Hypothesis

Exosome-Induced In Situ Oncogenic Transformation: A Hypothesis for Metastasis (EMMT)

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Exosome-Induced In Situ Oncogenic Transformation: A Hypothesis for Metastasis (EMMT)

Short Title: EMMT: Metastasis without Cell Migration

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Abstract

This Perspective proposes a novel conceptual model of metastasis termed Exosome-Mediated Malignant Transformation (EMMT). In this model, dissemination occurs not through physical migration of tumor cells [1–3] but via circulating tumor exosomes (CTEs). These vesicles deliver oncogenic prion-like proteins, epigenetic regulators, and retrotransposons that selectively target distant recipient cells with unresolved DNA damage. CTE cargo includes mutant p53 R175H [15–17], aggregation-prone chaperones Hsp90α/Hsf1, chromatin-modifying enzymes such as EZH2, non-coding RNAs (miR-105-3p, lncRNA HOTAIR, circRNA ciRS-7), ADAM10/CD9+ tetraspanins, Rab27a/nSMase2, LINE-1 ORF2p, PKM2/LDHA, HIF1α, and MET/EGFR receptor cytoplasmic precursor (RCP)-recycling complexes [12,13,22–28,39]. This cargo suppresses DNA repair genes (BRCA1/2, FANCD2) and tumor suppressors, thereby perpetuating chromatin instability in vulnerable cells. Genomically susceptible cells evade apoptosis and express anchor receptors that facilitate selective CTE docking. This triggers epigenetic remodeling, chromatin disorganization, and secondary somatic mutations [37–41]. The process, termed Genetic Fixation, represents an indirect reverse information flow (protein/RNA → DNA). It synthesizes principles from six Nobel laureates (Schekman, Blobel, Prusiner, Warburg, Crick, Szostak). EMMT resolves paradoxes of classical metastasis theory and outlines a testable experimental framework using acellular preparations. The model is schematized in Figure 1.

Keywords: metastasis; exosomes; epigenetics; DNA damage; fractal instability; protein-to-DNA information transfer; anchor receptors; organotropism; transfusion medicine

Introduction

Metastasis is conventionally defined as the dissemination and migration of tumor cells from primary sites to distant organs [1–3]. However, this paradigm encounters clinical paradoxes. These include marked genetic divergence between primary and metastatic tumors (>70% private mutations), enigmatic organotropism, and inconsistencies with the "seed and soil" hypothesis. Whole-genome and exome sequencing reveals that metastases often harbor private driver mutations and chromosomal rearrangements absent or infrequent in primary tumors. This suggests de novo oncogenic events at metastatic sites [14,40,54–59].

The Exosome-Mediated Malignant Transformation (EMMT) model posits that metastatic foci emerge through local malignant transformation of susceptible recipient cells in distant tissues, rather than via circulating tumor cell colonization. In this framework, CTEs serve as nanoscale "seeds" conveying oncogenic information. The "soil" consists of cells exhibiting chromatin instability and anchor receptor expression.

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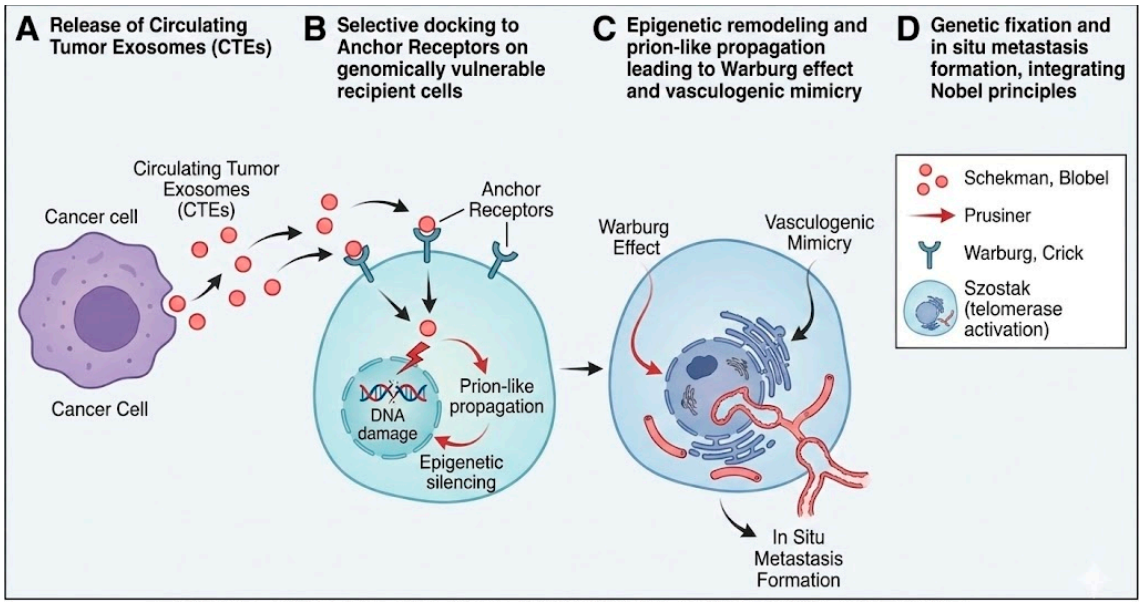

