What are the mechanisms of Plasmodium falciparum gametocyte interactions with bone marrow cells during malaria infection?

P. falciparum gametocytes interact with bone marrow cells through multiple stage-specific mechanisms, including receptor-mediated adhesion, extracellular vesicle signaling, and mechanical retention processes.

Abstract

Plasmodium falciparum gametocytes engage bone marrow cells through a range of mechanisms that vary by gametocyte stage and cell type. Messina et al. (2018) report that immature gametocytes adhere to human mesenchymal stem cells via trypsin-sensitive ligands that trigger angiogenic cytokine secretion. Neveu et al. (2020) describe gametocyte development within late erythroblasts, mediated by extracellular vesicles and glycophorin A, which delays erythroid maturation. Suresh et al. (2023) observe that soluble factors from mesenchymal stem cells enhance mosquito infectivity, while Corbett et al. (2021) note that interactions with bone marrow-derived macrophages induce tumor necrosis factor, MIP-2, and nitric oxide.

Additional studies detail alternative sequestration and retention pathways. Rogers et al. (2000) identify cytoadherence of stage III/IV gametocytes to stromal and endothelial cells via receptors such as ICAM-1, CD49c, CD166, and CD164, whereas Silvestrini et al. (2012) report minimal adhesion involving nonclassical mediators. Joice et al. (2014) describe extravascular accumulation with association to erythroblastic islands, and De Niz et al. (2018) along with Peatey et al. (2013) report that homing, transmigration, and physical retention rely on actin-dependent processes and membrane elasticity. None of the studies implicate classical PfEMP1-mediated adhesion.

In sum, the papers collectively indicate that P. falciparum gametocyte interactions with bone marrow cells depend on nonclassical adhesion mechanisms, mechanical retention, and host cell modification to secure an extravascular niche conducive to parasite development and transmission.

Paper search

Using your research question "What are the mechanisms of Plasmodium falciparum gametocyte interactions with bone marrow cells during malaria infection?", we searched across over 126 million academic papers from the Semantic Scholar corpus. We retrieved the 50 papers most relevant to the query.

Screening

We screened in papers that met these criteria:

- **Parasite Stage**: Does the study investigate P. falciparum gametocytes (not solely asexual stages)?
- **Tissue Type**: Does the study examine bone marrow tissue or cells (not exclusively peripheral blood)?
- **Mechanistic Analysis**: Does the study analyze molecular or cellular mechanisms (not purely descriptive or clinical outcomes)?
- **Study Type**: Is the study either primary research with original data OR a systematic review/meta-analysis specifically focused on gametocyte-bone marrow interactions?
- **Experimental Approach**: Does the study include either in vitro or in vivo experimental analysis of gametocyte-cell interactions?
- **Study Design**: Does the study go beyond a pure clinical case report by including mechanistic analysis?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Design Type**:

  Identify the specific type of study design used:

- Specify if it is an in vitro study, in vivo study, animal model, human study, or mixed methodology
- If an animal model, specify the exact animal species used
- Look in the methods section for explicit description of study design
- If multiple design types are used, list all in order of prominence
- If unclear, note "design not clearly specified"

Example answers:

- "In vivo rodent model using Plasmodium berghei"
- "In vitro cell culture study with human primary erythroblasts"
- "Mixed methodology: in vitro and in vivo components"

- **Experimental Model and Techniques**:

  Detail the specific experimental techniques and models used:

- List all key methodological approaches (e.g., intravital microscopy, cell-cell adhesion assays, co-culture experiments)
- Specify any specialized techniques used to observe or measure gametocyte interactions
- Include details about imaging or measurement technologies
- Note any genetic modifications or transgenic parasite lines used

Look in methods and techniques sections for comprehensive details.

- **Gametocyte Interaction Mechanisms**:

  Extract specific details about:

- Observed interactions between gametocytes and bone marrow cells
- Mechanisms of gametocyte movement, adhesion, or transmission
- Any molecular or cellular processes described
- Specific proteins or cellular structures involved in interactions

Focus on direct descriptions of interaction mechanisms in results and discussion sections. Prioritize direct observations and experimental findings over speculative statements.

- **Cellular Environment and Localization**:

  Describe gametocyte localization and cellular environment:

- Specific bone marrow compartments where gametocytes were observed
- Stages of gametocyte development in different cellular contexts

- Interactions with specific cell types (e.g., mesenchymal stem cells, erythroblasts)
- Any changes in gametocyte behavior within different cellular environments

Extract precise location descriptions from methods, results, and discussion sections.

