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FETAL MICROCHIMERISM AS A PARTICIPANT OF CARCINOGENESIS

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Abstract. During pregnancy, a small number of cells are exchanged between the mother's body and the fetus. This phenomenon is called microchimerism. Of particular interest is the study of the effect of microchimeric cells of the fetus on the mother's body. Modern literary data give conflicting results about the relationship of fetal microchimeric (FM) cells with cancer. This can be due to various methodological approaches in the study of the FM cells (in bloodstream and in the tumor itself). Studies examining microchimeric cells circulating in peripheral blood often associate them with "protective function", whereas research detecting microchimerism in affected tissues typically highlights their "negative or contributory role". An interesting aspect is the placental origin of the majority of FM cells, which determines their high invasiveness. Combined with the genomic conflict between the mother and the fetus, invasion reduces resistance to tumor diseases. A number of studies showed the ability of FM to stimulate angiogenesis, which can significantly affect the metastasis of the tumor. Conversely, the production of cytokines by FM cells within a tumor microenvironment may improve disease prognosis. A major challenge in studying FM cells is their detection in the mother's body. Most research has focused on women who gave birth to sons, as FM cells can be identified via the Y chromosome, a methodological bias that may skew results. Consequently, developing new methodological approaches to study FM cells could enhance our understanding of this phenomenon.

Keywords: microchimerism, invasion, tumors, fetal cells, metastasis

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ФЕТАЛЬНЫЙ МИКРОХИМЕРИЗМ КАК УЧАСТНИК КАНЦЕРОГЕНЕЗА

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Резюме. Явление микрохимеризма характеризуется миграцией небольшого количества клеток матери или плода через гематоплацентарный барьер, что приводит к образованию химерных тканей. Особый интерес представляет изучение влияния микрохимерных клеток плода на материнский организм. Современные исследования предоставляют противоречивые результаты о роли фетальных микрохимерных (ФМ) клеток в патогенезе онкологических заболеваний. Это противоречие может быть обусловлено методологическими подходами в исследовании ФМ клеток (в кровотоке и в самой опухоли). Как правило, исследования, которые анализируют циркулирующие в периферической крови микрохимерные клетки, связывают их с «защитной функцией», тогда как работы, выявляющие микрохимеризм в пораженной ткани, обычно указывают на их «негативную или способствующую развитию опухоли роль». Интересным аспектом является плацентарное происхождение большинства ФМ-клеток, что и обусловливает их высокую инвазивность. Совместно с геномным конфликтом между матерью и плодом инвазивность уменьшает устойчивость к опухолевым заболеваниям. В ряде исследований была показана способность ФМ-клеток к стимуляции ангиогенеза, что может существенно повлиять на метастазирование опухоли. В то же время выработка цитокинов ФМ-клетками в очаге опухоли может существенно улучшить прогноз течения заболевания. Особой сложностью в исследованиях ФМ-клеток является их детекция в организме матери. В большинстве случаев исследование касалось только женщин, имевших сыновей, ввиду наличия Y хромосомы в ФМ-клетках, что могло существенно повлиять на конечный результат. В этой связи поиск новых методических подходов в исследование ФМ-клеток может пролить свет на понимание этого явления.

Ключевые слова: микрохимеризм, инвазия, опухоли, фетальные клетки, метастазирование

INTRODUCTION

Cancer is one of the leading causes of human mortality worldwide [1]. Tumor risk is influenced by a multitude of factors, including age, sex, and environmental conditions. For instance, the incidence of cancers not related to the reproductive system is 2–3 times higher in men than in women [2, 3]. It is thought that tumors are, to a large extent, an inevitable consequence of multicellularity: as cells divide, the accumulation of somatic mutations is unavoidable. Some cells bypass the normal mechanisms of cell cycle control and immune surveillance, leading to the formation of neoplasms — abnormal cell clusters [4, 5]. Neoplasms may remain benign, with well-defined borders, and are typically not life-threatening. However, some neoplastic cells acquire the ability to invade surrounding tissues, which defines malignant tumors. These cells can also metastasize, spreading to new sites in the body, often (though not always) via the bloodstream. Tumor metastasis is life-threatening, and it is believed that the majority of cancer deaths are attributable precisely to metastases.