Figure 1. Schematic of Exosome-Mediated Malignant Transformation (EMMT).

Selective Targeting: Genomic Vulnerability Dichotomy

Following DNA damage, cells follow two distinct trajectories: a Stability Pathway (p53-p21-mediated repair or apoptosis) or a Chromatin Instability Pathway. The latter features persistent γH2AX foci, micronuclei, nuclear lamina defects, and chromosomal territory reorganization. These reflect unresolved double-strand breaks and replication stress [5–9,12,13].

Cells on the instability pathway fail to restore genomic integrity. Instead, they neo-express anchor receptors (e.g., $\alpha 6\beta 4$ for lung, $\alpha v\beta 5$ for liver, CD44v6, heparanase HSPG2), conferring susceptibility to CTE docking [6,33,46]. These receptors include de novo integrin heterodimers, selectin ligands, and heparan sulfate proteoglycans that match the integrin-tetraspanin signature on CTE surfaces (CD9/CD63/CD81). This molecular complementarity explains organotropism. Tissues enriched in genomically vulnerable, anchor receptor-positive cells preferentially bind and internalize cognate CTE subsets [6,25].

Functional Modification of the Central Dogma: Genetic Fixation

EMMT delineates an indirect reverse information flow from proteins/RNA to DNA. This integrates six foundational biological principles:

Step	Process	Fundamental Principle	References
I	Agent release	Schekman: vesicular trafficking	[10,64]
II	Targeting	Genomic vulnerability via anchor receptors	[6,46]
III	Translocation	Blobel: nuclear import (KPNA2/NLS)	[11,36]
IV	Induction	Prusiner: prion-like aggregation	[16,17,38]
V	Fixation	Crick (modified): Protein/RNA → DNA	[7,40,41]
VI	Bioenergetics	Warburg: aerobic glycolysis	[53]
VII	Survival	Szostak: TERT → ALT block	[18]

Upon anchor receptor engagement and endocytosis (CD44/macropinocytosis), CTEs fuse with endosomes (Rab5 → Rab7). They traffic protein-nucleic acid cargo to the cytoplasm and nucleus via Blobel's nuclear import signals [11,36]. Prion-like oncoproteins (p53 R175H + Hsp90) seed conformational remodeling of endogenous targets. This yields self-propagating aggregates with trans-dominant effects [15–17,38].

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Detailed Molecular Mechanisms of Genetic Fixation

