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Review

Developmental plasticity as a framework for paediatric cancer metastasis

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Metastasis is the principal cause of cancer-related mortality in children, yet its biological origins remain incompletely understood. Paediatric cancers frequently combine low mutation burdens with structural genomic alterations and phenotypic heterogeneity, suggesting that metastatic progression reflects interactions between genetic evolution and cellular plasticity. Here, we integrate genomic, epigenomic, developmental, and single-cell evidence to examine how oncogenic lesions and developmental origin define accessible cellular states, while epigenetic, metabolic, and microenvironmental signals regulate transitions between them. We propose a developmental plasticity framework in which genetic architecture constrains the cellular state landscape, while phenotypic adaptation shapes metastatic behaviour. We discuss evidence distinguishing plasticity from clonal selection, mechanisms driving state transitions, and opportunities to therapeutically intercept metastasis-permissive states or exploit vulnerabilities created during adaptation.

Significance

Paediatric cancers often harbour relatively low mutational burdens yet metastasise efficiently. We propose that developmental plasticity complements genetic evolution by enabling reversible transitions between proliferative, migratory, stem-like and immune-adaptive states. Early oncogenic lesions establish permissive developmental landscapes, while epigenetic, metabolic, and microenvironmental signals govern movement between states. Understanding these dynamic interactions may reveal opportunities to intercept metastasis by targeting state transitions or the therapeutic vulnerabilities they create, while complementing existing genotype-directed approaches in childhood cancers.

Integrating genetic evolution and developmental plasticity in paediatric metastasis

Cancer remains the leading cause of disease-related mortality in children and adolescents, with metastatic and relapsed disease accounting for most treatment failure [1–4]. Yet the biological basis of metastatic progression in childhood cancer remains incompletely understood. Classical models, derived largely from adult epithelial malignancies, emphasise progressive genetic diversification and selection of metastasis-competent subclones [5]. Paediatric cancers challenge this paradigm. They typically harbour a low somatic mutational burden, are frequently initiated by structural variants, fusion oncogenes or epigenetic dysregulation, and can display aggressive metastatic behaviour despite comparatively limited genomic evolution [6–15]. We propose that this apparent paradox can be reconciled through **developmental plasticity** (see Glossary). Many childhood cancers arise within embryonic or progenitor populations inherently capable of migration, lineage switching, and rapid epigenetic adaptation [16–23]. Early oncogenic events may therefore establish permissive developmental landscapes through which tumour cells reversibly access proliferative, migratory, stem-like, immune-evasive, and metabolically adaptive states, allowing metastatic competence to emerge without requiring extensive acquisition of new mutations.

Recent advances in single-cell and spatial profiling, **lineage tracing** and multi-omic analysis now provide an opportunity to integrate these dynamic cell states with tumour evolution, developmental identity, and the metastatic microenvironment. In this review, we synthesise genomic, epigenomic, developmental, and single-cell evidence across major paediatric malignancies to examine how developmental programmes are co-opted during dissemination and how epigenetic, metabolic, immune, and stromal interactions enable or stabilise **metastasis-competent states**. We consider genetic evolution and cellular plasticity as interacting rather than mutually exclusive processes and propose a unified framework in which early oncogenic lesions define

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the landscape of possible cell states, while reversible transitions within that landscape shape metastatic behaviour. Finally, we discuss how this framework could redirect therapeutic strategies towards identifying, intercepting, and constraining metastatic plasticity, with the potential to prevent dissemination, overcome treatment adaptation, and exploit vulnerabilities shared across otherwise genetically distinct childhood cancers.

The paediatric cancer genomic landscape: genetic evolution and phenotypic plasticity

Multiple large-scale sequencing studies performed over the last decade have repeatedly demonstrated that childhood tumours generally harbour lower somatic mutation burdens and fewer recurrently mutated genes than adult malignancies [24–31]. However, low mutation rates should not be equated with genomic stability. Many aggressive paediatric cancers undergo substantial genomic evolution through structural variation, copy number alteration, chromosomal instability, and selection of genetically distinct subclones during progression, treatment, and relapse. Indeed, these forms of genomic complexity are prominent in several malignancies discussed below, particularly osteosarcoma, neuroblastoma, and relapsed disease. Paediatric oncogenesis and metastatic progression therefore cannot be considered genetically static.

The important question is instead whether genomic evolution alone explains the acquisition of metastatic competence. In adult cancers, metastatic progression is frequently conceptualised as the endpoint of prolonged **clonal evolution** in which successive genetic alterations increase invasion, survival, and distant colonisation [32]. In paediatric cancer, however, aggressive metastatic behaviour can occur within comparatively constrained mutational landscapes, while genetically related tumour cells can display markedly different invasive, proliferative, or therapy-resistant phenotypes. These observations raise the possibility that genetic alterations establish and modify the evolutionary landscape, whereas nongenetic **state transitions** determine how individual cells navigate that landscape.

Matched primary-metastatic sequencing illustrates this interaction. In osteosarcoma, metastatic lesions can retain broad copy number relationships with the primary tumour while showing divergence in short variants [6], whereas medulloblastoma metastases may arise from restricted subclones already represented within the primary tumour [7]. Neuroblastoma similarly undergoes continuing structural and clonal evolution during progression [8]. Such findings demonstrate that genetic selection remains important but do not necessarily establish that newly acquired genetic alterations are sufficient to generate metastatic behaviour. A metastasis-founding clone may possess both heritable genetic features that increase fitness and sufficient phenotypic plasticity to respond to changing microenvironmental pressures during dissemination.

Thus, we propose an integrated model rather than a genetic-versus-nongenetic dichotomy. Oncogenic lesions, structural variation, copy number architecture, and developmental origin constrain the repertoire of states available to a tumour, while transcriptional, epigenetic, metabolic, and microenvironmental mechanisms influence transitions between those states. Genetic evolution may alter the boundaries of this landscape or stabilise previously reversible phenotypes, whereas plasticity enables rapid adaptation within it. The relative contribution of these processes is likely to differ substantially between tumour types and during different stages of disease.

Epithelial-mesenchymal plasticity as a core mechanism of metastatic competence

Although the developmental origins and genomic drivers of paediatric cancers differ substantially, several recurrent biological principles emerge across tumour types. First, metastatic progression is repeatedly associated with reversible transitions between cellular states rather than the

Glossary

Clonal evolution: the generation and selection of genetically distinct tumour cell populations over time, driven by heritable genomic alterations that confer differential fitness.
Developmental plasticity: the capacity of cells to access alternative developmental or lineage-associated states. In paediatric cancer, developmental plasticity may persist in, or be reactivated within, embryonic or progenitor cells, enabling adaptation during tumour progression and metastasis.
Differentiation therapy: a therapeutic strategy that promotes the maturation of malignant cells towards a more differentiated state, potentially reducing proliferative, stem-like, or metastatic properties.
Enhancer rewiring: the alteration of enhancer activity or enhancer–gene relationships that changes transcriptional programmes and cellular identity, often without alteration of the underlying DNA sequence.
Epigenetic priming: a chromatin configuration that renders particular genes or regulatory programmes accessible for subsequent activation, thereby facilitating rapid cell state transitions in response to appropriate signals.
Epipliancy: a conceptual framework in which the epigenetic state and developmental identity of a cell influence its susceptibility to oncogenic transformation and its subsequent capacity for phenotypic plasticity.
Epithelial-mesenchymal plasticity (EMP): the reversible movement of cells along a spectrum of epithelial and MES phenotypes, encompassing EMT, MET, and intermediate hybrid states.
Go-or-grow: a model describing reciprocal proliferative and migratory cellular behaviours whereby cells can transition between predominantly proliferative and predominantly motile states.
Immunometabolism: the reciprocal relationship between cellular metabolism and immune function. Within tumours, metabolic competition and metabolite accumulation can influence both cancer cell survival and antitumour immunity.
Lineage tracing: refers to experimental approaches that mark cells and follow their descendants over time, enabling the determination of cellular ancestry

acquisition of metastasis-specific mutations. Second, these state transitions are frequently rooted in embryonic developmental programmes. Third, epigenetic remodelling and chromatin plasticity consistently underpin aggressive phenotypes. Finally, metastatic competence is closely intertwined with metabolic adaptation, immune modulation, and niche remodelling. Together, these observations support a unifying model in which metastatic dissemination in childhood cancer reflects coordinated plasticity across developmental, transcriptional, and immunometabolic systems (Figure 1).

Epithelial-mesenchymal plasticity (EMP), the reversible capacity of cells to transition between epithelial and mesenchymal (MES) states, is increasingly recognised as a central driver of metastasis, therapy resistance, and tumour adaptation [17,33,34]. Although epithelial-to-MES transition (EMT) was initially characterised as a developmental programme regulating embryogenesis and tissue morphogenesis, many cancers co-opt this programme to acquire migratory, invasive, and stem-like phenotypes [35,36]. Importantly, EMT is not a binary process. Tumour cells instead occupy a continuum of intermediate epithelial/MES states, and these hybrid phenotypes appear to be particularly associated with metastatic competence owing to their simultaneous retention of motility, survival capacity, and proliferative potential [2,34,37].