During pregnancy in mammals, a bidirectional exchange of cells occurs between the mother and the fetus, which can lead to microchimerism [6, 7]. Various factors can influence microchimeric cells; for instance, prior abortions and surgical treatment during pregnancy enhance the migration of fetal cells into the maternal circulation. A complex pregnancy-related disorder such as preeclampsia also increases the number of fetal cells in the maternal bloodstream [8]. The appearance of fetal cells in the maternal body is termed fetal microchimerism (FM). The long-term persistence of fetal cells in the body after pregnancy can significantly impact maternal health, yet FM remains a poorly understood phenomenon [9, 10]. Interestingly, the infiltration of microchimeric cells into the host's body shares certain parallels with tumor metastasis.

Although fetal microchimeric cells, akin to tumor cells, possess the ability to migrate and evade the immune system, their long-term effects on the maternal organism remain incompletely studied, underscoring the need for further research in this field.

CANCER FROM AN EVOLUTIONARY PERSPECTIVE

Multicellularity and mammals

Malignant neoplasms are widespread diseases among multicellular organisms, occurring across various taxa from invertebrates [11] to vertebrates [12], with evidence detectable even in dinosaur fossils [13]. Comparative studies indicate that mammals exhibit higher rates of both neoplasms and malignant tumors compared to other vertebrates. M. Effron and colleagues were among the first to document this pattern, identifying neoplasms in 2.75% of mammals, 1.89% of birds, and 2.19% of reptiles [14]. Using more comprehensive data, Z.T. Compton et al. demonstrated that the average prevalence of neoplasms and cancer at time of death is highest in mammals (neoplasms: 15.28%, malignant tumors: 9.82%), followed by birds and reptiles (neoplasms: 6.40%, malignant tumors: 4.33%) and amphibians (neoplasms: 4.16%) [12]. However, another study found that mammals (4%) show only a slightly lower prevalence of malignant tumors than squamate reptiles [15]. The widespread occurrence of cancer among vertebrates and its variable frequency across different taxa suggest it serves as an evolutionary factor influencing natural selection [16]. Notably, pregnancy duration shows a negative correlation with the incidence of neoplasms, malignant tumors [8], and cancer mortality [17], suggesting that prolonged gestation may reduce cancer risk.

The placenta as a conduit for cellular exchange

Mammals possess a temporary extraembryonic organ —the placenta — essential for interaction between the maternal and fetal organisms. Its degree of invasiveness and integration with maternal tissues varies depending on placental type [18]. Placentation also represents a unique evolutionary adaptation that promotes the exchange of microchimeric cells. Microchimerism is characteristic of all placental mammals [19] and has been identified in numerous species with varying placental structures, including primates [20], mice [21, 22], dogs [23], and cattle [24]. During pregnancy, cells from two genetically similar yet distinct organisms remain in prolonged contact across the hematoplacental barrier [25]. Researchers have long observed that syncytiotrophoblast cells exhibit features resembling those of tumor cells: they can induce inflammation and angiogenesis, evade immune surveillance and apoptosis, and stimulate cell migration and invasion [25–28]. This pattern is observed across various cancer types, indicating a biological connection between placental functions and oncogenic mechanisms. Nevertheless, the reasons for the high tumor frequency in mammals and the role of placental invasiveness remain subjects of ongoing discussion [17, 28–30].

The placenta and genomic conflict

From an evolutionary standpoint, the “interests” of the fetus and mother diverge due to differences in their genetic makeup, leading to competition between them. Although their shared goals include survival and reproduction, the fetus may demand more resources than the mother is able to provide. This phenomenon is known as maternal-fetal (genomic) conflict [31]. The theory of genomic conflict proposes that behaviors advantageous for the transmission of fetal genes (e.g., excessive resource extraction from the mother) can result in competition that adversely affects the health

of both parties. This conflict also heightens the vulnerability of placental mammals to cancer. For example, trophoblast cells have evolved to acquire resources from maternal tissues. Much like tumor cells, they evade immune surveillance and possess invasive capabilities. Adaptations that facilitate efficient resource transfer to the fetus may concurrently elevate the risk of oncogenesis. Moreover, the dynamics of the conflict between maternal and paternal genes contribute to susceptibility to neoplastic diseases [32].

