to investigate the FAP-targeting NPs in imaging. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was also utilized to present the results.

Results: Five studies met the specified inclusion criteria and were finally selected for analysis. The extracted data was classified into two categories: general and specific data. The general group indicated that most studies have been conducted in Mexico and have increased since 2022, and the specific group showed that colorectal cancer and Nude mice have received the most research attention. Furthermore, FAP-targeted NPs have demonstrated superior diagnostic imaging capabilities, even compared to specific methods for each cancer type. Also, they have been safe, with no toxicity.

Conclusion: FAP-targeted NPs using different ligands, such as Fibroblast Activation Protein Inhibitor (FAPI), can accurately detect tumors and metastases, and outperform specific cancer peptides like PSMA in cancer diagnosis. They are also non-toxic and do not cause radiation damage to tissues. Therefore, FAP-targeted NPs have the potential to serve as a viable alternative to FAP-targeted radionuclides for cancer diagnosis.

Citation: Abbasi S, Khademi S, Montazerabadi AR, Sahebkar AH. FAP-Targeted Nanoparticle-based Imaging in Cancer: A Systematic Review. *J Biomed Phys Eng*. 2024;14(4):323-334. doi: 10.31661/jbpe.v0i0.2404-1754.

Keywords

Neoplasms; Fibroblast Activation Protein (FAP); Imaging; Nanoparticles (NPs); Molecular Imaging

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Received: 30 April 2024
Accepted: 12 June 2024

Introduction

Malignant tumors are a significant cause of mortality worldwide, and the tumor stroma is a critical component of the Tumor Microenvironment (TME). The TME significantly influences the spread, survival, and proliferation of cancer cells via numerous cell-signaling pathways [1-3]. Cancer-Associated Fibroblasts (CAFs), a heterogeneous group of cells, play a critical role in the TME [4-6]. Furthermore, Fibroblast Activation Protein (FAP) is highly expressed not only

in CAFs on the stroma and cell membrane of approximately 90% of epithelial cancers [7], but also in active extracellular matrix remodeling conditions, such as liver cirrhosis [8, 9].

Nanoparticles (NPs) targeting FAP have been suggested as promising tools for detecting and diagnosing cancers because FAP-expressing cells are associated with tumor growth, angiogenesis, and metastasis [10, 11]. Consequently, targeting FAP-expressing cells with NPs leads to highly specific and sensitive cancer diagnoses using imaging techniques [11, 12]. Different types of NPs have been used for targeted-FAP imaging, such as magnetic and gold nanoparticles that are functionalized with ligands like antibodies or peptides [13-16].

FAP-targeted NPs have the potential not only for diagnosis but also for cancer treatment [17, 18]. However, challenges associated with the development of FAP-targeted NPs include stability, biodistribution, and toxicity [19-21]. Furthermore, different imaging modalities are used in combination with FAP-targeted NPs, such as Computed Tomography [CT], Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), optical imaging, and Single Photon Emission Computed tomography (SPECT) [18, 22-24]. MRI can provide images with high spatial resolution, while CT scans provide high spatial resolution in fast acquisition time. Additionally, imaging undertaken with PET scans has high specificity and sensitivity to detect FAP-expressing cells [25, 26]. Therefore, the selection of imaging modalities can affect the performance of FAP-targeting NPs in cancer diagnosis and treatment monitoring.

This systematic review aimed to investigate the use of FAP-targeted NPs for cancer diagnosis through imaging modalities.

Material and Methods

Method

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline and the methodological framework proposed by O'Malley and Arksey [27]. This framework provides a systematic approach to reviewing literature, including the identification of study questions, related studies, selection of included studies, providing a vital element chart, and reporting findings [28]. The PRISMA guidelines are science-based criteria that provide concise items for use in meta-analyses, systematic and scoping reviews. The present study used the PRISMA-ScR guidelines for the review process [29].

Identification of the research question

This systematic review aimed to provide a comprehensive overview of the FAP effects on cancer diagnosis using imaging modalities by addressing the following questions: 1) which cancers can be detected through FAP-targeting NPs 2) which imaging modalities are most effective in detecting FAP-expressing cancer cells, and 3) which NPs are used for imaging the targeted FAP.