The metastatic cascade depends not only on EMT induction but also on its reversibility. Disseminating tumour cells frequently undergo EMT-like transitions to invade and survive systemic dissemination before reacquiring epithelial features through MES-to-epithelial transition (MET) during metastatic colonisation [38,39]. These transitions are primarily governed by transcriptional, epigenetic, and microenvironmental mechanisms rather than the acquisition of new mutations. EMT-associated transcription factors, including SNAIL, TWIST, and ZEB family proteins, cooperate with chromatin remodellers, cytokine signalling, and metabolic adaptation to generate dynamic and reversible **phenotypic states** [34,40]. Metastatic competence, therefore, emerges less as a fixed genetic property and more as an adaptive state-transition process.

This framework is particularly relevant to paediatric cancer because many childhood tumours arise from embryonic or progenitor populations that physiologically possess high developmental plasticity. Neural crest-derived cells, which contribute to neuroblastoma and potentially subsets of Ewing sarcoma, normally undergo coordinated EMT, migration and lineage specification during embryogenesis [20,21,41]. Consequently, oncogenic transformation frequently occurs within cells already primed for phenotypic flexibility. Developmental programmes that normally govern embryonic migration and tissue colonisation may therefore be reactivated or incompletely extinguished during tumourigenesis, generating metastasis-permissive states without requiring extensive mutational evolution [21].

Neuroblastoma: developmental state transitions and epigenetic metastasis

Neuroblastoma provides one of the clearest examples that metastatic competence in paediatric cancer can emerge through reversible developmental plasticity rather than progressive genetic diversification. Derived from neural crest progenitors, neuroblastoma displays extensive intratumoral heterogeneity and dynamic transitions between transcriptional cell states [23]. Two principal identities have been defined. An adrenergic (ADRN) state associated with sympathoadrenal differentiation and a MES state associated with migration, invasion, and therapy resistance [42]. Crucially, these states are interconvertible through epigenetic reprogramming, defining a noradrenergic-to-MES transition analogous to, but molecularly distinct from, classical EMT [42].

Mechanistically, these transitions are driven by **enhancer rewiring** and chromatin remodelling rather than by the acquisition of new mutations. NOTCH3 signalling induces a feed-forward

and the direct measurement of phenotypic state transitions.

Metastasis-competent state: a cellular phenotype that provides tumour cells with properties required for one or more stages of metastatic dissemination or colonisation. Such states may be transient and reversible rather than genetically fixed.

Phenotypic states: cellular configurations defined by coordinated transcriptional, epigenetic, metabolic, and functional properties rather than genotype alone.

State transitions: movements of a cell from one phenotypic state to another through changes in transcriptional, epigenetic, metabolic, or signalling programmes. Transitions may be reversible, stabilised by cellular memory, or subsequently subject to clonal selection.

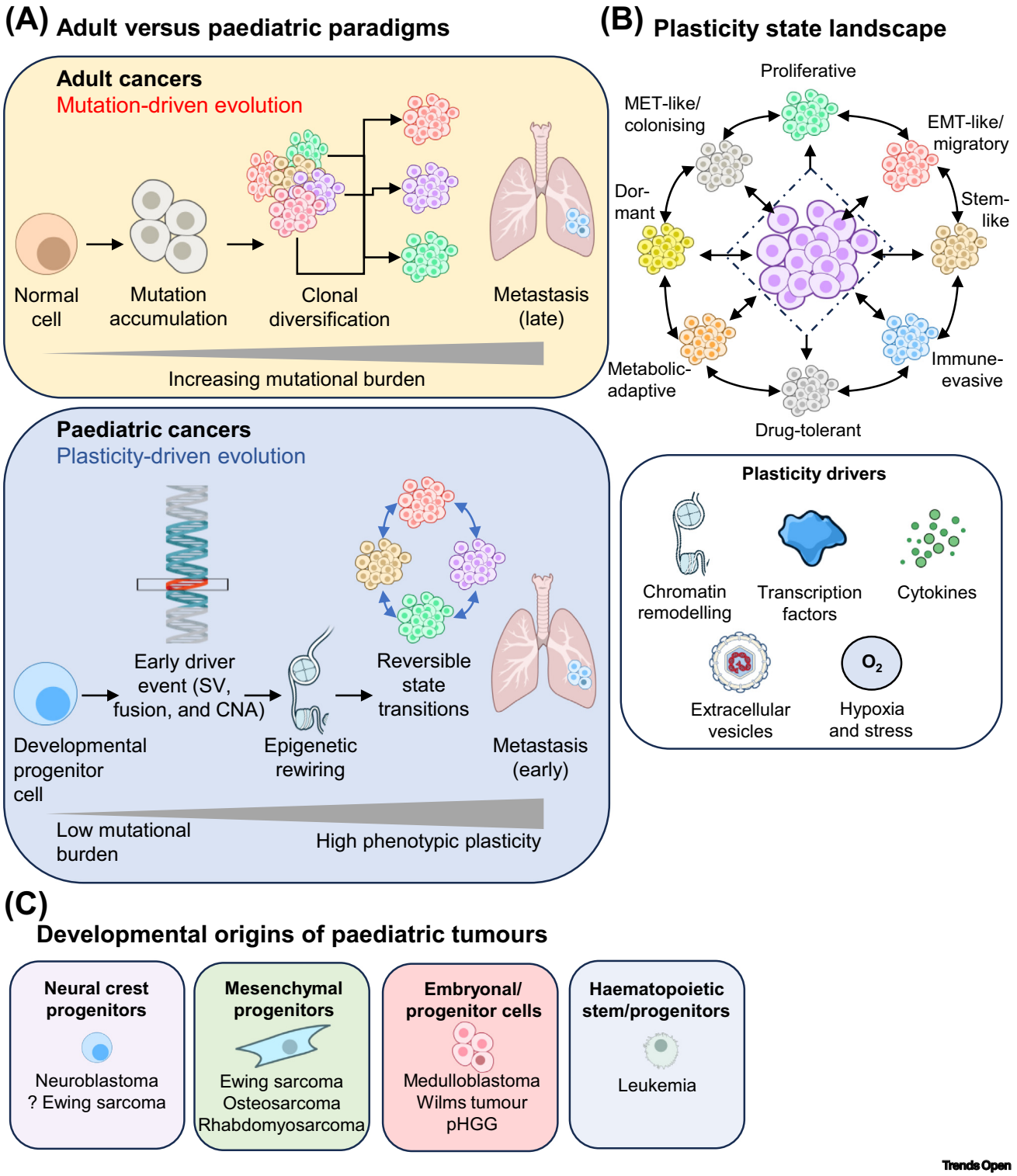


Figure 1. Developmental plasticity as a framework for paediatric cancer metastasis. (A) Comparison of simplified models of metastatic evolution in adult and paediatric cancers. Classical models derived predominantly from adult cancers emphasise sequential mutation accumulation, clonal diversification, and selection, with

(Figure legend continued at the bottom of the next page.)

transcriptional circuit that remodels the H3K27ac landscape, suppresses ADRN super-enhancers and establishes a MES-associated chromatin state [43]. This transition is rapid, reversible and maintained epigenetically. Importantly, both MES and ADRN populations retain tumourigenic capacity *in vivo*, indicating that metastatic competence is not genetically restricted to a fixed subclone but instead represents a reversible phenotypic state accessible to multiple tumour cells [43].

Single-cell and spatial multi-omic studies have further refined this model. Developmentally intermediate neuroblastoma states are characterised by extensive **epigenetic priming** and poised chromatin accessibility landscapes that are permissive for future state transitions [42]. Rather than requiring additional genomic evolution, neuroblastoma cells appear preconfigured for rapid phenotypic adaptation. Similarly, metastatic neuroblastoma cells transcriptionally resemble early sympathetic neuroblasts, directly linking metastatic plasticity to developmental lineage programmes [44]. Together, these findings support a model in which metastasis reflects persistence or reactivation of embryonic neural crest-like states [45] rather than the acquisition of metastasis-specific mutations (Figure 2).

Epigenetic machinery is central to the maintenance of these plastic states. SWI/SNF chromatin-remodelling ATPases establish permissive MES chromatin landscapes in ADRN neuroblastoma cells, facilitating lineage switching, invasion, and chemotherapy resistance [46]. Depletion of SWI/SNF ATPases suppresses enhancer accessibility, disrupts transcription factor occupancy, and constrains phenotypic plasticity, highlighting that aggressive behaviour is maintained by epigenetic architecture rather than by genomic complexity [46].

Importantly, developmental plasticity in neuroblastoma is closely integrated with immune and metabolic adaptation. ADRN and MES states differ not only transcriptionally but also in antigen presentation, interferon responsiveness, stromal interaction, and sensitivity to immune surveillance [42,46–50]. MYCN-driven ADRN programmes may contribute to immune-cold phenotypes through reduced antigen presentation, whereas MES-like states can exhibit enhanced invasiveness, altered cytokine output, and differential susceptibility to innate immune recognition [44,48,50]. These findings suggest that neuroblastoma cells transition not simply between proliferative and migratory states but also between broader immunometabolic phenotypes with distinct capacities for immune evasion and metastatic adaptation (Figure 2).