The intricate interplay between cooperation and conflict during pregnancy mirrors the evolutionary pressures that shape maternal and fetal health, and illuminates the role of microchimerism in host biology. Microchimerism can exert either beneficial or detrimental effects depending on context: the state of the immune system, the localization of microchimeric cells, the presence of multiple generations of such cells, as well as the age and health status of the organism.

EVOLUTIONARY VULNERABILITIES IN CANCER AND PREGNANCY RISK

The profound biological connection between a mother and her developing fetus is an evolutionary trait that confers numerous advantages but can also establish specific vulnerabilities. For example, documented cases exist of maternal tumor cell transmission to the fetus. The reverse process is rare, largely because cancer incidence is strongly age-dependent. Cancer is diagnosed in 0.02–0.1% of pregnancies. The most frequent tumor types identified during pregnancy include breast cancer, cervical cancer, malignant melanoma, and lymphomas [33]. When transmitted to the fetus, these malignancies are diagnosed as the same histological type as in the mother [34]. Cases of metastatic transmission from mother to fetus are most frequently associated with a compromised hematoplacental barrier (approximately 84.7% of reported cases) [35], suggesting that the placenta acts as a temporary barrier that limits certain forms of cellular exchange.

Choriocarcinoma represents another striking example of the transfer of cancerous FM cells from the fetus to the mother. This tumor is an aggressive malignancy derived from trophoblastic cells and constitutes the most prevalent form of true embryonic trophoblastic neoplasia [36]. This carcinoma type arises from epithelial tissue and demonstrates a propensity for early systemic metastasis [37]. Conversely, a hydatidiform mole, though initially benign, frequently results from fertilization of a defective ovum, yielding a zygote with exclusively paternal chromosomes [38]. These non-viable zygotes implant in the uterine wall and form proliferative tissue masses. In severe instances, these formations may undergo malignant transformation into invasive choriocarcinoma within the maternal host, with documented cases metastasizing to both maternal and fetal compartments [38–40]. Choriocarcinomas appear to circumvent maternal immune rejection by leveraging a fundamental characteristic of trophoblastic tissue — the absence of HLA class I and II antigen expression [40–42].

Beyond the gestational period itself, a woman's reproductive history — including the number of pregnancies and their timing — significantly impacts the risk of developing various tumors in parous women. This suggests that parity and pregnancy-associated factors involve a complex interplay of hormonal and biological changes that can either elevate or reduce cancer risk depending on the specific context [43–49]. Epidemiological studies provide compelling evidence for the association between pregnancy and neoplastic diseases; nevertheless, the underlying mechanisms remain poorly understood, largely because factors such as maternal health status, fertility, and age — which frequently represent confounding variables — are seldom comprehensively considered in these analyses.

CLINICAL CASES LINKING CANCER AND MICROCHIMERISM

Microchimerism has been documented in various neoplastic types across multiple studies, underscoring its potential impact on tumor biology. Microchimeric cells have been identified in several cancer types, including breast carcinoma [50–53], thyroid cancer [54–56], glioblastoma and meningioma [57], ovarian cancer [58], cervical cancer [59], skin cancer and melanoma [60, 61], as well as leukemia [62] (Fig. 1). Recent reviews have emphasized that male-origin microchimeric cells may promote both tissue regeneration and tumor development, highlighting their dual functionality [63]. Nevertheless, the mechanisms governing these interactions remain incompletely elucidated.

Multiple methodological approaches are utilized for microchimerism detection, including polymerase chain reaction (PCR) for Y-chromosome sequence identification, fluorescence *in situ* hybridization (FISH) for X and Y chromosome analysis, and immunohistochemical (IHC) staining. Current predominant methodologies focusing on Y-chromosome detection enable fetal cell identification in biological specimens from mothers with previous male fetus pregnancies.