Search strategy

The search strategy involved a combination of relevant keywords and MeSH terms to retrieve all relevant studies on FAP-targeted NPs for cancer diagnosis. The electronic databases used in the search included PubMed, Scopus, ScienceDirect, and Google Scholar, and the search was restricted to articles published in the English language up to March 27, 2023, without any geographic or time restrictions. The search strategy included the following keywords: ("cancer" OR "neoplasms" OR "tumor") AND ("nanoparticles") AND (("FAP") OR ("fibroblast activation protein")) AND ("imaging"). The search terms were combined using Boolean operators: "AND" and "OR" to ensure the inclusion of all relevant articles.

The search strategy generated a total of 4,388 citations from the four databases, which were then imported into the Endnote X9

reference management tool (Clarivate Analytics, Philadelphia, PA, USA). After eliminating duplicate and irrelevant studies through title and abstract screening, 23 articles were selected for full-text review. Of these, 18 studies did not meet the inclusion criteria, resulting in five articles that were eligible for data extraction (Figure 1).

Inclusion criteria

Studies were considered eligible if they satisfied the following criteria: a) the use of NPs for cancer imaging diagnosis in the context of FAP expression, and b) publishing in a peer-reviewed journal.

Exclusion criteria

Studies that satisfied the following criteria were excluded: (1) reviews, editorials, or conference abstracts, and (2) articles that did not use any NPs for cancer imaging in the context of FAP expression.

Data extraction

Two reviewers independently screened the titles, abstracts, and full texts of the identified studies based on the inclusion and exclusion criteria. Any discrepancies were resolved through discussion and consensus.

Data synthesis

A narrative synthesis of the findings was conducted due to the heterogeneity of the included studies in terms of study design, NP type, FAP targeting strategy, imaging modality, and cancer types.

Screening Procedure

The authors conducted a meeting to extract the following data from the articles: study design, methodology, conceptualization, and data. In the initial screening step, the authors independently assessed the abstract and title of retrieved articles to exclude irrelevant studies that did not meet the criteria. The screened

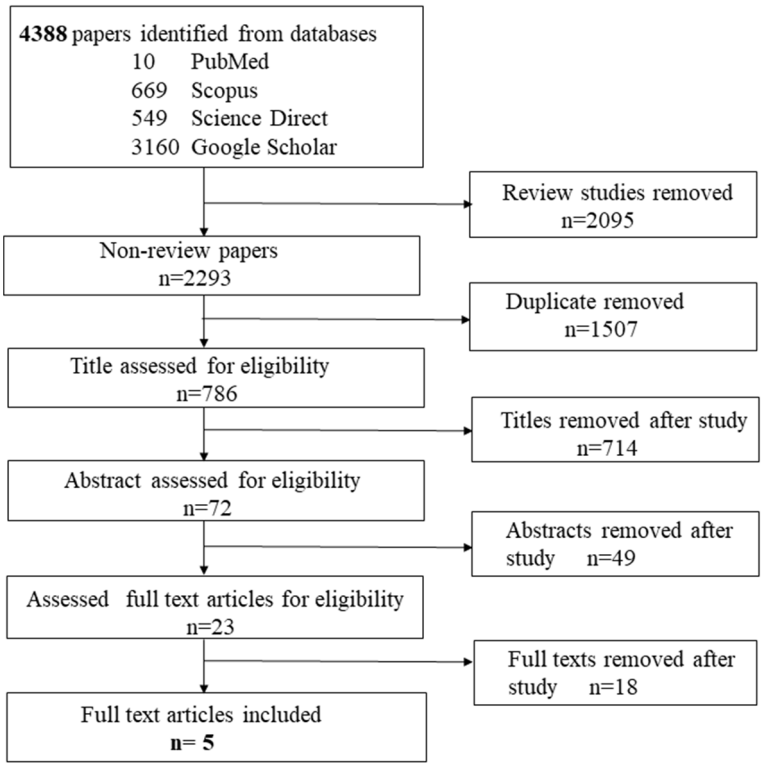

Figure 1: Study selection flowchart.

studies were then double-checked by the first author and confirmed articles were discussed by groups to reach a consensus. Finally, the full texts of selected studies were reviewed, resulting in identifying eligible studies to extract data.