Genomic studies paradoxically reinforce this plasticity model. Metastatic neuroblastoma clones are frequently established early during embryogenesis and may remain dormant for years before relapse [8]. Although progression is accompanied by ongoing structural variation and convergent evolution targeting loci such as *MYCN, TERT* and *MDM2-CDK4*, different genetic trajectories repeatedly converge upon similar aggressive phenotypes [8]. This convergence suggests that

metastasis emerging relatively late during tumour evolution. In many paediatric cancers, an early driver event, including a structural variant (SV), fusion oncogene or copy number alteration (CNA), occurs within a developmentally permissive progenitor cell and can induce extensive epigenetic and transcriptional rewiring despite a relatively low mutational burden. This architecture may facilitate metastatic competence through reversible phenotypic adaptation rather than requiring extensive sequential mutation acquisition. (B) Proposed plasticity-state landscape. Tumour cells can occupy and transition between proliferative, epithelial-to-mesenchymal transition (EMT)-like/migratory, stem-like, immune-evasive, drug-tolerant, metabolically adaptive, dormant, and mesenchymal-to-epithelial transition (MET)-like/colonising states. Transitions are potentially bidirectional and are influenced by chromatin remodelling, transcription factor activity, cytokine signalling, hypoxia and other cellular stresses, and extracellular vesicle-mediated communication. These states should be regarded as overlapping and dynamic rather than discrete identities or an obligatory linear metastatic sequence. (C) Developmental origins may provide an intrinsic substrate for plasticity in childhood cancer. Candidate developmental contexts include neural crest progenitors in neuroblastoma and potentially subsets of Ewing sarcoma; mesenchymal progenitors in Ewing sarcoma, osteosarcoma, and rhabdomyosarcoma; embryonal/progenitor populations in medulloblastoma, Wilms tumour, and paediatric high-grade glioma (pHGG); and haematopoietic stem/progenitor populations in childhood leukaemia. Question marks denote proposed or unresolved developmental relationships.

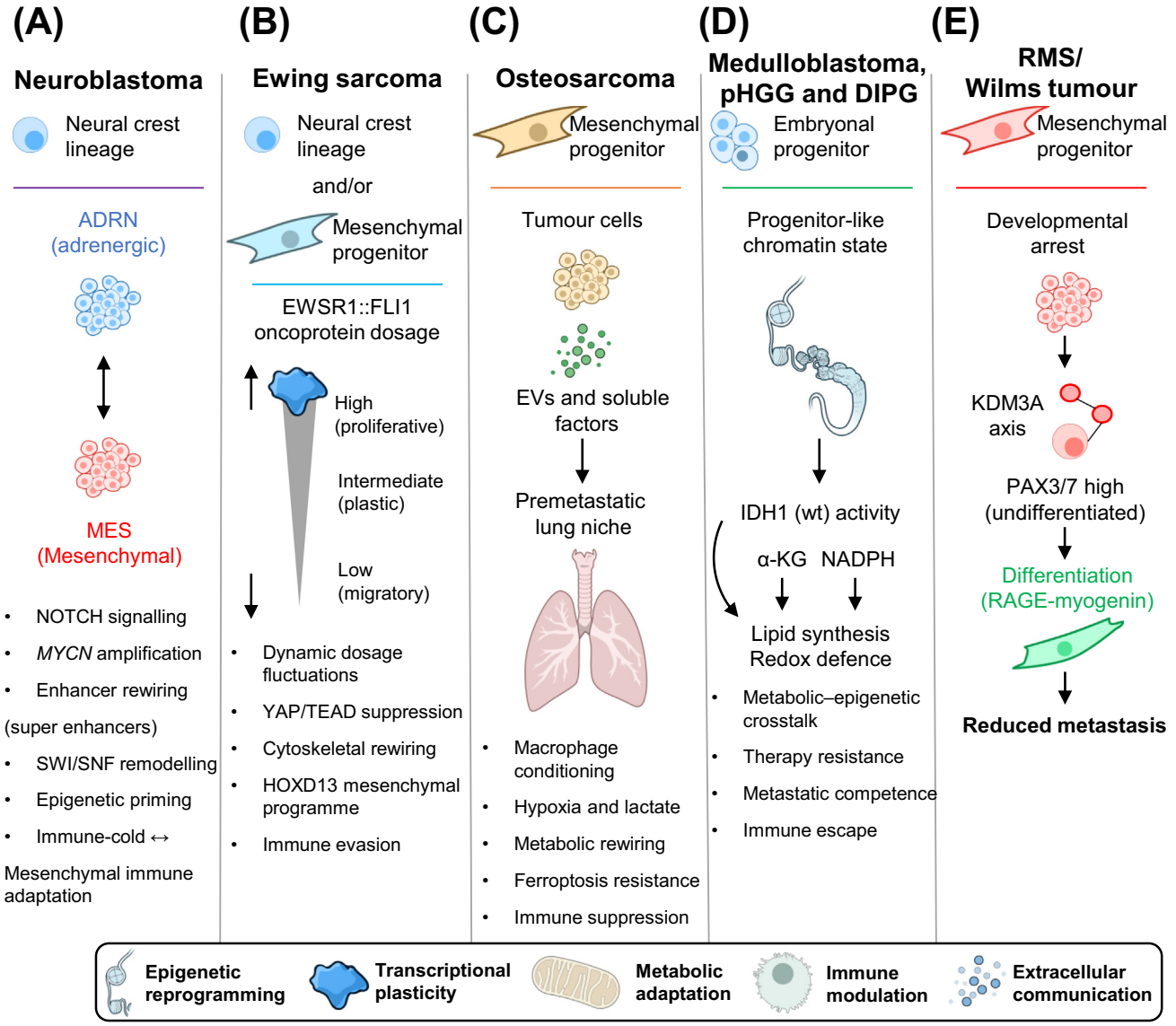


Figure 2. Mechanisms supporting metastatic plasticity across paediatric cancers. Representative examples illustrate how distinct paediatric cancers may exploit developmental, transcriptional, epigenetic, metabolic, immune, and extracellular programmes to generate metastasis-permissive states. (A) Neuroblastoma: neural crest-derived tumour cells can interconvert between adrenergic (ADRN) and mesenchymal (MES) identities through mechanisms involving NOTCH signalling, MYCN-associated enhancer regulation, SWI/SNF-dependent chromatin remodelling, and epigenetic priming, accompanied by altered immune phenotypes. (B) Ewing sarcoma: dynamic EWSR1::FLI1 activity generates a continuum between highly proliferative and less migratory states, with intermediate states potentially supporting plasticity, YAP/TEAD signalling, cytoskeletal rewiring, HOXD13-associated mesenchymal programmes, and immune adaptation contribute to this phenotype. (C) Osteosarcoma: tumour-derived extracellular vesicles (EVs) and soluble factors can condition the pulmonary microenvironment before overt colonisation, while macrophage reprogramming, hypoxia, lactate accumulation, metabolic rewiring, and ferroptosis resistance may support metastatic survival and immune suppression. (D) Medulloblastoma and paediatric high-grade glioma (pHGG), including diffuse intrinsic pontine glioma (DIPG): progenitor-like chromatin states and metabolic–epigenetic crosstalk, exemplified by wild-type IDH1-associated α-ketoglutarate (α-KG), NADPH, lipid metabolism, and redox regulation, can support therapy resistance, immune escape, and metastatic competence. (E) Rhabdomyosarcoma (RMS)/Wilms tumour: developmental arrest and epigenetic reprogramming can maintain poorly differentiated states; in RMS, KDM3A-associated signalling and high PAX3/7 activity support an undifferentiated phenotype, whereas activation of RAGE–myogenin differentiation programmes is associated with reduced metastatic behaviour. Collectively, these examples illustrate convergent routes to metastatic plasticity rather than a single conserved molecular pathway. EWSR1::FLI1: EWS RNA binding protein 1::Fli-1 proto-oncogene, ETS transcription factor; HOXD13: homeobox D13; IDH1: isocitrate dehydrogenase 1; KDM3A: lysine demethylase 3A; MYCN: MYCN proto-oncogene, bHLH transcription factor; NOTCH: Notch receptor 1; PAX3/7: paired box gene 3/paired box 7; RAGE: AGER (Advanced Glycosylation End-Product Specific Receptor); SWI/SNF: SWItch/Sucrose Non-Fermentable; YAP/TEAD: Yes1 Associated Transcriptional Regulator/Transcriptional Enhanced Associate Domain.

metastatic behaviour is determined less by specific mutations and more by the acquisition of permissive phenotypic states.

Ewing sarcoma: fusion oncoprotein dosage and reversible metastatic states

Ewing sarcoma further illustrates how metastatic competence can emerge through dynamic regulation of oncogenic transcriptional states rather than through progressive mutational diversification. The defining fusion oncoprotein, most commonly EWSR1::FLI1, functions as a master regulator of chromatin organisation and transcriptional identity [51]. Notably, EWSR1::FLI1 activity is heterogeneous and dynamically regulated within tumours.

Ewing sarcoma cells reversibly transition between EWSR1::FLI1^{high} proliferative states and EWSR1::FLI1^{low} migratory states [51] (Figure 2). This '**go-or-grow**' dichotomy represents a prototypical plasticity system in which metastatic competence arises through reversible transcriptional adaptation rather than acquisition of additional mutations [2,52]. Mechanistically, EWSR1::FLI1 modulates cytoskeletal organisation and migratory capacity through suppression of MRTFB/YAP1/TEAD signalling and perturbation of Rho-actin feedback loops [53]. HOXD13 further antagonises EWSR1::FLI1-mediated repression, promoting MES transcriptional programmes and reinforcing migratory cell states [54].