TUMORS OF THE FEMALE REPRODUCTIVE SYSTEM

In gynecologic oncology, FM has been examined in multiple studies that reveal its complex and occasionally paradoxical role in tumor development among parous women. In their investigation, D. Cha et al. identified Y-chromosome-bearing cells in cervical cancer tissues from all patients when analyzing large specimens (1.5×2 cm), with fewer detected in small biopsy

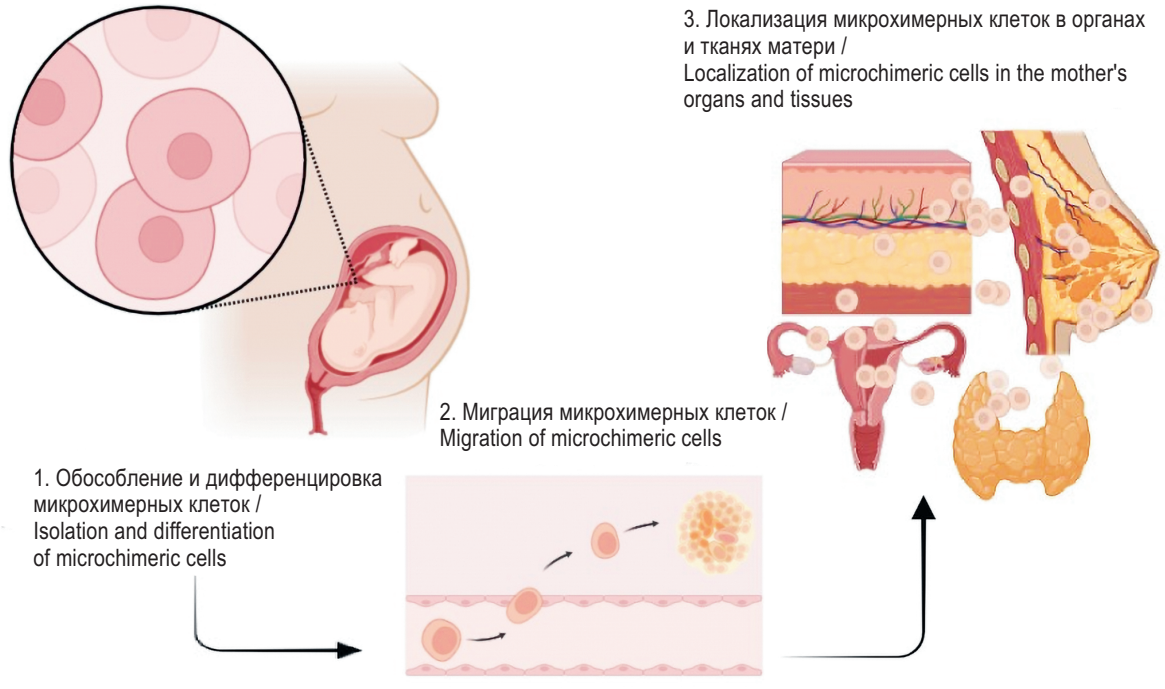

Fig. 1. **The influence of microchimeric cells on the maternal body during pregnancy (created with BioRender.com). 1. Microchimeric cells originate from the placenta and enter the maternal bloodstream. 2. Once in the bloodstream, fetal cells spread throughout the mother's body. 3. Some cells integrate into maternal tissues, forming long-lived microchimeric populations associated with autoimmune diseases and cancer**

Рис. 1. **Влияние микрохимерных клеток на организм матери во время беременности (сделано с помощью BioRender.com). 1. Микрохимерные клетки в основном обособляются из плаценты и попадают в материнский кровоток. 2. Попав в кровь, фетальные клетки распространяются по организму матери. 3. Часть клеток интегрируется в материнские ткани, формируя долгоживущие микрохимерные популяции, которые ассоциируют с аутоиммунными заболеваниями и онкологией**

samples (0.1×0.5 cm). No such cells were observed in the control group [59]. Within tumor tissue, these cells expressed both CD45 (a component of signaling pathways regulating mitosis, growth, and differentiation) and cytokeratin (an intermediate filament of epithelial cells), potentially indicating their participation in immune responses or incorporation into tumor epithelium. Nevertheless, their effect on disease progression remains uncertain. S. Hallum et al. found an inverse correlation between microchimerism and ovarian cancer risk. Blood analysis of 700 women revealed Y-chromosome presence in 46% of ovarian cancer patients versus 65.9% in controls. Women with microchimerism had substantially reduced cancer risk (hazard ratio = 0.44), suggesting a potential protective effect [59]. I. Hromadnikova et al. observed that microchimeric cells occur more frequently in benign endometrial disorders than in uterine cancer [64]. However, among cancer patients, low microchimerism prevalence correlated with more favorable prognosis. Subsequent research by S. Hallum et al. confirmed microchimerism detection in 65.9% of control group women compared to only 54% with endometrial cancer, further supporting the protective role hypothesis [65]. Yet no relationship was established between FM cell concentration and cancer risk.

