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Review

Neural Induction: the General Principle for Embryogenesis and Tumorigenesis

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Abstract: Some concepts/hypotheses have been proposed to explain the general rules behind the complexity of tumorigenesis. Characterization of the property of cancer cells and neural stem cells indicates that neural stemness underlies tumorigenicity and pluripotency, leading to the proposal that tumorigenesis represents a process of progressive loss of original cell identity and gain of neural stemness. This reminds of a most fundamental process required for the development of the nervous system and body axis during embryogenesis, i.e., embryonic neural induction. The principle of neural induction is that, in response to extracellular signals that are secreted by the Spemann-Mangold organizer in amphibians or the node in mammals and inhibit epidermal fate in ectoderm, the ectodermal cells assume the neural default fate and turn into neuroectodermal cells. These cells further differentiate into the nervous system and also some non-neural cells via interaction with adjacent tissues. Failure in neural induction leads to failure of embryogenesis, and ectopic neural induction due to ectopic organizer or node activity or activation of embryonic neural genes causes a formation of secondary body axis or conjoined twins. A similar principle underlies tumorigenesis. Increasing evidence has demonstrated that the core property of cancer cells is neural stemness. Therefore, cancer cells are cells with the loss of original cell identity and gain of neural stemness, and consequently tumorigenicity and pluripotency, due to various intra-/extracellular insults in postnatal animals. Unlike that pluripotent cells (embryonic pluripotent cells, neural stem cells and cancer cells) can differentiate and integrate into embryonic development, cancer cells are capable of self-renewal and differentiation, but cannot integrate into normal tissues in a postnatal animal, ultimately leading to tumor formation. Neural induction and the unique property of neural stemness provide an inclusive explanation for embryogenesis, conjoined twin formation and tumorigenesis. Based on these findings, I discuss about some confusion in cancer research, e.g., epithelial-mesenchymal transition, and propose to distinguish the causality and associations, and the causal and supporting factors involved in tumorigenesis, and suggest revisiting the focus of cancer research. Integration of evidence from developmental and cancer biology indicates that neural stemness determines tumorigenicity and pluripotency, and neural induction drives embryogenesis in gastrulating embryos but a similar process drives tumorigenesis in a postnatal animal.

Keywords: neural induction; embryogenesis; tumorigenesis; conjoined twin; Spemann organizer; node; neural default model; neural stemness; tumorigenicity; pluripotency; epithelial-mesenchymal transition; tumor microenvironment

1. Introduction

Understanding the nature of cancer initiation and progression has experienced wild fluctuations, from the initial chaos of phenomenological description of cancer to the trials of simplification of cancer regulation to single molecules or molecular events, and then followed by indefinite complexity of genetic and phenotypic heterogeneities and regulatory mechanisms (Weinberg, 2014). Millions of cancer literatures have shown that almost all aspects of biological research play a role in cancer, and nearly every gene is associated with cancer (de Magalhães, 2022). Some hypotheses/concepts have been used to generalize the rules behind the complexity of tumorigenesis, including notably the mutation

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theory, aneuploidy and chromosome instability, Warburg effect, epithelial-to-mesenchymal transition (EMT), etc. However, none of them can integrate the complexity of cancer because they explain cancer initiation and progression in some aspects but meet serious challenges in others (Hanselmann and Welter, 2016; Paduch, 2015; Rubin, 1985; Soto and Sonnenschein, 2011). Cancer research is not the business only for biological and medical researchers. Astrophysicists also have their opinions about cancer. They consider cancer progression as an atavistic reversion (Lineweaver et al., 2021). Besides biological and medical studies, quantum physics, the study on the discrete units of matter and energy throughout the universe, is also suggested as the governing rule of cancer (Bordonaro, 2019; Hameroff, 2004; Laster et al., 2019). Despite the universality of physics, it is critical to find a link to integrate different data and phenomena from cancer research. It is also critical to distinguish causality and associations, and figure out the causal and supporting factors from the observations of cancer research. In the review, I will discuss my findings about the central role of neural stemness in cell tumorigenicity and pluripotent differentiation potential. This gives rise to an inclusive conceptual paradigm that integrates different features of tumorigenesis. I propose that tumorigenesis represents a distorted replay of neural induction and subsequent tissue differentiation during embryogenesis, a critical process required for neural development and normal body axis formation.