Recent work using degron-mediated modulation of endogenous EWSR1::FLI1 levels has provided particularly compelling evidence that oncoprotein dosage itself functions as a nongenetic regulator of metastatic plasticity [55]. Partial depletion of EWSR1::FLI1 promoted prometastatic behaviour, whereas near-complete loss suppressed these phenotypes, revealing that intermediate transcriptional states may paradoxically maximise metastatic competence [55]. Moreover, transient fluctuations in EWSR1::FLI1 activity generated persistent transcriptional reprogramming linked to enhanced extravasation and metastatic burden [55]. These findings highlight the importance of dynamic state transitions rather than static oncogenic signalling.

Immune adaptation is likely tightly integrated into this system. The low mutational and neoantigen burden of Ewing sarcoma limits classical T cell-mediated immune recognition [56]. Consequently, immune escape may depend less on immune editing of antigenic subclones and more on reversible transcriptional states that alter antigen presentation, cytokine secretion, metabolic fitness, and stromal interaction. The Ewing sarcoma model, therefore, extends beyond the simple 'go-or-grow' paradigm towards a broader framework in which proliferation, migration, and immune evasion are coordinated outputs of fusion-driven plasticity.

Osteosarcoma: metastatic plasticity as an immunometabolic ecosystem

Osteosarcoma provides an important extension of the plasticity framework because it combines substantial structural genomic complexity with strong evidence that metastatic progression is governed by nonmutational microenvironmental and immunometabolic programmes. Although osteosarcoma exhibits significant chromosomal instability and extensive copy number alterations [57], metastatic lesions frequently retain the broad genomic architecture of the primary tumour despite relatively limited conservation of short variants [11,12,57,58]. These findings suggest that metastatic competence reflects broader transcriptional and microenvironmental states rather than discrete metastasis-specific mutations.

The pulmonary tropism of osteosarcoma underscores the importance of systemic tumour–microenvironment communication. Osteosarcoma-derived extracellular vesicles can remodel stromal and immune compartments within the lung before overt metastatic colonisation, transferring proteins, RNAs, metabolites, and lipid mediators that condition permissive metastatic niches

(Figure 2) [59,60]. These vesicles influence macrophage behaviour, endothelial activation, extracellular matrix organisation, and immune recruitment, effectively propagating metastatic programmes into nonmalignant tissues.

Single-cell and microenvironmental studies further demonstrate extensive immunometabolic remodelling in osteosarcoma metastasis [11,61–65]. Myeloid populations, including tumour-associated macrophages and suppressive inflammatory states, contribute to T cell dysfunction and metastatic adaptation. Simultaneously, hypoxia, lactate accumulation, mitochondrial rewiring, amino acid competition, and redox buffering generate metabolically hostile environments that suppress immune surveillance while promoting tumour survival [66,67]. Metastatic competence therefore emerges through coordinated interactions between tumour plasticity, stromal education, and metabolic niche conditioning.

Therapeutically, these findings suggest that osteosarcoma metastasis may require simultaneous disruption of tumour cell plasticity, immunosuppressive macrophage states, metabolic adaptation [68], and regulated cell death resistance, including ferroptosis and cuproptosis resistance, rather than escalation of cytotoxic therapy alone.

Medulloblastoma: epigenetic and metabolic plasticity in metastatic progression

Medulloblastoma further illustrates how metastatic competence in paediatric cancer can emerge through epigenetic and metabolic adaptation. Group 3 medulloblastomas, particularly those harbouring *MYC* amplification, exhibit the highest rates of dissemination and have among the poorest outcomes in paediatric neuro-oncology [69]. Yet, despite their aggressive behaviour, metastatic progression frequently occurs without acquisition of extensive metastasis-specific mutational architectures.

Metastatic medulloblastoma lesions are genetically divergent from the primary tumour yet remarkably similar to one another, suggesting that metastasis reflects selection of a permissive cellular state [7]. Critically, only rare subpopulations within the primary tumour exhibit metastatic capacity, consistent with a model in which dissemination arises from phenotypically plastic tumour cells occupying transient, metastasis-competent states [7].

Recent single-cell and multi-omic studies have refined this framework. A persistent progenitor-like population is enriched within recurrent Group 3 medulloblastomas and is characterised by distinct chromatin accessibility landscapes coupled to metabolic reprogramming [69]. These therapy-resistant cells display epigenetically maintained transcriptional states linked to wild-type isocitrate dehydrogenase 1 (IDH1) activity, highlighting how metabolic pathways can stabilise aggressive phenotypes independently of additional genetic mutations [69]. IDH1-dependent metabolic adaptation may support metastatic survival through maintenance of NADPH buffering, glutamine-dependent biosynthesis, redox control, and α-ketoglutarate-linked chromatin regulation within hypoxic and macrophage-enriched niches (Figure 2). Notably, pharmacological inhibition of IDH1 reversed resistance-associated chromatin states and restored radiosensitivity, directly demonstrating that metastatic and therapy-resistant phenotypes remain epigenetically reversible [69]. IDH1 inhibition is further linked to cuproptosis sensitivity through epigenetic suppression of *MYC* and dihydrolipoyl transacetylase, reinforcing the close integration between metabolism, chromatin regulation and cell state plasticity in medulloblastoma progression [70].

Similar principles appear operative in paediatric high-grade glioma (pHGG), including diffuse intrinsic pontine glioma (DIPG) (Figure 2). These tumours are frequently driven by epigenetic

lesions involving Histone 3 variants and chromatin regulatory pathways [71]. EMT-associated transcriptional programmes and MES transitions have increasingly been implicated in therapeutic resistance and invasion, suggesting that aggressive behaviour in paediatric brain tumours is similarly sustained through epigenetic adaptability and developmental state switching [71].

Rhabdomyosarcoma and Wilms tumour: developmental arrest as metastatic plasticity

Rhabdomyosarcoma (RMS) represents a paradigmatic example of metastasis arising through failed developmental maturation. Derived from skeletal muscle progenitors unable to complete terminal differentiation, RMS cells remain locked in partially differentiated and highly plastic states that retain migratory and invasive potential. Mechanistically, metastatic competence in RMS is strongly linked to epigenetic regulation. The histone demethylase KDM3A promotes invasion, transendothelial migration, and metastasis through a KDM3A–Ets1–MCAM regulatory axis in both fusion-positive and fusion-negative RMS [72] (Figure 2). This same pathway operates in Ewing sarcoma despite profound differences in cellular origin and genomic architecture, suggesting that metastatic competence across paediatric sarcomas converges upon shared epigenetic plasticity programmes [72].

Developmental transcription factors reinforce these permissive states. Elevated expression of PAX3 and PAX7 maintains migratory and invasive phenotypes through modulation of adhesion pathways, whereas activation of a RAGE–myogenin differentiation axis suppresses metastasis by promoting terminal differentiation [73] (Figure 2). These findings support a broader principle in paediatric oncology. Metastatic progression frequently reflects persistence of incompletely differentiated developmental states that remain reversible under appropriate transcriptional or epigenetic pressure.

Wilms tumour provides complementary evidence that metastatic competence may arise independently of extensive genomic diversification. Relapse-associated alterations in Wilms tumour often occur late during evolution, contrasting with neuroblastoma and RMS, where aggressive programmes are frequently established near tumour initiation [9]. Some Wilms tumours evolve through unexpectedly normal tissue-like clonal architectures with relatively limited mutational accumulation [74]. The capacity of these genomically constrained tumours to metastasise strongly supports the notion that metastatic competence can emerge through developmental and epigenetic plasticity (Figure 2).

Paediatric leukaemia: plasticity within immunometabolic niches

Although metastasis is classically discussed in the context of solid tumours, childhood leukaemias provide an important extension of the plasticity framework because malignant progression occurs within an intrinsically immune and metabolic organ system: the bone marrow. In both acute lymphoblastic leukaemia and acute myeloid leukaemia, relatively low mutational burden, early initiating lesions and lineage–state heterogeneity interact dynamically with stromal, vascular and immune components of the marrow niche [29,75,76]. Within this context, disease progression depends not solely on the acquisition of additional mutations, but also on the ability of malignant cells to occupy adaptive states permissive for persistence under metabolic, therapeutic, and immune stress. The bone marrow niche supports such plasticity through cytokine signalling, hypoxia, chemokine gradients, mitochondrial transfer, extracellular vesicle exchange, and direct stromal interaction [77]. These processes alter oxidative stress buffering, apoptotic thresholds, nutrient access, and immune surveillance, thereby generating sanctuary environments that support minimal residual disease and relapse.

Importantly, malignant haematopoietic cells also remodel their surrounding ecosystem. Leukaemic cells can reprogramme macrophages, endothelial cells, MES stromal populations, and T cells, creating reciprocal immunometabolic feedback loops that reinforce tumour persistence. Plasticity-driven adaptation in childhood leukaemia therefore extends beyond dissemination to include dormancy, therapeutic tolerance, and long-term survival within protective niches.

Across these malignancies, the developmental context, mechanisms, and experimental evidence supporting metastatic plasticity vary considerably, as do the resulting therapeutic opportunities (Table 1).