BREAST CANCER

Research on microchimerism in breast cancer (BC) presents conflicting findings that vary by tissue type and pregnancy history. A protective effect of FM was demonstrated by V.K. Gadi et al. [10, 53], who reported higher detection rates in healthy women (56%) compared to BC patients (26%), with an odds ratio of 0.29. Y-chromosome-bearing microchimeric cells were identified in 63% of healthy tissue specimens versus 26% in tumor areas. Corresponding results were reported by M. Kamper-Jørgensen's research team, which detected microchimerism in 70% of healthy women but only 40% of BC patients [53]. Using FISH, FM was identified in 85% of controls compared to 64% in carcinoma samples [66]. These collective findings suggest that FM may potentiate immune surveillance, thereby inhibiting oncogenesis.

In contrast, G. Dubernard et al. reported a tumor-promoting role of FM, with FM cells detected in stromal regions of 90% of malignant neoplasms from BC patients [50].

Recent in vitro investigations using MCF-7 breast adenocarcinoma cell cultures with CD34+ umbilical cord blood demonstrated suppressed tumor cell proliferation, indicating

potential protective functions of microchimerism in BC [67–69]. The role of microchimerism in BC remains context-dependent: while exhibiting protective properties in circulation and healthy tissues, it may paradoxically support tumor growth in established malignancies, particularly pregnancy-associated cancers. Additional studies are required to elucidate the precise mechanisms and contextual factors governing these differential effects.

SKIN NEOPLASMS

In dermatologic oncology, S. Nguyen Huu and colleagues examined the role of male-origin FM in the development and progression of skin tumors, encompassing both benign and malignant types [60, 61]. These investigations illuminate FM's potential contribution to tumorigenesis, particularly during pregnancy. Their initial study focused on cutaneous papillomas — benign skin growths. Utilizing transgenic mice expressing enhanced green fluorescent protein (eGFP) combined with FISH for Y-chromosome detection, the researchers identified fetal cells within tumors. Cells of male origin were found in 75% of papillomas, while being absent in the healthy skin of the same animals [60]. This finding demonstrates a specific association between FM cells and tumor tissue. Notably, these FM cells expressed various molecular markers, suggesting their potential involvement in tumor progression. These results challenge the hypothesis of microchimerism's protective role.

Melanomas — malignant tumors posing significant risk during pregnancy due to their aggressive clinical course — were similarly investigated. Employing both human specimens and mouse models (B16 line), S. Nguyen Huu et al. used FISH and IHC to detect FM cells in 63% of human melanomas and 57% of murine tumors. Importantly, in 50% of cases, FM cells expressed endothelial markers (CD34, CD31, von Willebrand factor), indicating their participation in angiogenesis — the process of new blood vessel formation within tumors that is crucial for tumor growth and metastasis [61].

Examination of benign nevi demonstrated FM cell presence in merely 12% of cases, substantially lower than the frequency observed in malignant melanomas. This evidence corroborates the hypothesis about microchimerism's potential involvement in either malignant transformation or progression of cutaneous tumors [62]. FM cell participation in melanoma angiogenesis additionally proposes a mechanistic pathway through which these cells might promote tumor growth and metastasis during pregnancy.

The study by U. Mahmood et al. documented that male fetus-derived cells persist within cesarean section scars for many years post-delivery and are identifiable as keratinocytes [70].

Consequently, FM may substantially contribute to the pathogenesis of skin neoplasms, particularly malignant variants, potentially modulating their progression via angiogenesis promotion. These collective findings underscore the need for further investigation into microchimerism's functions within dermatologic oncology.

THYROID CARCINOMA

V. Cirello and colleagues investigated FM in papillary thyroid cancer and assessed its influence on disease progression. The study enrolled 63 women who had delivered male offspring before cancer diagnosis. Subsequent FISH analysis revealed a statistically significant increase in FM cells within tumor tissue compared to surrounding normal tissue [54].