2. Embryonic neural induction

How the nervous system is formed and body axis is established had been a primary focus of embryological study. Almost a century ago, a paramount work done by Spemann and Mangold showed that a small group of cells, the dorsal blastopore lip of a newt gastrula embryo, were capable of inducing formation of secondary body axis or a conjoined twin when they were transplanted to the ventral side of a host gastrula embryo. The secondary body axis, which contained neural tube, somites, pronephros and gut, were derived from the host, whereas the transplanted dorsal blastopore differentiated mostly into notochord (Spemann and Mangold, 1924; Spemann and Mangold, 2001). The dorsal lip was then named as the "Spemann-Mangold organizer". The organizer is not only able to induce a body axis containing neural tissues in a gastrula embryo, normal embryogenesis is also dependent on organizer activity. This has been confirmed by different ways. When two dorsal blastomeres of an embryo at 4-cell stage were removed, the resulting embryo could not form an organizer and gastrulated weakly, and formed eventually a "belly piece" that contained no neural and dorsal structures (Spemann, 1938). Embryos without organizers can also be obtained by irradiating fertilized eggs with ultraviolet light, depleting beta-catenin mRNA in oocytes, excision of the Nieuwkoop center during blastula stage or directly removing the organizer during gastrula stage, etc. (Gerhart, 2001). The resulting embryos formed no neural plate and axial mesoderm, resembling those observed by Spemann (1938), which could be rescued by transplantation of organizers. Sagittal bisection of a blastula embryo generates two nearly normal embryos because both sides of the bisected embryos contain a half of the dorsal lip. If an embryo is bisected through the equatorial plane, the resulting dorsal half embryo develops into also an almost normal embryo because it contains the dorsal lip, whereas the ventral half without the dorsal lip forms a belly piece (De Robertis, 2009; Sosa et al., 2019).

The subsequent pursuit of the mechanisms underlying the induction of neural tissue and body axis by the organizer was rather a dramatic process. The failure of endeavors trying to explain organizer activity with physic-chemical rules and the failure in searching for neural inducers in that era turned the optimistic anticipation at the beginning into a pessimistic end (De Robertis, 2009). Revival of the research began until the end of 1980s because of a critical observation. Amphibian blastula ectodermal explants differentiated into only epidermal tissues when they were cultured in neutral saline in vitro. Surprisingly, when the explants were disaggregated into single cells for a few hours first and then re-aggregated again, ectodermal cells differentiated into neural cells exclusively (Grunz and Tacke, 1989), suggesting that removal of an extracellular signal is required for the

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ectoderm to adopt a neural fate, and neural fate might be a the "default fate" of ectodermal cells. Afterwards, genes with localized expression in the organizer that showed the activity of neural induction and secondary axis formation were identified, including *noggin*, *chordin*, *cerberus*, etc. (Bouwmeester et al., 1996; De Robertis, 2006; De Robertis and Kuroda, 2004; Harland, 2000; Sasai et al., 1994; Smith and Harland, 1992). They encode for secreted proteins that inactivate the signaling pathways promoting epidermalizaton of ectoderm and ventralization of body axis, particularly the BMP signaling, via direct binding to the ligands (Anderson and Stern, 2016; De Robertis, 2006; De Robertis and Kuroda, 2004; Harland, 2000). Moreover, inhibition of the receptor for activin, a BMP-related ligand of the TGFbeta family, led to neuralization of ectoderm in absence of inducing factors and rescue of ventralized embryos (Hemmati-Brivanlou and Melton, 1994). In contrast to the initial aim for finding neural inducers, these lines of evidence demonstrate that the fate of ectoderm is neural by default and epidermal fate is induced, and the organizer promotes neural fate by inhibiting the signals that promote epidermal fate in ectoderm. This is the "neural default model" of ectoderm (Muñoz-Sanjuán and Brivanlou, 2002; Weinstein and Hemmati-Brivanlou, 1997).