Data items

In this step, some data for eligible studies were extracted in two categories (general and specific data), as follows: 1) general data: study titles, aim, conclusion, author (s), study location (country), the publication year, and 2) specific data: information on NPs used, such as size and type, as well as cell lines and their respective quantities.

Tabulating the data

All data were independently extracted by the authors, and a checklist (as mentioned above) was then designed for the findings (data item section), i.e., the first author assembled the extraction results with a double-check. Also, the first author prepared a preliminary list according to two studies [9, 30] to extract the NPs' role in FAP imaging. The obtained list was assessed in the meetings, resulting in general and specific sets.

Results

General information

This section presents a comprehensive overview of the included articles, such as study title, aims, conclusions, publication years, and journals (Table 1).

Table 1: First author's name, and publication year

Ref.	Authors et al.	Journals
[31]	Nicole Dmochowska	Nano micro small
[32]	Diana Trujillo-Benítez	Molecules
[33]	Myrna Luna-Gutiérrez	Pharmaceutics
[34]	Tania Hernández-Jiménez	Nanomaterials
[35]	Qianwen Yu	Controlled Release

Out of the Five eligible studies, three articles were authored by researchers from Mexico (44%), while the remaining articles were contributed by authors from the USA (14%), China (14%), Italy (14%), and Australia (14%), indicating a worldwide scope of research. The initial paper was published in 2020, whereas three articles were published in 2022, and the most recent article was published in 2023 (Figure 2).

Specific information

In reviewed studies [31-35], the utilization of FAP-targeting NPs resulted in better delineation of prostate cancer using MRI modality, than PSAM, a specific prostate peptide [31]. These targeted NPs exhibited superior tumor penetration and higher uptake compared to the other NP formulations [35], and have demonstrated success in treating tumors [33]. Administration of FAP-targeted NPs led to reducing in tumor volume [34].

However, the importance of NP toxicity and safe exposure levels has led to the development of NPs with less toxic profiles [34, 35]. According to the research findings, the use of NPs targeting FAP holds promise for accurate cancer diagnosis [31, 33, 35]. Table 2 presents the conclusions and novelties of the reviewed studies.

In addition, all reviewed studies [31-35] have focused on exploring the sensitivity and accuracy of the FAP-targeting NPs method by comparing the obtained results to those of other studies. Nevertheless, there are undoubtedly many ambiguous and unknown issues that need investigating further. Additionally, the significance of NPs toxicity, which is associated with their safe exposure levels, has prompted efforts to design or develop NPs with lower toxicity profiles [34, 35].

The hydrodynamic diameter is a critical parameter in the characterization of NPs because it provides information on their effective size and diffusion behavior, which is essential for determining their potential applications in