The combined implementation of FISH and IHC facilitated identification of FM cells expressing thyroglobulin — a protein produced specifically by thyroid follicular cells and employed as a diagnostic and monitoring biomarker for this malignancy. FM cells were detected in both neoplastic and normal tissues. Crucially, CD45-positive FM cells were exclusively identified within tumors, implying their potential engagement in immune surveillance. Additionally, both tumor and normal tissue contained cells negative for both CD45 and thyroglobulin expression, suggesting progenitor-like characteristics with capacity for transdifferentiation into diverse cell lineages.

In subsequent investigations, V. Cirello et al. established that elevated FM cell levels in peripheral blood correlate with more favorable thyroid cancer outcomes. Patients with detectable FM cells demonstrated reduced primary tumor dimensions, decreased incidence of lymph node metastases, and superior survival prognosis [55, 56]. These observations indicate that FM may confer protective effects in thyroid carcinoma, potentially through activation of antitumor immune responses by genetically non-maternal FM cells. Therefore, FM appears to exercise dual functions: integrating into thyroid parenchyma while simultaneously modulating neoplastic proliferation and enhancing clinical endpoints (Fig. 2).

BRAIN TUMORS

The study by L. Broestl et al. investigated FM in glioblastomas and meningiomas—the most prevalent primary brain tumors. Using quantitative PCR to detect male DNA in tumor tissue from women with previous male offspring, researchers identified FM cells in 80% of glioblastomas and 50% of meningiomas [57]. These data were confirmed through FISH analysis targeting X and Y chromosomes. The results demonstrate considerable prevalence and likely biological significance of FM in brain tumor development and progression. Interestingly, M. Kamper-Jørgensen and colleagues obtained contrasting results in their peripheral blood study. This research, comprising 73 brain neoplasms and 505 control samples, detected

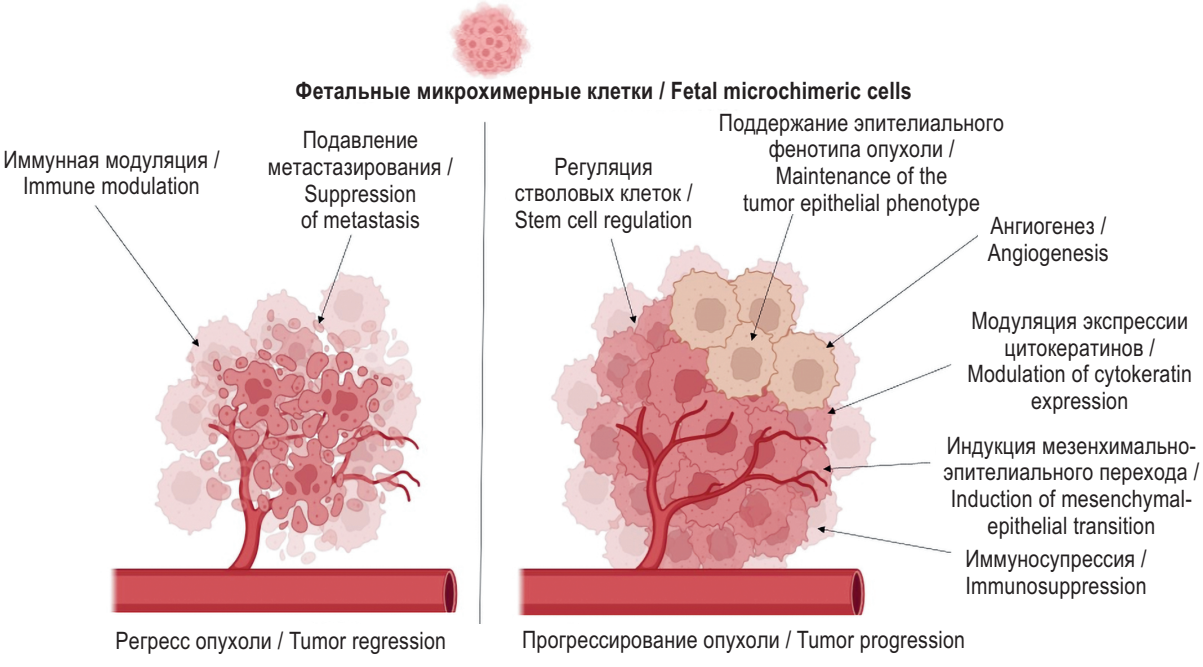

Fig. 2. Potential contribution of fetal microchimeric cells to tumorigenesis (created with BioRender.com)

Рис 2. Потенциальный вклад фетальных микрохимерных клеток в опухолеобразование (сделано с помощью BioRender.com)

FM cells in 46.5% of tumor patients versus 65.9% of controls. Women with detectable FM showed a 50% lower incidence of brain tumors [71].