Neural induction is a prerequisite for body axis formation, which includes differentiation of not only the nervous system, but also differentiation of mesodermal and endodermal tissues such as somite and gut. Neural induction means activation or upregulation of a spectrum of neural genes, forming a regulatory network defining neural plate or embryonic neural cells. Ectopic activity of organizer led to formation of conjoined embryos. Likewise, ectopic stimulation of genes with specific or enriched expression in embryonic neural cells, for example, the proto-oncogenes *eed*, *yy1*, *ski*, *egfr*, *erbb2*, *erbb4* in *Xenopus*, *gelsolin* and *msxB* in zebrafish, causes also formation of a partial secondary body axis or a conjoined embryo, which contains both neural and non-neural tissues (Amaravadi et al., 1997; Kanungo et al., 2003; Nie et al., 2006; Phillips et al., 2006; Satijn et al., 2001). These genes are components of the regulatory network for embryonic neural cells. Their ectopic expression will activate the neural regulatory network, leading to gain of neural fate in non-neural cells and formation of a second body axis. By contrast, disruption of these genes caused defects in neural and axial differentiation in mouse embryos, ultimately leading to embryonic development arrest at early stages (Faust et al., 1995; Donohoe et al., 1999; Berk et al., 1997; Threadgill et al., 1995; Britsch et al., 1998; Gassmann et al., 1995). Moreover, neural plate, the undifferentiated precursor tissue of the central nervous system, specifies somite size and is required for somite development during early embryogenesis (Mariani et al., 2001). These results suggest the critical importance of embryonic neural genes and neural precursor cells in tissue differentiation. Neural stemness is the general stemness, and represents the ground state of cell tumorigenicity and pluripotent differentiation potential due to the advantage of neural state pre-determined by evolution (Xu et al., 2021; Cao, 2022). Pluripotent differentiation potential of neural stem/progenitor cells and tumorigenicity were experimentally demonstrated by chimeric embryo and xenograft teratoma formation assays (Cao, 2022; Clarke et al., 2000; Tropepe et al., 2001; Xu et al., 2021). Contribution of neural stemness to neural differentiation and formation of the nervous system is self-evident during normal embryogenesis. However, its contribution to non-neural differentiation is not obvious. Neural crest cells are pluripotent and share regulatory network with cleavage stage embryos, differentiating into peripheral nervous system and many types of non-neural tissues/cells, such as melanocytes, skeletal and connective tissues, and medulla cells of the adrenal gland, etc. Locating between neural plate (the precursor tissue of central nervous system) and epidermal ectoderm, neural crest is induced by interactions between neural plate and adjacent tissues (Buitrago-Delgado et al., 2015; Gilbert and Barresi, 2016; Knecht and Bronner-Fraser, 2002; Pla and Monsoro-Burq, 2018; Selleck and Bronner-Fraser, 1995). This means that pluripotency of neural crest cells is derived from neural plate cells. Neuromesodermal progenitors in the most posterior region of elongating embryos give rise to both spinal cord and paraxial mesoderm. These cells are presumably originated from anterior neural plate (Henrique et al., 2015; Sambasivan and Steventon, 2021). Therefore, neural induction generates neural precursor

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cells, which give rise to the differentiation of not only neural tissues, but non-neural tissues as well.

The studies above on neural induction and body axis formation were primarily performed with amphibian species, newts and African clawed frog (*Xenopus laevis*), because these animals have large sized eggs, forming embryos that develop in vitro and facilitate observation and micromanipulation. The functional homologue has been identified in all classes of vertebrates, such as in fish, bird and mammalian embryos, known as the node, which exhibits the activity for neural induction and body axis formation similar to Spemann organizer by using conserved molecular mechanisms (Gerhart, 2001; Martinez Arias and Steventon, 2018; Thisse and Thisse, 2015). The neural default state of amphibian blastula ectoderm is also adopted by mammalian embryonic stem cells (ESCs). Amphibian blastula ectodermal cells are the equivalents of ESCs. They have the potential of differentiation into cell types of all three germ layers. ESCs are usually cultured in medium containing high-concentration of fetal bovine serum (FBS). They adopt a neural fate and turn into primitive neural stem cells (NSCs) when cultured in defined serum-free medium (Smukler et al., 2006; Tropepe et al., 2001; Ying et al., 2003a). In this cell fate transition, BMP signaling plays a critical role in maintaining pluripotency and inhibiting neural fate in ESCs (Ying et al., 2003b; Malaguti et al., 2013), a similar mechanism as observed in amphibian ectodermal cells.

In summary, either extracellular signals by the organizer or node or ectopic activation of neural genes in non-neural cells can cause the gain of neural fate in non-neural cells during gastrulation, i.e., neural induction, and leads to the formation of a secondary body axis or a conjoined twin. This field of studies set up the paradigm for understanding how neural tissue and body axis are initiated to form during early embryogenesis, and was ever a main field of research in developmental biology but seemed to be obsolete in recent years. Neural induction is fundamental for neural tissue formation and embryogenesis. Nevertheless, aberrant occurrence of a neural induction or a similar process might be associated with some most sophisticated pathological effects. It was proposed that a conjoined twin is formed when a secondary organizer-like activity is present in a gastrulating embryo, such as a human embryo (Levin, 1999). A neural induction-like process could also occur erroneously in different somatic cells in postnatal and adult animals, which might be the general cause of tumorigenesis.