Phylogenetic evidence reveals interacting genetic and nongenetic routes to metastasis

Although clonal evolution clearly occurs in paediatric cancer, phylogenetic studies increasingly suggest that metastasis cannot be explained solely by progressive acquisition of metastasis-specific mutations. The evolutionary histories of multiple paediatric malignancies demonstrate extensive collateral phylogenetic branching across tumour regions [9]. However, aggressive tumours exhibit elevated diversity from the earliest stages of clonal expansion, and relapse-associated lesions in neuroblastoma and RMS frequently arise from initiating evolutionary events rather than late-stage mutation accumulation [9]. In this sense, many paediatric tumours appear to be 'born bad', with metastatic potential established early during tumourigenesis.

Further support for this model comes from metastatic tracing studies demonstrating that multiple genetically distinct subclones from the same tumour can independently seed metastases, including dissemination to identical metastatic sites [28]. Intermetastatic seeding was also common [28]. These observations are difficult to reconcile with models requiring the acquisition of highly specific metastasis-promoting mutations. Instead, they suggest that metastatic competence reflects a broadly accessible phenotypic state that can emerge across genetically diverse cellular backgrounds.

Paediatric tumour evolution reflects an interplay among genetic diversification, epigenetic reprogramming, and microenvironmental adaptation [75]. Together, these findings support a model in which genomic lesions establish permissive developmental and epigenetic landscapes, whereas metastatic progression may subsequently depend on reversible phenotypic adaptation superimposed upon this evolving genetic architecture.

Epigenetic architecture underpins metastatic plasticity

The machinery enabling metastatic plasticity in paediatric cancer operates across multiple layers of epigenetic regulation, including chromatin remodelling, histone modifications, DNA methylation, and noncoding RNA networks [38,78–80]. Compared with adult tumours, many paediatric cancers display disproportionately strong dependence on epigenetic dysregulation [78]. Developmental epigenetic programmes appear particularly important. Neural crest differentiation and sympathoadrenal lineage specification are tightly controlled by epigenetic regulators during normal development, and these same mechanisms are co-opted during neuroblastoma progression [81]. Similarly, paediatric brain tumours rely heavily on epigenomic abnormalities rather than extensive mutational evolution [82].

The concept of 'epipliancy' provides a useful unifying framework [83]. In this model, the epigenetic configuration of the cell of origin determines susceptibility to transformation and shapes the degree of subsequent phenotypic plasticity (Figure 1). EMT-associated transcription factors cooperate with oncogenic signalling pathways to generate stem-like states, suppress

Table 1. Developmental plasticity across paediatric cancers: mechanisms, predictions, and therapeutic opportunities

Paediatric cancer	Developmental/oncogenic context	Metastasis-associated plasticity	Principal mechanisms	Testable prediction	Potential therapeutic opportunity
Neuroblastoma	Neural crest/sympathoadrenal developmental origin; MYCN and other early oncogenic events	Reversible ADRN ↔ MES state transitions	NOTCH signalling; enhancer rewiring; SWI/SNF-dependent chromatin remodelling; epigenetic priming; altered immune phenotype	ADRN and MES identities should interconvert longitudinally without requiring new driver mutations, and altering transition probability should modify invasion, treatment response, and metastatic fitness	Constrain lineage switching; promote differentiation; target chromatin regulators or state-specific immune/metabolic dependencies
Ewing sarcoma	EWSR1::FLI1-driven transcriptional and chromatin reprogramming within a developmentally permissive cellular context	Dynamic transitions between proliferative and migratory states according to EWSR1::FLI1 activity	Fusion oncoprotein dosage; MRTFB/YAP/TEAD and Rho-actin signalling; HOXD13-associated programmes; transcriptional memory	Metastatic fitness should vary nonlinearly with EWSR1::FLI1 activity, with intermediate or low states promoting dissemination without acquisition of metastasis-specific mutations	Prevent entry into or persistence of metastasis-permissive states; target downstream dependencies created by altered fusion activity
Osteosarcoma	MES/osteogenic context combined with marked chromosomal instability and copy number alteration	Immunometabolic and tumour microenvironmental adaptation	Extracellular vesicles; macrophage and stromal reprogramming; hypoxia; lactate; mitochondrial/redox adaptation; ferroptosis resistance	Metastatic fitness should depend partly on reversible tumour and niche states despite genomic complexity; perturbing niche conditioning or metabolic adaptation should impair pulmonary colonisation without requiring major genomic change	Disrupt premetastatic niche formation, macrophage states, metabolic adaptation, redox buffering, or ferroptosis resistance
Medulloblastoma/pHGG	Developmentally immature neural progenitor states; MYC-associated programmes in Group 3 medulloblastoma; epigenetic lesions in pHGG	Progenitor-like, therapy-resistant and metabolically adaptive states	Chromatin remodelling; IDH1-associated metabolic–epigenetic coupling; NADPH/redox control; α-KG-linked epigenetic regulation; histone/chromatin dysregulation	Aggressive progenitor-like states should remain at least partly reversible, and experimentally reversing their metabolic or epigenetic programme should restore treatment sensitivity or reduce metastatic fitness	Target metabolic–epigenetic coupling and dependencies of resistant progenitor-like states; promote differentiation or resensitisation
RMS	Developmentally arrested skeletal muscle progenitors; PAX3/7-associated developmental programmes	Persistence of incompletely differentiated migratory and invasive states	KDM3A–Ets1–MCAM signalling; PAX3/7 activity; epigenetic regulation; impaired terminal differentiation	Forcing differentiation or disrupting regulators that maintain immature states should reduce metastatic behaviour independently of extensive genomic change	Promote terminal differentiation; inhibit epigenetic/state maintenance pathways; target vulnerabilities associated with immature cell states
Wilms tumour	Embryonal renal developmental context; relatively constrained genomic evolution in some tumours	Persistence or reactivation of developmentally permissive cell states	Developmental and epigenetic programmes, with variable contribution from later genetic evolution	Metastasis-competent states should be identifiable within developmentally defined populations and may precede substantial genetic divergence	Identify and constrain metastasis-permissive developmental states and the pathways required for their maintenance
Childhood leukaemia	Early initiating lesions within haematopoietic progenitors; lineage–state heterogeneity within the bone marrow ecosystem	Reversible dormancy, persistence, and therapy-tolerant states	Hypoxia; cytokine/chemokine signalling; stromal interactions; mitochondrial transfer; extracellular vesicles; immune and metabolic remodelling	Residual malignant cells should reversibly alter state in response to niche and treatment pressures; disrupting these interactions should reduce persistence without necessarily changing genotype	Target tumour–niche interactions, metabolic dependencies, and reversible therapy-tolerant states to prevent minimal residual disease and relapse

α-KG: α-ketoglutarate

differentiation programmes, and promote metastatic adaptability [83]. This framework is particularly relevant to paediatric cancer because transformation frequently occurs within cells already occupying highly permissive developmental epigenetic states.

Consistent with this model, regulators of EMP, including histone deacetylases, Tet2 hydroxylase, and the Mbd3/NuRD complex, exert profound effects on metastatic competence [84]. Similarly, SWI/SNF chromatin-remodelling ATPases establish permissive MES chromatin states in neuroblastoma and directly regulate lineage switching, invasion, and chemotherapy resistance [46]. These findings reinforce the concept that metastatic progression in childhood cancer is fundamentally sustained by dynamic epigenetic state regulation.

Cancer stem cells and metastatic niche adaptation

The cancer stem cell (CSC) model intersects closely with the plasticity paradigm because stemness itself represents a dynamic and reversible state [85–87]. Nonstem tumour cells can reacquire CSC-like properties through EMT-associated reprogramming and related plasticity mechanisms, generating populations capable of tumour initiation, therapy resistance, and metastatic colonisation [33,37,87]. This framework is particularly relevant in paediatric cancer because many childhood tumours arise directly from stem or progenitor populations with inherent developmental flexibility [88]. In Ewing sarcoma, for example, EWSR1::FLI1 reprogrammes MES stem cells towards embryonic stem cell-like transcriptional states through modulation of SOX2 and miR-145 signalling [89]. A single oncogenic lesion can therefore induce widespread developmental reprogramming and generate metastasis-permissive CSC-like phenotypes.

Metastatic colonisation further depends on reciprocal interactions between CSCs and supportive stromal niches. Periostin-dependent niche signalling is essential for the maintenance of metastatic CSC populations through amplification of Wnt signalling pathways [90]. These observations reinforce the idea that metastatic competence reflects coordinated interactions between plastic tumour cells and permissive microenvironments.

From cellular heterogeneity to plasticity: establishing causality

A major challenge for the developmental plasticity model is distinguishing true state interconversion from selection of pre-existing, phenotypically stable subpopulations. Single-cell transcriptomic or epigenomic analyses can identify coexisting proliferative, migratory, stem-like, or therapy-tolerant populations, but the presence of multiple states does not itself demonstrate plasticity. Similarly, enrichment of a particular transcriptional state within metastases cannot distinguish whether cells acquired that phenotype during dissemination or whether a pre-existing metastasis-competent population was preferentially selected.