These conflicting data emphasize the complexity and multifunctional nature of microchimerism in oncogenesis. While direct detection of FM cells within tumor tissue may indicate participation in neoplastic processes, systemic presence of such cells in circulation appears to confer protection. This dichotomy may reflect distinct mechanisms of microchimerism action dependent on anatomical context — intratumoral FM might promote tumor growth, whereas systemic FM likely modulates immune surveillance and exhibits protective functions. Current evidence underscores the need for additional research to elucidate precise mechanisms of FM involvement in central nervous system tumor development, along with its potential clinical relevance for prognosis and treatment. Particularly valuable would be investigation of biological behavior differences in microchimeric cells according to their tissue distribution.

HEMATOLOGIC MALIGNANCIES

Umbilical cord blood transplantation represents a therapeutic procedure wherein hematopoietic stem cells derived from cord blood are utilized to restore bone marrow function in patients with marrow compromise secondary to underlying disease or chemotherapy. This approach constitutes a significant alternative to conventional bone marrow transplantation, particularly for patients lacking fully matched donors, since cord blood permits greater HLA disparity. The investigation by S.B. Kanaan and colleagues examined microchimerism's role in cord blood transplantation and its effect on leukemia relapse risk. The study cohort comprised 95 recipients of single or double umbilical cord blood transplants. Detailed microchimerism assessment using HLA-specific quantitative PCR was performed in 36 patients. Analysis identified maternal-origin microchimeric cells in bone marrow and peripheral blood specimens from 19.4% of patients, with cellular persistence maintained for up to one year following transplantation [62].

Patients with detectable microchimerism showed substantially reduced relapse rates, mortality, and treatment failure — a clinically consequential finding. These observations suggest microchimerism-mediated protection potentially operating through multiple mechanisms. Primarily, microchimeric cells may execute immunomodulatory functions. Secondarily, they potentially provide hematopoietic support promoting blood cell reconstitution. Tertiarily, they may directly target residual malignant populations through antitumor activity. The obtained results carry significant implications for optimizing hematopoietic stem cell transplantation methodologies and developing innovative relapse prevention strategies. These findings emphasize the necessity for continued exploration of microchimerism's therapeutic potential within hematologic oncology. Particular research interest focuses on establishing optimal protocols for microchimerism induction and maintenance to enhance transplantation outcomes.

Gastrointestinal Tract Tumors

Research on microchimerism's role in gastrointestinal tract carcinogenesis, particularly colorectal cancer, has produced contradictory findings. M. Kamper-Jørgensen et al. performed an epidemiological investigation examining the association between FM and colorectal cancer. Through analysis of peripheral blood samples from women, they discovered higher FM prevalence among those who later developed colorectal cancer compared to healthy control subjects. Specifically, male-origin FM cells were identified in 70% of women subsequently diagnosed with colorectal cancer, while controls demonstrated only 46% prevalence. These observations suggest microchimerism's potential involvement in this malignancy's pathogenesis [53].

Expanding upon this research focus, M. Kamper-Jørgensen examined FM's influence on post-diagnosis survival. This subsequent work evaluated peripheral blood FM cells' effects on clinical outcomes in women diagnosed with both breast cancer and colorectal cancer. Results revealed superior survival rates among FM-positive women for both cancer types [72]. Among colorectal cancer patients specifically, microchimerism detection correlated with substantially reduced mortality risk compared to FM-negative cases. These collective findings indicate that the temporal context of microchimerism detection — whether occurring before or after diagnosis — carries significant implications for understanding its role in colorectal cancer development and prognostic outcomes.