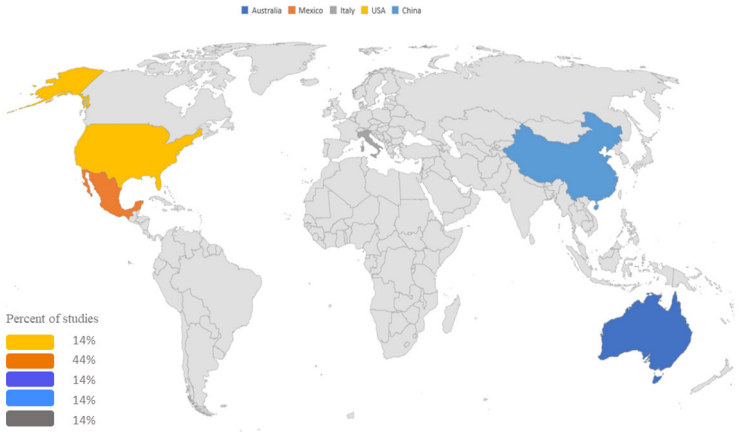

Figure 2: Geographical variation of included studies

Table 2: Novelties and conclusion included articles

Ref.	Novelty	Conclusion
[31]	Comparing FAP and PSMA effects on image contrast for prostate tumor delineation	FAP-targeted NPs outperformed PSMA-targeted NPs in delineation of prostate cancer
[32]	Evaluating a novel FAPI radiopharmaceutical based on the ^{99m}Tc structure in SPECT imaging method	The novel FAPI was suitable for SPECT imaging of tumor microenvironment
[33]	Assessing the therapeutic and dosimetry response of Lu_2O_3-iFAP as well as Lu_2O_3-iPSMA NPs in nuclear medicine	$^{177}Lu_2O_3$-iPSMA and $^{177}Lu_2O_3$-iFAP could potentially prevent colorectal tumor progression by leading to prolonged tumor retention
[34]	Developing [^{177}Lu] Lu-iFAP/iPSMA NPs using GMP-compliant radiopharmaceutical processes, and assessing their toxicity	Toxicity of [^{177}Lu] Lu-iFAP/iPSMA was selective to malignant tumors without any histological changes in healthy tissues
[35]	Constructing a new responsive NPs to the membrane biomarker FAP-α on CAFs as well as laser irradiation of NIR	The new NP greatly combined photothermal therapy with chemotherapy with a better drug delivery method for treatment.

FAP: Fibroblast Activation Protein, PSMA: Prostate-Specific Membrane Antigen, NP: Nanoparticles, FAPI: Fibroblast Activation Protein Inhibitor, SPECT: Single Photon Emission Computed Tomography, GMP: Good Manufacturing Practices, CAF: Cancer-Associated Fibroblast, NIR: Near Infrared

imaging, drug delivery, and catalysis. Additionally, the mean diameter of NPs is defined as the average diameter of the particles in a given sample or their size distribution [36-38]. Smaller NPs can easily penetrate cell membranes, while larger NPs are more likely to be cleared by the immune system. Also, the size and surface properties of NPs can also have an effect on their interactions with other biomolecules [39, 40]. It is crucial to note that NPs with smaller sizes may show greater toxicity due to their ability to interact with cellular components and potentially penetrate cell membranes, and larger NPs can also have highly toxicity because of their potential to induce tissue damage and inflammation.

Consequently, some criteria must be considered, such as physicochemical properties, dose, biological effects, distribution, cellular uptake, and accumulation to accurately evaluate the NPs toxicity.

In this systematic review, we analyzed the characteristics of three types of NPs, namely iron oxide, Lu_2O_3, and HSA-PTX@CAP-ITSL, based on parameters, such as their hydrodynamic and mean diameter. Table 3 provides information on the hydrodynamic and mean diameters of the NPs, showing that their sizes are mostly within an acceptable range of toxicity.

The results of the current study indicate that FAP targeting NPs did not cause any significant changes in tissue morphology, in comparison with the control group, which has no NPs [39]. In addition, some recent evidence reveals that NPs may exhibit selective toxicity towards malignant tumors without any histological changes in healthy tissues, as observed in mice following intravenous injection [34]. Therefore, some NPs may have potential as targeted agents for cancer diagnosis, with minimal side effects on healthy tissues.

The reviewed articles investigated various cancers that colorectal cancer was the most commonly studied (40%, Figure 3a). Two cell culture media were predominantly utilized,

Table 3: Characteristics of nanoparticles

Ref.	NPs	NP diameter size (nm) Hydrodynamic / Mean
[31]	iron oxide	60–65 / 16.2±3.5 nm
[32]	Lu_2O_3	No report / No report
[33]	Lu_2O_3	105±20 / 36±7
[34]	Lu_2O_3	95±22 / 23.4
[35]	HSA-PTX@CAP-ITSL	123.9±1.9 / Not report