- **Primary Outcomes and Significant Findings**:

  Extract the most significant research findings:

- Primary outcomes directly related to gametocyte interactions
- Quantitative measurements of interaction mechanisms
- Novel observations about gametocyte behavior
- Implications for understanding malaria transmission

Focus on results section and author's explicit statements about key findings. Prioritize numerical data and direct experimental observations.

Results

Characteristics of Included Studies

Study	Study Design	Cell Types Investigated	Gametocyte Stages Studied	Key Mechanisms Examined	Full text retrieved
Messina et al., 2018	Laboratory-based cell culture with human primary bone marrow mesenchymal stem cells and Plasmodium falciparum gametocytes	Human bone marrow mesenchymal stem cells, Plasmodium falciparum gametocytes	Immature and mature gametocytes	Adhesion to human bone marrow mesenchymal stem cells, cytokine and growth factor secretion, angiogenesis	Yes
Neveu et al., 2020	Mixed methodology: laboratory-based and animal/human components	Human erythroblasts, bone marrow smears	Immature and mature gametocytes	Development within erythroblasts, delay of erythroid differentiation, extracellular vesicle-mediated effects	Yes

Study	Study Design	Cell Types Investigated	Gametocyte Stages Studied	Key Mechanisms Examined	Full text retrieved
Suresh et al., 2023	Mixed methodology: laboratory-based cell culture with human primary cells and animal mosquito model	Mesenchymal stem cells, Plasmodium falciparum gametocytes, mosquitoes	Early and mature gametocytes	Mesenchymal stem cell-mediated enhancement of infectivity, soluble factors	No
Corbett et al., 2021	Laboratory-based cell culture with immortalized mouse C57Bl/6 bone marrow-derived macrophages and transgenic Plasmodium falciparum	Mouse bone marrow-derived macrophages, Plasmodium falciparum gametocytes	Early and late gametocytes	Phagocytosis, induction of inflammatory mediators	Yes
Rogers et al., 2000	Laboratory-based study with human bone marrow cells	Human bone marrow stromal and endothelial cells	Stage III, IV, V gametocytes	Cytoadherence, receptor identification (ICAM-1, CD49c, CD166, CD164)	No
Silvestrini et al., 2012	Laboratory-based cell culture with human endothelial cell lines	Endothelial cell lines (including bone marrow-derived)	Immature and mature gametocytes, asexual stages	Adhesion properties, tissue specificity, receptor involvement	Yes
Joice et al., 2014	Mixed methodology: animal/human study and laboratory-based components	Human bone marrow (autopsy), erythroid precursors	All gametocyte stages	Localization, association with erythroblastic islands, phagocytosis	Yes

Study	Study Design	Cell Types Investigated	Gametocyte Stages Studied	Key Mechanisms Examined	Full text retrieved
De Niz et al., 2018	Mixed methodology: animal rodent model (Plasmodium berghei) and human autopsy study	Mouse bone marrow, human autopsy samples	Immature and mature gametocytes	Homing, transmigration, deformability, actin-dependence	Yes
Peatey et al., 2013	Laboratory-based cell culture with erythroid progenitors	Erythroid progenitors, Plasmodium falciparum gametocytes	Developing gametocytes	Enhancement of gametocyto-genesis, membrane elasticity	No
Neveu et al., 2018	Laboratory-based cell culture with human primary erythroblasts and erythroid cell lines	Human erythroblasts, erythroid cell lines, gametocyte-infected erythrocytes	Immature gametocytes	Adhesion assays, STEVOR protein role, membrane topology	Yes

Study Design:

- Laboratory-based only:6 studies
- Mixed methodology (laboratory-based and animal/human):4 studies
- Animal/human only:We didn't find mention of any studies using only animal or human methods.

Cell Types Investigated:

- Plasmodium falciparum gametocytes:4 studies
- Human bone marrow mesenchymal stem cells or mesenchymal stem cells:2 studies
- Human erythroblasts, erythroid precursors, progenitors, or cell lines:4 studies
- Endothelial cells (including lines):2 studies
- Stromal cells:1 study
- Macrophages (mouse bone marrow-derived):1 study
- Mosquitoes:1 study
- Mouse bone marrow:2 studies
- Human bone marrow (autopsy or smears):3 studies
- Gametocyte-infected erythrocytes:1 study

Gametocyte Stages Studied:

- Immature or early gametocytes:5 studies
- Mature or late gametocytes:5 studies

- All gametocyte stages:1 study
- Specific stages III, IV, and V:1 study
- Developing gametocytes:1 study
- Asexual stages:1 study
- Exclusive focus on only one stage:We didn't find mention of studies focusing exclusively on only one of immature or mature stages; most included both or all.