Direct demonstration of plasticity, therefore, requires temporal and lineage-resolved evidence. Ideally, individual tumour cells should be followed as they enter and exit defined states, with state transitions linked experimentally to changes in metastatic behaviour. Genetic barcoding and lineage tracing can establish whether multiple phenotypic states arise from common ancestral clones, while inducible reporters and live-cell imaging can determine the direction and kinetics of transitions. Combining lineage information with single-cell transcriptomic, chromatin accessibility, and genomic profiling is particularly powerful because it can distinguish phenotypic switching within the same genetic lineage from the expansion of genetically distinct subclones. State-specific perturbation provides a further level of evidence. If experimentally increasing or decreasing the probability of a defined transition alters invasion, dissemination, or metastatic colonisation without the corresponding acquisition of new genetic drivers, this provides stronger support for a causal role of plasticity.

Several systems discussed in this review approach this standard of evidence. In neuroblastoma, experimentally induced and reversible transitions between ADRN and MES identities demonstrate that these states are not simply genetically distinct populations [43,44,47]. In Ewing sarcoma, controlled modulation of endogenous EWSR1::FLI1 abundance directly alters proliferative and prometastatic phenotypes, while transient fluctuations can produce persistent transcriptional consequences [51,55]. Nevertheless, for many other paediatric malignancies, evidence remains predominantly associative. Observations of developmental, metabolic, or immune-state heterogeneity should therefore be regarded as evidence of candidate plasticity programmes until lineage-resolved experiments establish interconversion and demonstrate that altering transition dynamics changes metastatic outcome.

An additional challenge is separating plasticity from selection because the two processes can operate simultaneously. A transient state induced by treatment or the microenvironment may increase survival and subsequently undergo clonal selection, while genetic alterations acquired during progression may stabilise a phenotype that was initially reversible. Future studies should therefore combine lineage tracing with repeated genomic and epigenomic measurements before, during, and after metastatic or therapeutic selection. Such approaches would allow metastatic evolution to be resolved as an interaction between heritable clonal selection and reversible state change rather than forcing these processes into mutually exclusive models.

What drives plasticity under therapeutic stress?

The capacity for state switching is determined partly by developmental origin and oncogenic architecture, but therapy can provide a powerful selective and instructive pressure that exposes this latent plasticity. Rather than a single conserved ‘plasticity gene’, paediatric cancers appear to rely on tumour-specific lineage regulators embedded within broader stress-responsive transcriptional, epigenetic, and metabolic networks. Examples discussed above include NOTCH- and SWI/SNF-dependent regulation of ADRN–MES identity in neuroblastoma, dynamic EWSR1::FLI1 activity and YAP/TEAD-associated signalling in Ewing sarcoma, KDM3A-associated developmental programmes in RMS, and metabolism-linked chromatin regulation in medulloblastoma. These regulators can be viewed as components of the molecular machinery that define which state transitions are accessible within a particular developmental and genetic context.

How therapy activates these programmes remains less well resolved. Cytotoxic treatment imposes several simultaneous stresses, including DNA damage, replication stress, oxidative stress, nutrient limitation, and altered cell–cell communication. Surviving cells can consequently activate stress-responsive signalling and transcriptional programmes while treatment-induced changes in chromatin accessibility alter the regulatory elements available to lineage-defining transcription factors. These processes need not generate an entirely new phenotype; instead, therapy may shift the probability with which cells enter pre-existing developmental states already encoded within the tumour’s regulatory landscape.

Treatment also remodels the tumour ecosystem. Cell death and tissue injury alter cytokine and chemokine signalling, extracellular vesicle release, nutrient availability, oxygenation, and interactions with macrophages, fibroblasts, and other stromal populations. These environmental changes can reinforce tumour-intrinsic stress responses and stabilise drug-tolerant, MES-like, stem-like, or metabolically adaptive states. Therapy-induced plasticity should, therefore, be considered an ecosystem response in which cell-intrinsic stress signalling, chromatin reprogramming, and microenvironmental remodelling act together.

An important distinction is that these mechanisms may either induce a state change or select cells that already occupy a favourable state. Both processes are likely to occur, and their relative contributions may vary by tumour and treatment. Longitudinal lineage tracing combined with single-cell genomic and epigenomic profiling before and after therapy will therefore be required to distinguish induction from selection [3]. This distinction is therapeutically important. Preventing induction requires targeting the mechanisms responsible for transition, whereas eliminating a pre-existing resistant state requires identifying and exploiting dependencies specific to that population.

Which paediatric cancers are most susceptible to plasticity?

The extent to which paediatric cancers depend on cellular plasticity is unlikely to be uniform. We propose that susceptibility is greatest where oncogenesis preserves or reactivates developmentally permissive regulatory landscapes rather than irreversibly fixing a differentiated cellular identity. Tumours arising from embryonic or progenitor populations may have a particularly broad repertoire of accessible states because lineage-defining transcription factors, developmental enhancers, and chromatin remodelling systems remain active or are readily reactivated [91]. Neuroblastoma provides a strong example, in which alternative ADRN and MES identities are encoded within related enhancer landscapes, while Ewing sarcoma illustrates how a dominant fusion oncoprotein can continuously remodel transcriptional identity and thereby alter access to proliferative and migratory states.

This does not imply that genomically complex tumours are intrinsically less plastic. Osteosarcoma demonstrates that extensive chromosomal instability and phenotypic plasticity can coexist [92]. In such cancers, genetic heterogeneity may broaden the range of accessible phenotypes or alter the probability with which particular states emerge. Conversely, genetic or epigenetic alterations may occasionally restrict plasticity by stabilising particular cell identities. The relevant determinant may therefore be less the absolute mutation burden than the extent to which tumour fitness remains dependent on flexible lineage, chromatin, and stress-response programmes.

This distinction could have therapeutic value. Tumours in which metastasis depends strongly on reversible lineage or transcriptional states may be particularly amenable to **differentiation therapy** or interventions that constrain state transitions. By contrast, cancers dominated by extensive clonal diversification may require the combined targeting of genetic subclones and their associated adaptive states. Prospective measures of chromatin accessibility, lineage–state heterogeneity, and experimentally determined transition capacity may therefore prove to be more informative predictors of susceptibility to plasticity-directed therapy than mutation burden alone. However, this remains a hypothesis that will require systematic comparison across tumour types using common lineage-resolved and functional assays.

Therapeutic implications: can plasticity be targeted?

If metastatic progression in paediatric cancer is enabled by reversible cellular plasticity, therapeutically constraining state transitions represents an attractive but challenging strategy. Unlike a recurrent mutation or a constitutively active kinase, plasticity is not a discrete molecular target. It is an emergent property of interconnected transcriptional, epigenetic, metabolic, and microenvironmental networks. Moreover, the same developmental programmes that permit tumour adaptation frequently operate in normal progenitor populations and tissue repair, creating potential therapeutic windows that may be particularly narrow in children. The objective may therefore not be to eliminate plasticity altogether, but rather to identify and disrupt the regulatory nodes, transition states, or dependencies that malignant cells require to enter, maintain, or exit metastasis-competent states.

Epigenetic regulation provides one potential point of intervention because chromatin remodelling can stabilise otherwise reversible phenotypes. Histone demethylase inhibition, for example, impairs metastatic phenotypes in Ewing sarcoma and RMS [72]. However, epigenetic regulators typically control broad transcriptional programmes and are rarely specific to a metastatic state. Their inhibition may consequently affect normal developmental programmes while simultaneously creating alternative adaptive states.

A further challenge is temporal. Inhibiting a regulator that maintains one aggressive state could select for, or facilitate a transition towards, another. Effective epigenetic therapy may require identification of state-specific dependencies and longitudinal monitoring of the phenotypic consequences of treatment rather than assuming that suppression of one state equates to suppression of metastatic competence.

Differentiation therapy offers a complementary strategy for malignancies arising from developmentally arrested progenitors. The clinical use of retinoids in neuroblastoma provides proof-of-principle that manipulating developmental state can contribute therapeutically [16], while emerging understanding of NOTCH, PHOX2B, and HOXD13 regulatory networks may reveal additional opportunities to constrain plasticity [16,43,54]. Regardless, differentiation is unlikely to represent a universal solution. Paediatric tumours contain heterogeneous and potentially interconverting populations, and forcing one differentiation trajectory may leave alternative states unaffected. Furthermore, differentiation may suppress proliferation without necessarily eliminating disseminated cells, raising the possibility of residual populations capable of subsequent reprogramming.

Ewing sarcoma illustrates an additional hazard. The relationship between oncogenic activity and metastatic phenotype may be nonlinear. Partial perturbation of a plasticity-regulating oncogenic programme could shift cells into a more migratory or stress-adapted state rather than eliminating them. Therapeutic success may depend not simply on whether a pathway is inhibited, but on the magnitude, duration, and timing of inhibition. This argues for pharmacodynamic approaches capable of resolving cell state responses during treatment and, where necessary, combinations that prevent escape into alternative phenotypic states.

Metabolic and immune dependencies may offer a more tractable means of targeting the consequences of plasticity, rather than plasticity itself. Metastasis-associated states can depend on altered redox buffering, amino acid utilisation, lactate metabolism, mitochondrial function, adaptation to hypoxia, and resistance to regulated cell death [18,19,67]. These dependencies may represent liabilities created by adaptation. A cell that acquires the metabolic capacity to survive dissemination or a hostile metastatic niche may simultaneously become disproportionately dependent on the pathway supporting that state. Targeting such dependencies could destabilise metastasis-competent populations while also modifying immunosuppressive microenvironments. However, metabolic flexibility creates another potential route of escape, and substantial overlap between tumour and normal tissue metabolism may limit therapeutic windows. These considerations are particularly important in children, in whom developing tissues have distinct metabolic and developmental requirements.