NP: Nanoparticles

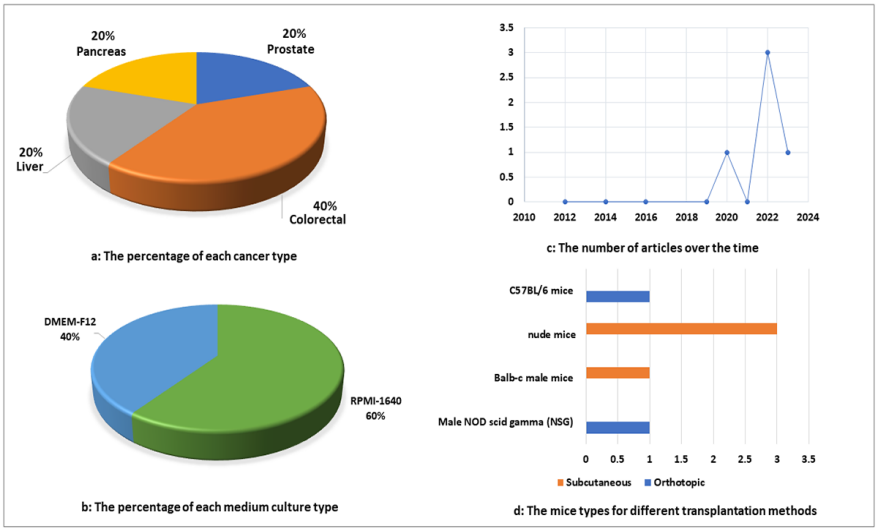

Figure 3: Classified information about the included articles: **a**) article numbers over time, **b**) cell culture types, **c**) number of articles published, and **d**) aims of included studies

DMEM (40%) and RPMI (60%) (Figure 3b). The number of published articles has been also increasing over time, showing a growing interest in this field (Figure 3c). In molecular imaging studies, different mouse strains were mostly used, including Non-obese Diabetic/Severe Combined Immunodeficiency (NOD/SCID) for xenograft models due to their immunodeficiency [41-43], and BALB/c mice, preferred for their high productivity and relatively low cost [44-46]. Figure 3d illustrates the frequencies of mouse strains and their respective tumor-injected positions.

According to the findings, a diverse range of human and murine cell lines are used, such as CT26, C26, C32, N30, and U87MG cells, which have high expression levels of FAP [40]. Overexpression of FAP can decrease tumor cell proliferation and invasion in lung cell carcinoma [41, 42], underscoring the significance of FAP in cancer progression. Figure 4 shows that the maximum seeded cells were 1×10^6, regardless of the cell line. Just one study [33] studied a patient, a 67-year-old woman with unresectable liver metastases from colorectal cancer, in addition to cell line HCT116.

Discussion

FAP, as a cell surface protein, is highly expressed in the TME of many cancers, including colorectal cancer [43-45]. Various targeting methods have been developed to detect FAP using NPs or radionuclides, and these methods have been advanced through the use of different imaging modalities such as PET, SPECT, MRI, and CT [9, 30].

The FAP-targeting radionuclide approach is promising for cancer diagnosis and treatment, involving the use of radiolabeled antibodies or peptides that target FAP using radionuclides detected through imaging modalities. FAPI, a small peptide that specifically binds to FAP, has recently been radiolabeled and employed by PET in preclinical studies [46-48]. While many studies have investigated the use of FAP-targeting radionuclides, especially ^{68}Ga, for cancer diagnosis [25, 26, 49-53], only a few articles have explored the potential of NPs