Key Mechanisms Examined:

- Adhesion or cytoadherence:4 studies
- Cytokine or growth factor secretion:1 study
- Angiogenesis:1 study
- Development or differentiation:2 studies
- Extracellular vesicle-mediated effects:1 study
- Mesenchymal stem cell-mediated enhancement of infectivity or soluble factors:1 study
- Phagocytosis:2 studies
- Induction of inflammatory mediators:1 study
- Receptor identification or involvement:2 studies
- Tissue specificity:1 study
- Localization or association with erythroblastic islands:1 study
- Homing, transmigration, deformability, or actin-dependence:1 study
- Enhancement of gametocytogenesis or membrane elasticity:1 study
- STEVOR protein role or membrane topology:1 study

Thematic Analysis

Physical Interactions and Adhesion Mechanisms

Study	Interaction Type	Cell Types Involved	Molecular Mediators	Functional Outcome
Messina et al., 2018	Adhesion (trypsin-sensitive, not involving ICAM-1)	Immature gametocytes, human bone marrow mesenchymal stem cells	Trypsin-sensitive ligands (not PfEMP1/ICAM-1)	Induction of angiogenic cytokines, facilitation of gametocyte release
Neveu et al., 2020	Development within host cell	Gametocytes, late erythroblasts	Not PfEMP1; glycophorin A, extracellular vesicles	Delay in erythroid maturation, gametocyte maturation
Suresh et al., 2023	Enhancement of infectivity	Gametocytes, mesenchymal stem cells	Soluble factors (no mention found)	Increased oocyst numbers in mosquitoes

Study	Interaction Type	Cell Types Involved	Molecular Mediators	Functional Outcome
Corbett et al., 2021	Phagocytosis, immune activation	Gametocytes, mouse bone marrow-derived macrophages	Tumor necrosis factor, MIP-2, nitric oxide	Inflammatory mediator production, possible impact on gametocyte survival
Rogers et al., 2000	Cytoadherence (not involving CD36)	Stage III/IV gametocytes, stromal/endothelial cells	ICAM-1, CD49c, CD166, CD164	Stage-specific adhesion, possible retention in bone marrow
Silvestrini et al., 2012	Minimal adhesion	Immature gametocytes, endothelial cells	Not ICAM-1 or CD36	Suggests alternative sequestration mechanisms
Joice et al., 2014	Localization, non-adhesive retention	Gametocytes, erythroblastic islands	Pfs16, CD71	Extravascular accumulation, reduced phagocytosis
De Niz et al., 2018	Homing, transmigration	Gametocytes, bone marrow endothelium	Actin, P-selectin (hypothesized)	Extravascular localization, mobility
Peatey et al., 2013	Physical retention	Gametocytes, erythroid progenitors	Membrane elasticity (no specific protein)	Enhanced gametocytogenesis, retention in marrow
Neveu et al., 2018	Lack of adhesion	Gametocyte-infected erythrocytes, erythroblasts	STEVOR (not exposed)	No specific adhesion, alternative mechanisms likely

Key patterns across these 10 studies:

- Interaction Type:
  - Adhesion, cytoadherence, or retention mechanisms:6 studies (including minimal, physical, non-adhesive, and lack of adhesion)
  - Development within host cell:1 study
  - Enhancement of infectivity:1 study
  - Phagocytosis or immune activation:1 study
  - Homing or transmigration:1 study
- Molecular Mediators:
  - Adhesion molecules (ICAM-1, CD49c, CD166, CD164, CD71, P-selectin, glycophorin A):4 studies

  - Non-classical, unknown, or alternative mediators (trypsin-sensitive ligands not PfEMP1/ICAM-1, not ICAM-1/CD36, STEVOR not exposed, membrane elasticity, soluble factors, actin):7 studies
  - Immune mediators (tumor necrosis factor, MIP-2, nitric oxide):1 study
  - Extracellular vesicles:1 study
  - Pfs16:1 study
  - Classical PfEMP1-mediated adhesion:We did not find mention of this in the included studies.
- Functional Outcome:
  - Retention, sequestration, or accumulation in bone marrow or extravascular space:5 studies
  - Effects on gametocyte maturation, development, or enhanced gametocytogenesis:3 studies
  - Facilitation of gametocyte release or increased mobility:2 studies
  - Immune or inflammatory responses:2 studies
  - Increased infectivity to mosquitoes:1 study
  - Induction of angiogenic cytokines:1 study
  - Delay in erythroid maturation:1 study
  - Alternative mechanisms for sequestration or retention:2 studies

Among the included studies, we did not find evidence for classical PfEMP1-mediated adhesion. Several studies suggested alternative or non-classical mechanisms for gametocyte retention and development in the bone marrow.