Targeting plasticity is therefore feasible in principle, but is unlikely to be achieved through a single broadly acting ‘anti-plasticity’ drug. A more realistic strategy may be to identify when tumour cells become vulnerable during state transitions, determine which dependencies are necessary to maintain metastasis-competent states, and therapeutically prevent or exploit those transitions. Single-cell and spatial profiling, longitudinal liquid biopsy [3], and functional metabolic approaches

may ultimately enable such states to be monitored during treatment. Rather than replacing genotype-directed therapy, targeting plasticity could provide a complementary strategy: genomic alterations identify the oncogenic architecture of the tumour, but dynamic cell state information identifies how that tumour is adapting and which vulnerabilities are accessible at a particular time. The central translational challenge will be to convert this dynamic information into biomarkers and treatment schedules capable of constraining adaptation without disrupting the developmental plasticity required by normal paediatric tissues [93].

Reconciling genetic evolution with plasticity

A plasticity-based model of paediatric metastasis should complement, rather than replace, clonal evolution. Genetic alterations can influence metastatic fitness and provide the heritable architecture within which phenotypic states emerge. The central proposition is not that metastasis is genetically independent, but that genotype alone may be insufficient to explain when and how metastatic competence is expressed. Early oncogenic and developmental contexts can define a landscape of accessible cellular states, while epigenetic, transcriptional, and microenvironmental signals determine movement within that landscape. Metastatic potential consequently reflects an interaction between relatively stable genetic constraints and dynamic phenotypic adaptation.

This framework makes several testable predictions. Genetically similar cells should be capable of occupying functionally distinct states; metastasis-competent phenotypes should arise and regress without requiring new driver mutations; and perturbing regulators of state transitions should alter dissemination independently of major genomic change. Conversely, recurrent genetic alterations specifically enriched in metastases and sufficient to confer metastatic behaviour would argue for a greater contribution from conventional clonal selection. Plasticity and selection are unlikely to operate independently. Transient states may expose cells to different selective pressures, whereas genetic evolution may stabilise previously reversible phenotypes. Metastasis may, therefore, emerge from reciprocal interactions between genetic selection and nongenetic state transitions rather than from either mechanism alone.

One useful abstraction is to represent this behaviour as a stochastic state transition system, in which tumour cells move between semistable proliferative, migratory, stem-like, immune-adaptive, or therapy-tolerant states [2]. Markov-type frameworks provide an intuitive means of describing such interconversion and distinguishing reversible states from absorbing outcomes such as cell death or durable metastatic colonisation [94–96]. However, simple Markov models also expose an important limitation of the framework. Biological transitions are unlikely to be memoryless. Chromatin remodelling, treatment exposure, and microenvironmental conditioning can leave molecular ‘memory’ that alters the probability of subsequent transitions, while spatial constraints and cell–cell interactions further shape the available state landscape. Plasticity should be viewed not as unrestricted switching between interchangeable phenotypes, but as a constrained and history-dependent process whose boundaries are imposed by genotype, developmental origin, and microenvironment.

The key challenge is, consequently, to establish causality. Observing multiple transcriptional states, even at single-cell resolution, does not demonstrate that cells transition between them or that such transitions drive metastasis. Longitudinal lineage tracing, state-specific perturbation, and paired genomic–epigenomic measurements will be required to distinguish true plasticity from coexistence or selection of stable subclones. The value of the developmental plasticity model will ultimately depend on whether it can predict which states are accessible, which transitions confer metastatic fitness, and which can be therapeutically intercepted.

Immunometabolism and metastatic adaptation

The plasticity framework has major implications for tumour immunology and **immunometabolism**. Although paediatric cancers have traditionally been considered relatively immunologically 'cold' owing to low mutational burden and limited neoantigen repertoires, metastatic competence cannot be understood solely through tumour-intrinsic genetics. Metastatic progression ultimately requires successful negotiation of immune surveillance, stromal interaction, and metabolic competition within both primary and distant tissue environments.

Importantly, immune competence is not restricted to specialised haematopoietic populations. Virtually all cells possess innate damage-sensing pathways, antigen processing machinery, and inflammatory signalling capacity. Through MHC-I-mediated antigen presentation, tumour cells continuously interact with cytotoxic T cells and natural killer (NK) cells, creating dynamic immunological selection pressures that shape metastatic evolution (Figure 3). Consequently, tumour cells should be considered not simply according to their mutational status but also according to their broader immunophenotypic state, including whether they occupy immune-visible or immune-suppressed configurations (Figure 3).

EMP is increasingly recognised as a major regulator of tumour immunophenotype. EMT-associated states suppress antigen presentation, increase immune checkpoint signalling, alter cytokine secretion, and promote acquisition of stem-like and therapy-resistant phenotypes [97–102]. Simultaneously, EMT-associated metabolic rewiring can generate profoundly immunosuppressive microenvironments through lactate accumulation, hypoxia adaptation, altered amino acid metabolism, and resistance to oxidative stress (Figure 3). Although MES-like states may increase susceptibility to NK cell recognition in certain contexts, MET does not necessarily fully restore immune visibility, suggesting that immune adaptation may persist beyond phenotypic reversion.

In paediatric cancers, immune evasion appears to emerge through a combination of initiating oncogenic lesions and subsequent nonmutational plasticity. Fusion oncogenes, *MYC* amplification, *SMARCB1* loss, and Histone 3 mutations establish permissive transcriptional and epigenetic frameworks, but metastatic immune escape is amplified through reversible alterations in chromatin accessibility, lineage state, extracellular vesicle signalling, metabolism, and stromal education [2]. Tumour cells thereby adapt dynamically to immune pressure without requiring extensive additional mutational diversification.

The low neoantigen burden characteristic of childhood cancers further amplifies the importance of these nongenetic mechanisms. Even when neoantigens are present, the surrounding immunological context critically determines whether effective antitumour responses occur. Developmental immune tolerance during early life may also contribute to permissive windows in which embryonal cancer cells evade efficient immune elimination [56]. Consequently, metastatic progression likely reflects not only cancer cell adaptation but also the developmental and immunological context.

Importantly, oncogenic lesions do not merely alter tumour-intrinsic transcriptional programmes. Through extracellular vesicles, soluble metabolites, cytokines, hypoxia signalling, and therapy-induced stress responses, tumour cells actively reprogramme surrounding stromal and immune populations [59–65] (Figure 3). Macrophages, regulatory T cells, and myeloid-derived suppressor cells can become metabolically conditioned towards immunosuppressive phenotypes that support metastatic survival and niche conditioning. In this sense, childhood cancers should not be viewed as purely mutation-autonomous diseases but rather as dynamic ecosystem disorders sustained through reciprocal tumour–microenvironment interactions [103].