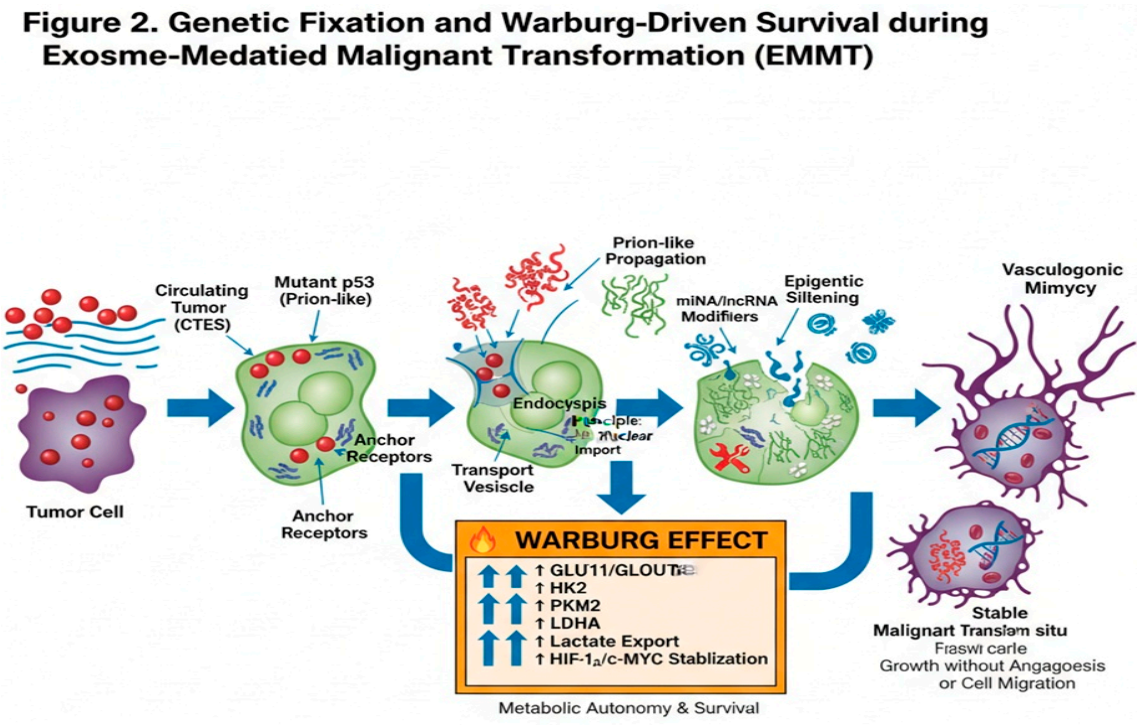

Figure 2. Molecular mechanisms of genetic fixation.

A. LINE-1 Retrotransposition and De Novo Genomic Insertions

CTEs transport active LINE-1 elements, including reverse transcriptase ORF2p, RNA-binding ORF1p, and endogenous retroviruses [22–25,65]. Post-uptake, LINE-1 mRNA translates in recipient cytoplasm, facilitated by hypomethylated L1 promoters (TET1 downregulation) and somatic stressors. Insertions disrupt tumor suppressors or activate oncogenes (MET amplification; MYC enhancer hijacking). This engenders secondary mutations and fractal genomic instability [40,41,65].

B. Prion-like Propagation of Mutant p53 (R175H)

Mutant p53 R175H in CTEs aggregates with chaperones Hsp90α, Hsf1, and DNAJB1 [15–17,26]. In recipients, these seed wild-type p53 conversion [26–30,38]. This elicits gain-of-function effects, including integrin/EGFR recycling via RCP, NF-κB p65 priming, and YAP/TAZ nuclear translocation. Together, these foster invasiveness without cell migration [27–30,38].

C. Epigenetic Repression and Chromatin Remodeling

Exosomal non-coding RNAs (miR-105-3p, lncRNA HOTAIR, circRNA ciRS-7, RN7SL1) recruit Polycomb complexes (EZH2) to PTEN/TP53/RB1 loci. This imposes H3K27me3 marks and CpG island (CGI) hypermethylation [28,43,47–50]. miR-105 upregulates ZEB1, suppresses tight junctions (CLDN1/7), and inhibits DNA repair genes (RAD51, 53BP1), thereby fixing epigenetic silencing [33–35,47–50].

D. Metabolic Fixation and Bioenergetic Autonomy

Recipient cells activate the Warburg effect, upregulating PKM2, LDHA, GLUT1/3, and stabilizing HIF1α. Exosomal modulators reinforce this shift, providing biosynthetic precursors and local acidosis for niche maturation [25,32,51–53]. Exosomal reverse transcriptase and DNA polymerases generate complementary DNA insertions from RNA cargo. This enacts Genetic Fixation and extends Crick's central dogma [40,41].

[Image showing molecular mechanisms of genetic fixation including LINE-1 retrotransposition, prion-like p53 propagation, and epigenetic remodeling]

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Metabolic Reprogramming and Vasculogenic Mimicry

Metabolic Reprogramming (Warburg Effect): Upregulation of glucose transporters and glycolytic enzymes (HK2, PKM2, LDHA) yields energy autonomy and acidosis [51–53].