DISCUSSION

Microchimeric cells constitute a cellular population transferred between different organisms of the same species. Their precise functions within recipient tissues remain incompletely characterized. Of 20 studies examining microchimerism-cancer associations, findings show notable contradictions: some report these cells' propensity to promote carcinogenesis, while others indicate protective functions [6, 11, 55, 73–77]. Recent investigations [63] highlight the complex duality of FM cells in tumor pathogenesis, demonstrating their capacity to participate in tissue repair while simultaneously facilitating neoplastic growth — evidence of their dichotomous impact on the maternal organism. Microchimeric cells evade maternal immune surveillance through unidentified mechanisms, maintaining capabilities for survival, proliferation, and differentiation within host tissues. While they likely utilize pathways similar to malignant cells, direct evidence establishing causal relationships between microchimerism and oncogenesis remains unavailable.

From the genomic conflict perspective, no definitive conclusion should be anticipated regarding whether microchimeric cells confer cancer protection or enhance risk. Earlier predictions derived from genomic conflict theory [25] proposed heightened maternal-fetal cellular antagonism (and consequent potential cancer progression) in resource-critical tissues including mammary gland, thyroid, and brain. However, contemporary microchimerism research in parous women with breast cancer contradicts these projections, revealing predominantly protective associations in both thyroid and mammary carcinomas. Nevertheless, comprehensive evaluation of microchimeric cells' oncological roles remains constrained by methodological challenges.

The nature of the biological specimen under examination can significantly impact conclusions about FM's role in cancer development. Studies analyzing microchimeric cells circulating in peripheral blood typically correlate them with protective functions, while research detecting microchimerism within pathological tissues generally indicates detrimental or tumor-promoting activities. It may be hypothesized that blood-circulating microchimeric cells participate in immune surveillance, whereas within tumor microenvironments they might become co-opted by neoplasms and facilitate disease progression. This biological complexity highlights the need for investigations that account for multifactorial interactions between rare cellular populations and host immunity. Direct comparisons across existing studies remain problematic since microchimerism likely exerts protective, pathogenic, or neutral effects contingent upon specific contextual factors. Future research designs should systematically incorporate critical contextual variables including patient age, parity status, examined tissue type, diagnostic timing, and the extent of genomic similarity between maternal and microchimeric cells.

Fetal microchimerism present within tumor tissues can modulate tumor microenvironment formation. Unlike malignant cells, microchimeric cells lack hallmark features such as genomic instability, yet retain capacity to participate in tumor pathobiology. Counter to immune surveillance theory concerning microchimerism and cancer, microchimerism may promote tumor microenvironment development in a manner analogous to cancer-associated fibroblasts (CAFs). Over half of examined studies identifying microchimeric cells in neoplastic tissues suggest their potential involvement in disease progression. Positioned as crucial tumor microenvironment constituents, they promote cancer advancement through supporting malignant proliferation, extracellular matrix reorganization, and stimulation of angiogenesis and immunosuppression. Such activities contribute to establishing immunosuppressive niches that facilitate tumor immune evasion. CAFs secrete diverse cytokines and chemokines capable of recruiting immune cells while simultaneously suppressing antitumor immunity. Investigations reveal microchimeric cells within tumors express CAF-characteristic markers

and may engage in angiogenesis and tumor progression. For example, G. Dubernard and colleagues demonstrated these microchimeric cells localize within breast cancer stromal compartments and express mesenchymal markers, indicating potential CAF differentiation and extracellular matrix remodeling participation [50]. Correspondingly, S. Nguyen Huu et al. documented microchimeric cells in melanoma tissues expressing angiogenic markers including CD34, CD31, and von Willebrand factor, potentially promoting angiogenic processes within tumor microenvironment [60].

CONCLUSION

Fetal microchimerism remains an incompletely characterized phenomenon, yet accumulating evidence reveals its dichotomous functions in cancer pathology. FM cells demonstrate capacity to engage in regenerative mechanisms, potentially conferring beneficial effects. Conversely, their protracted persistence within the maternal system correlates with potential contributions to neoplastic pathogenesis.

Consequently, FM cells may significantly modulate cancer progression trajectories, underscoring the imperative for continued research to delineate the molecular pathways through which microchimerism influences tumor development and clinical outcomes.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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