Cellular Homing and Migration

Study	Interaction Type	Cell Types Involved	Molecular Mediators	Functional Outcome
De Niz et al., 2018	Homing, transmigration	Gametocytes, bone marrow/spleen endothelium	Actin, P-selectin (hypothesized)	Extravascular localization, high deformability, mobility
Joice et al., 2014	Extravascular accumulation	Gametocytes, bone marrow parenchyma	No mention found	Retention in extravascular space, association with erythroblastic islands
Peatey et al., 2013	Retention via elasticity	Gametocytes, erythroid progenitors	Membrane elasticity	Enhanced retention in marrow
Messina et al., 2018	Angiogenesis induction	Gametocytes, human bone marrow mesenchymal stem cells	Cytokines and growth factors	Potential facilitation of gametocyte release

Key findings from these 4 studies:

- Interaction types:Each study focused on a distinct interaction: homing/transmigration, extravascular accumulation, retention via elasticity, or angiogenesis induction.
- Cell types:All studies involved gametocytes, with each pairing a different additional cell type.
- Molecular mediators:Actin and P-selectin (hypothesized), membrane elasticity, and cytokines/growth factors were each reported in one study. One study did not mention a specific mediator.
- Functional outcomes:Extravascular localization, high deformability, mobility, retention in extravascular space, association with erythroblastic islands, enhanced retention in marrow, and facilitation of gametocyte release were each reported in only one study.

We did not find mention of any study reporting more than one interaction type or more than one molecular mediator (except for De Niz et al., which listed two mediators). Each study focused on a distinct interaction, cell pairing, mediator, and outcome.

Host Cell Modifications

Study	Interaction Type	Cell Types Involved	Molecular Mediators	Functional Outcome
Neveu et al., 2020	Infection, differentiation delay	Gametocytes, late erythroblasts	Extracellular vesicles, glycophorin A	Delayed erythroid maturation, increased oxidative stress
Suresh et al., 2023	Infectivity enhancement	Gametocytes, mesenchymal stem cells	Soluble factors	Increased mosquito infectivity
Messina et al., 2018	Cytokine induction	Gametocytes, human bone marrow mesenchymal stem cells	Angiogenic cytokines	Enhanced angiogenesis, possible gametocyte release
Corbett et al., 2021	Immune activation	Gametocytes, bone marrow-derived macrophages	Tumor necrosis factor, MIP-2, nitric oxide	Inflammatory mediator production, possible impact on gametocyte survival

Key findings from these 4 studies:

- Interaction types:Each study examined a different interaction: infection/differentiation delay, infectivity enhancement, cytokine induction, or immune activation.
- Cell types:All studies involved gametocytes, with each pairing a different additional cell type.
- Molecular mediators:Each study identified different mediators: extracellular vesicles, glycophorin A, soluble factors, angiogenic cytokines, tumor necrosis factor, MIP-2, and nitric oxide.
- Functional outcomes:Delayed erythroid maturation/increased oxidative stress, increased mosquito infectivity, enhanced angiogenesis/possible gametocyte release, and inflammatory mediator production/possible impact on gametocyte survival were each unique to a single study.

We did not find mention of any overlap in interaction type, molecular mediator, or functional outcome across these four studies, except that all studies involved gametocytes.