Vasculogenic Mimicry: Early foci form CD31-negative vascular channels expressing endothelial markers (EphA2, TIE1/2) and MMPs. This enables in situ growth independent of angiogenesis [19–21].

Resolution of Critical Paradoxes

- **Genetic Divergence:** Attributable to de novo transformation [14,40,54–59].
- **Organotropism:** Governed by anchor receptor-mediated targeting ($\alpha 6\beta 4$ lung, $\alpha v\beta 5$ liver) [6,33,46].
- **Pre-metastatic Niche:** Concurrent with metastasis via stromal/immune reprogramming [58,59,72].

Enhanced Experimental Approach

- **Targeting:** Induce chromatin instability and anchor receptor expression via localized irradiation (2 Gy) [13,39].
- **Induction:** Administer purified acellular tumor exosomes (10^9 EVs/mL) systemically [24,32,64].
- **Proof:** Confirm preferential tumorigenesis in the irradiated organ, with exosome-derived insertions (L1Hs), prion aggregates (p53), and vasculogenic mimicry signatures absent tumor cell migration [37–41].

[Image illustrating the experimental setup for testing EMMT using acellular exosome injections and localized irradiation]

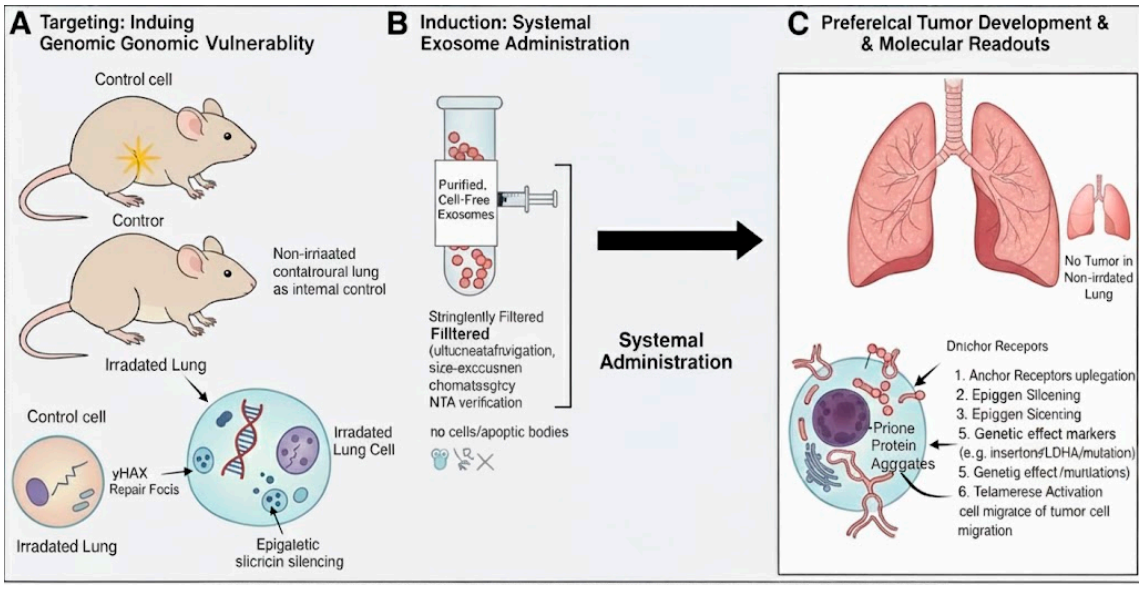

Figure 3. Experimental Validation of EMMT.

Conclusions

Exosome-Mediated Malignant Transformation (EMMT) provides a coherent theoretical framework resolving key paradoxes of classical metastasis—including genetic divergence, organotropism, and epithelial-mesenchymal transition dispensability—through in situ transformation mediated by circulating tumor exosomes, challenging cell migration-centric models. Genetic Fixation extends the central dogma via indirect protein/RNA-driven genomic and epigenomic alterations in susceptible recipient cells, unifying vesicular trafficking, prion-like

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propagation, epigenetic remodeling, metabolic reprogramming, and retrotransposon activity into a biologically testable model. EMMT suggests translational research directions: circulating tumor exosome evaluation as oncogenic vectors, anchor receptor targeting to block docking, and engineered exosome strategies modulating pathogenic signaling. This positions EMMT as a unifying paradigm for metastasis biology and therapeutic innovation [6,15,42,46].

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