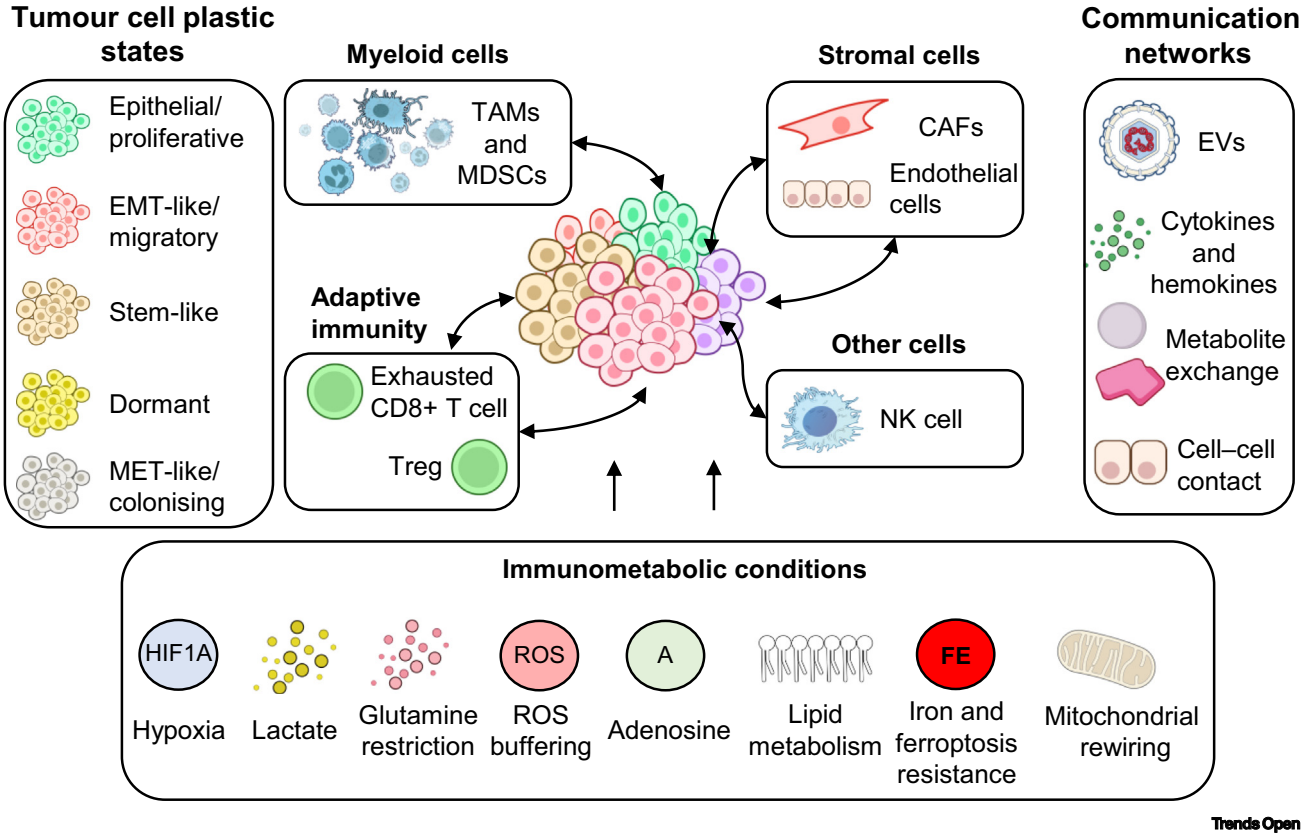


Figure 3. Immunometabolic ecosystems supporting plasticity and metastatic adaptation in paediatric cancer. Metastatic competence emerges through reciprocal interactions between plastic tumour cell states and the immune, stromal, and metabolic components of the tumour microenvironment. Tumour cells may occupy and transition between epithelial/proliferative, epithelial-to-mesenchymal transition (EMT)-like/migratory, stem-like, dormant, and mesenchymal-to-epithelial transition (MET)-like/colonising states. These phenotypes interact dynamically with myeloid populations, including tumour-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs); adaptive immune populations, including exhausted CD8+ T cells and regulatory T (Treg) cells; natural killer (NK) cells; cancer-associated fibroblasts (CAFs); and endothelial cells. Bidirectional communication is mediated through extracellular vesicles (EVs), cytokines and chemokines, metabolite exchange and direct cell–cell contact, enabling tumour cells to modify their surrounding ecosystem while microenvironmental signals influence tumour cell state. These interactions occur within metabolically heterogeneous conditions characterised by hypoxia and hypoxia-inducible factor 1α (HIF-1α) signalling, lactate accumulation, glutamine restriction, reactive oxygen species (ROS) and redox buffering, adenosine signalling, altered lipid metabolism, iron availability and ferroptosis resistance, and mitochondrial rewiring. Collectively, the model proposes that metastatic plasticity is an ecosystem-level property in which tumour state, immune function, and metabolic adaptation are mutually reinforcing. Arrows indicate reciprocal interactions rather than an obligatory sequence or established direction of causality; individual components and dependencies are expected to vary between tumour types, metastatic sites, and stages of disease.

These observations create important therapeutic opportunities. Metabolic adaptation may represent a selective vulnerability in low-mutational-burden cancers because tumour and immune compartments frequently converge upon shared metabolic dependencies. Therapeutic disruption of ferroptosis resistance, redox buffering, mitochondrial adaptation, or amino acid utilisation may simultaneously destabilise tumour plasticity and reverse immunosuppressive microenvironments [11,12,18,19,67,100]. Indeed, emerging evidence from TSC2-driven tumours, Ewing sarcoma, and osteosarcoma demonstrates that metabolic rewiring contributes directly to ferroptosis resistance and therapeutic tolerance [11,12,104,105].

Targeting the downstream biological consequences of plasticity, including metabolic adaptation, immune suppression, and regulated cell death resistance, may prove more effective than approaches focused exclusively on static genomic alterations. Importantly, these strategies also offer the possibility of reprogramming suppressive immune infiltrates towards

proinflammatory states, thereby restoring antitumour immunity while simultaneously constraining metastatic adaptation.

Concluding remarks

The developmental plasticity framework offers a way to reconcile the relatively constrained genomic landscapes of many paediatric cancers with their capacity for profound phenotypic heterogeneity, therapeutic adaptation, and metastatic progression. Rather than replacing clonal evolution, it proposes that oncogenic lesions and developmental origin define the range of cellular states available to a tumour, while epigenetic, metabolic, immune, and microenvironmental pressures govern transitions between them. Its principal advantage is conceptual integration: metastasis becomes a dynamic process that may be intercepted, rather than an irreversible phenotype encoded by a metastatic clone.

The major challenge is now to demonstrate these transitions directly in patients. As highlighted in the Outstanding questions section, a critical priority is to determine how metastasis-competent states can be prospectively identified and monitored. Single-cell RNA sequencing has revealed extensive cellular heterogeneity, but a snapshot of different transcriptional states cannot establish plasticity or determine their direction of travel. Longitudinal sampling will be essential [3]. Single-cell multi-omics integrating the transcriptome, chromatin accessibility, and genotype could distinguish state transitions from clonal selection, while lineage tracing and cellular barcoding in experimental models can establish ancestry and transition kinetics directly. Spatial transcriptomics and proteomics should further determine where metastasis-permissive states emerge and how they interact with immune and stromal niches. In patients, serial profiling of circulating tumour cells and cell-free nucleic acids may ultimately provide a practicable means of following these processes without repeatedly sampling inaccessible tumours. Integrating such measurements through computational state transition models could shift the paediatric oncology field from cataloguing cellular states towards predicting their trajectories.

A second outstanding question is what determines whether a plastic state remains reversible or becomes stabilised. We speculate that this distinction is unlikely to depend on a single molecular switch. Instead, repeated treatment or microenvironmental selection may progressively reinforce initially transient states through chromatin remodelling, transcriptional feedback, and metabolic–epigenetic coupling, eventually reducing the probability of returning to the original state. Testing this model will require time-resolved perturbation experiments that combine lineage tracing with single-cell epigenomics, metabolomics, and functional phenotyping before, during, and after defined selective pressures. Such experiments could identify not only the molecular determinants of state transitions but also the temporal windows during which these states remain reversible and therefore most amenable to therapeutic intervention.

These experimental approaches nevertheless have important limitations. Cell dissociation can erase spatial information and perturb transcriptional states; lineage tracing remains considerably easier in experimental systems than in patients; circulating populations may incompletely represent metastatic lesions; and increasingly sophisticated multi-omics datasets risk producing ever more detailed descriptions without demonstrating causal relationships. Plasticity itself is also difficult to define operationally. Evidence of heterogeneity should not be equated with evidence of interconversion, and associations between particular states and metastasis do not establish that those states are necessary or sufficient for dissemination. The strongest tests of the framework will therefore combine longitudinal observation with state-specific perturbation and a functional demonstration that altering transition probabilities changes metastatic outcomes.

Outstanding questions

How can metastasis-competent plastic states be prospectively identified and monitored in patients?

What determines whether a plastic state transition is reversible or becomes epigenetically fixed?

To what extent do developmental immune tolerance and the neonatal/paediatric immune environment shape metastatic permissiveness?

Do partial or fluctuating levels of fusion oncoproteins, rather than their presence or absence, represent a general mechanism of metastatic plasticity across paediatric sarcomas and other fusion-driven tumours?

Do plastic alternate-state populations pre-exist within tumours and undergo selection during therapy, or are they actively induced through state transitions in response to treatment?

Therapeutically, these considerations argue against the existence of a universal 'antiplasticity' drug. A more realistic objective may be to exploit vulnerabilities created during particular transitions or prevent tumour cells from entering, maintaining, or escaping metastasis-permissive states. This will require biomarkers capable of resolving dynamic tumour states alongside genotype, and, potentially, treatment schedules adapted to the times when particular vulnerabilities emerge. Such approaches also carry risks. Restricting one transition could select an alternative adaptive trajectory, whereas broadly targeting epigenetic or metabolic plasticity could disrupt normal developmental and regenerative processes, which is an especially important consideration in children.

The decisive test of the developmental plasticity model will be predictive rather than descriptive. Can knowledge of a tumour's current state and its accessible trajectories predict where it will move next, which cells will disseminate, and when a therapeutic vulnerability will emerge? Advances in longitudinal single-cell and spatial multi-omics, lineage-resolved experimental systems, liquid biopsies, and computational modelling now make these questions increasingly tractable. If metastatic progression can ultimately be mapped as a constrained series of state transitions, the opportunity is not simply to understand plasticity but also to anticipate and intercept it before adaptation becomes metastatic disease.

Author contributions

D.G. and D.W.S. jointly conceptualised this article, wrote the draft, and reviewed and edited the final paper.

Acknowledgements

No funding was required for the writing of this article.

Declaration of interests

The authors declare no competing interests.

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This study demonstrated that Ewing sarcoma cells reversibly fluctuate between EWSR1::FLI1^{high} proliferative and EWSR1::FLI1^{low} migratory and invasive states. Importantly, this occurs without the acquisition of a new genetic clone, providing a particularly clear experimental demonstration that fluctuations in the activity of the dominant oncogenic driver can generate metastasis-associated phenotypic plasticity.

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This is arguably the classic paediatric cancer plasticity study. It identified adrenergic and mesenchymal neuroblastoma states, associated with distinct super-enhancer landscapes and transcription factor networks. Crucially, the states can interconvert, and experimentally expressing PRRX1 can reprogramme the adrenergic transcriptional and enhancer landscape towards the mesenchymal state.

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