Summary Table: Mechanistic Interactions

Study	Interaction Type	Cell Types Involved	Molecular Mediators	Functional Outcome
Messina et al., 2018	Adhesion, cytokine induction	Immature gametocytes, human bone marrow mesenchymal stem cells	Trypsin-sensitive ligands, angiogenic cytokines	Angiogenesis, gametocyte release
Neveu et al., 2020	Intracellular development, differentiation delay	Gametocytes, late erythroblasts	Extracellular vesicles, glycophorin A	Delayed erythroid maturation, gametocyte maturation
Suresh et al., 2023	Infectivity enhancement	Gametocytes, mesenchymal stem cells	Soluble factors	Increased mosquito infectivity
Corbett et al., 2021	Phagocytosis, immune activation	Gametocytes, bone marrow-derived macrophages	Tumor necrosis factor, MIP-2, nitric oxide	Inflammatory mediator production
Rogers et al., 2000	Cytoadherence	Stage III/IV gametocytes, stromal/endothelial cells	ICAM-1, CD49c, CD166, CD164	Stage-specific adhesion
Silvestrini et al., 2012	Minimal adhesion	Immature gametocytes, endothelial cells	Not ICAM-1 or CD36	Alternative sequestration mechanisms
Joice et al., 2014	Extravascular localization	Gametocytes, erythroblastic islands	Pfs16, CD71	Retention, reduced phagocytosis
De Niz et al., 2018	Homing, transmigration	Gametocytes, bone marrow/spleen	Actin, P-selectin (hypothesized)	Extravascular localization, mobility
Peatey et al., 2013	Physical retention	Gametocytes, erythroid progenitors	Membrane elasticity	Enhanced gametocytogenesis, retention
Neveu et al., 2018	Lack of adhesion	Gametocyte-infected erythrocytes, erythroblasts	STEVOR (not exposed)	No specific adhesion

Interaction Types:

- Adhesion-related interactions (including adhesion, cytoadherence, minimal adhesion, physical retention, and lack of adhesion):5 studies
- Cytokine induction or immune activation:2 studies
- Extravascular localization, homing, or transmigration:3 studies
- Infectivity enhancement, intracellular development, differentiation delay, and phagocytosis:Each reported in 1 study

Cell Types Involved:

- Gametocytes or related forms (including immature gametocytes, stage III/IV gametocytes, and gametocyte-infected erythrocytes):9 studies
- Mesenchymal stromal cells (mesenchymal stem cells or human bone marrow mesenchymal stem cells):2 studies
- Erythroblasts, late erythroblasts, or erythroid progenitors:3 studies
- Endothelial or stromal cells:3 studies
- Bone marrow or spleen:1 study
- Bone marrow-derived macrophages, erythroblastic islands, and gametocyte-infected erythrocytes:Each involved in 1 study

Molecular Mediators:

- Unique molecular mediators in each study, with no mediator reported in more than one study.
- ICAM-1, CD49c, CD166, and CD164:1 study
- Trypsin-sensitive ligands and angiogenic cytokines:1 study
- Extracellular vesicles and glycophorin A:1 study
- Soluble factors, tumor necrosis factor, MIP-2, nitric oxide, Pfs16, CD71, actin, P-selectin, membrane elasticity, and STEVOR (not exposed):Each reported in 1 study
- No molecular mediator was reported in more than one study.

Functional Outcomes:

- Adhesion, retention, or sequestration outcomes (including stage-specific, physical, and alternative mechanisms):6 studies
- Gametocyte release, maturation, or enhanced gametocytogenesis:3 studies
- Extravascular localization or mobility:2 studies
- Angiogenesis, delayed erythroid maturation, increased mosquito infectivity, inflammatory mediator production, reduced phagocytosis, and no specific adhesion:Each reported in 1 study

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Synthesis

Key insights from the included studies:

- Diversity of Mechanisms:The included studies indicate that Plasmodium falciparum gametocyte interactions with bone marrow cells involve a range of mechanisms, including non-classical adhesion, physical retention, cellular homing, and host cell modification.

- Stage- and Cell-Type Specificity:Mechanisms are highly specific to gametocyte stage and the type of bone marrow cell involved. Immature gametocytes are frequently associated with the extravascular bone marrow niche and interact with mesenchymal stem cells, erythroblasts, and macrophages.
- Absence of Classical Pathways:Classical cytoadherence pathways, such as those involving PfEMP1, were not identified in the included studies. Instead, alternative receptors (such as ICAM-1, CD49c, CD166, CD164, CD71, P-selectin, and glycophorin A) or physical properties (such as deformability and membrane elasticity) were implicated.
- Host Cell Responses:Host cell responses to gametocyte interactions included altered cytokine secretion, delayed erythroid maturation, and enhanced infectivity, which may influence the bone marrow environment and facilitate parasite transmission.
- Evidence Base Limitations:The majority of studies used laboratory-based or animal models, with relatively few including animal or human data. The diversity of experimental systems and incomplete mechanistic characterization limit the ability to compare the relative importance of specific pathways across studies.

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