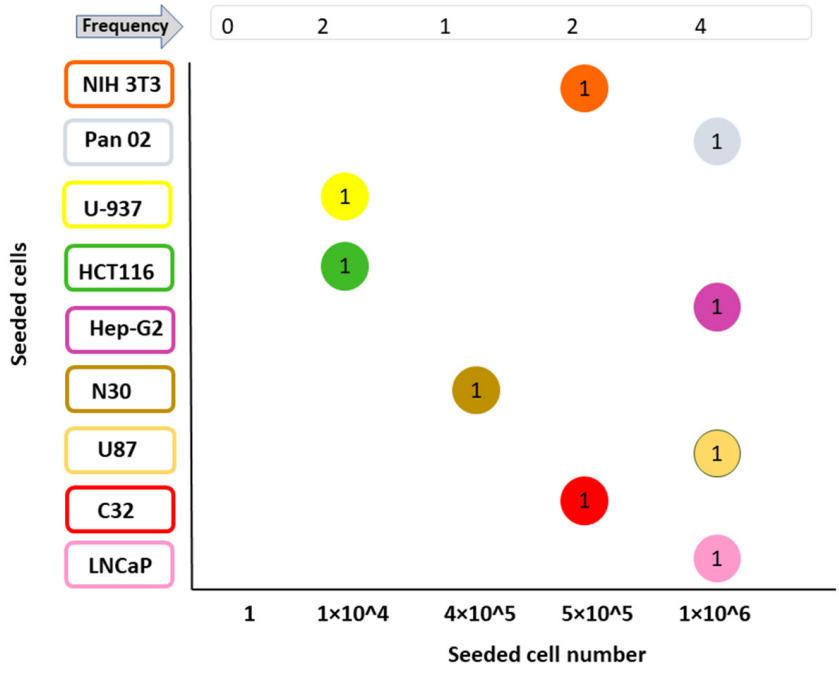

Figure 4: Cell lines and their counts used in included articles

for FAP-targeting [31-35].

NPs can be specifically targeted and bound to certain biomolecules or cells, enhancing the specificity and sensitivity of imaging methods and enabling more accurate detection with reduced side effects than radionuclides [54, 55]. Moreover, NPs have greater specificity in targeting and higher contrast in imaging compared with radionuclides, while radionuclides can provide quantitative measurements with higher sensitivity

The FDA-approved radionuclides targeting FAP have shown high sensitivity in cancer diagnosis [52-54]. However, PET scans have limitations, including limited spatial resolution compared to other imaging modalities like CT and MRI, ionizing radiation exposure that can pose risks with repeated scans over time, higher costs, and limited availability due to the need for professional expertise and equipment [55-57].

To overcome these limitations, researchers are exploring alternative imaging-based diagnostic techniques. CT scans offer better resolution, lower radiation exposure, and more affordable costs than PET scans. Therefore, studies are focusing on using NPs as suitable agents for CT imaging. However, selecting appropriate NPs and their properties is crucial for achieving high sensitivity and specificity in imaging.

Although NP-based approaches targeting FAP have the potential to outperform radionuclide-based approaches with fewer adverse effects, few studies [31-35] have investigated this approach due to it being a relatively new field. Thus, we conducted a systematic review to identify studies that have investigated targeting FAP with NPs. To the best of our knowledge, this systematic review is the first study to investigate the use of FAP-targeting NPs with imaging techniques.

Our review of five articles published from 2020 to 2023 revealed a noticeable increase in the applications of FAP-targeting NPs in cancer research using imaging methods. We classified the extracted information into general and specific groups, including cancer type, NPs, mice, and medium culture types. FAP-targeted NPs have fewer adverse side effects and have shown promising results in various studies, such as Lu_2O_3-based FAP and PSMA evaluations for dosimetry and therapeutic response [33], toxicity in vitro and in vivo studies [34], and dual-responsive lipid-albumin NPs targeted CAFs to enhance drug perfusion [35].

Our study showed that FAP-targeting NPs can better delineate prostate cancer than PSMA using MRI and penetrate tumors better with higher uptake than other NP formulations, leading to effective tumor treatment and diagnosis. Treatment with FAP-targeted NPs may result in a significant reduction in tumor volume.

Conclusion

FAP-targeting NPs can provide precise detection of tumors and metastases using imaging methods. FAP-targeted NPs may have significantly better diagnostic performance compared to specific peptides for cancer, such as PSMA for prostate cancer, highlighting the great accuracy and sensitivity of this approach. While FAP targeting with radionuclides is currently being studied in clinical trials, NPs can be a good alternative to overcome the harmful effects of radionuclides.

Authors' Contribution

The study was conceived and designed by S. Abbasi and AR. Montazerabadi. The draft was revised by AH. Sahebkar and S. Khademi. S. Abbasi conducted the analysis and wrote the initial draft, which was further revised by AR. Montazerabadi and S. Khademi. Finally, AH. Sahebkar completed the final version of the paper. All the authors read, modified, and approved the final version of the manuscript.

Funding

There is no funding for this study.

Conflict of Interest

None

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