3. Neural induction and tumorigenesis

As analyzed above, neural induction during embryogenesis means that a non-neural (ectodermal) cell turns into a neural precursor cell in response to either an extracellular signal inhibiting non-neural cell property or intracellular stimulation of embryonic neural genes. Ectopic neural induction during gastrulation causes a conjoined twin. Tumorigenesis represents a process of gradual loss of original cell identity and gain of neural stemness (Cao, 2017), a process reflecting the neural induction effect. One obvious example for the comparability of tumorigenesis as a conjoined twin formation should be the teratocarcinomas/teratomas, which are composed of disorganized but histologically identifiable tissues or organs derived from all three germ layers, such as undifferentiated neural epithelial tissue and differentiated nerves from ectoderm, gut and glandular tissues from endoderm, and cartilaginous and muscle tissues from mesoderm. Teratocarcinomas/teratomas are usually found in the gonads, but they can also form in extragonadal tissues/organs (Agrawal et al., 2010; Gatcombe et al., 2004; Chao et al., 2004; Singhal et al., 2008). The mechanism underlying teratocarcinoma/teratomas formation has been rarely reported. In mouse, an inactivation mutation in the gene *Dnd1*, which encodes a master regulator for vertebrate germ cell development, causes progressive loss of germ cells and incidence of testicular teratoma (Liu and Collodi, 2010; Youngren et al., 2005). The pluripotent property of embryonal carcinoma cells (ECs) derived from teratocarcinoma were well characterized, which enlightened the studies on pluripotency of ESCs later on (Andrews, 2002; Barbaric and Harrison, 2012; Solter, 2006). ECs form teratocarcinomas when

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transplanted into immunodeficient mouse hosts and contribute to formation of chimeric embryos when transferred into blastocysts. EC pluripotent cell lines are characteristic of neural precursor or progenitor cells, they can be differentiated into neurons when treated with retinoic acid (RA) (Pleasure and Lee, 1993; Bain and Gottlieb, 1998; Negraes et al., 2012), a reagent inducing neuronal differentiation from NSCs. Neural precursor/progenitor cells, which are tumorigenic and are capable of teratoma formation in immunodeficient mice (Xu et al., 2021), were isolated from teratocarcinoma/teratoma (Hasgekar et al., 1996; Kim et al., 2019). Therefore, ECs are characteristic of neural stemness, tumorigenicity and pluripotent differentiation potential, which are coupled cell properties (Cao, 2022; Zhang et al., 2022). Like neural induction during embryonic development, teratocarcinomas/teratomas are the consequence of the progressive loss of original cell identity and gain of neural stemness, i.e., gain of tumorigenicity and pluripotency, in both germ and somatic cells.

A much broader range of tumorigenesis is the formation of cancers that have been found in most adult tissues/organs. Growing evidence has shown that cancer cells, or generally tumorigenic cells, are characteristic of NSCs. Like NSCs and ECs, cells from different cancer types are capable of neuronal differentiation in response to inhibition of endogenous cancer promoting factors, which have a specific or enriched expression in embryonic neural cells during vertebrate embryogenesis, and play essential roles in maintaining neural stemness in both cancer cells and NSCs (Chen et al., 2021; Lei et al., 2019; Lu et al., 2017; Zhang et al., 2017; Zhang et al., 2022). In general, most genes (if not all) that promote cancers or are upregulated in cancer cells are neural stemness genes or genes with enriched expression in embryonic neural cells during vertebrate embryogenesis. Cancer cells share both regulatory networks and cell property with NSCs or embryonic neural cells (Zhang et al., 2017; Cao, 2022). By contrast, non-neural tissue-specific genes and genes promoting differentiation are downregulated/silenced in cancer cells, and a major part of tumor suppressor genes are non-neural genes (Zhang et al., 2017; Cao, 2017; Cao, 2022). This mode of expression change of cancer related genes means the progressive loss of original cell identity and gain of neural stemness, and consequently, the gain of tumorigenicity and pluripotency in cancer cells during tumorigenesis. For example, when the key muscle differentiation gene *Myod1* was knocked out in myoblast cells, the cells lost their myoblast identity and gain of neural stemness, tumorigenicity and pluripotent differentiation potential (Xu et al., 2021). Intestinal stem cells in *Drosophila* turned into a NSC-like state in response to the loss of a transcription repressor, and consequently, caused the formation of neuroendocrine tumor (Li et al., 2020). Neurons can also be dedifferentiated into an NSC-like state when a factor repressing NSC and cell cycle genes and maintaining neurons in a differentiated state was removed, leading to acquirement of tumorigenicity and tumor formation (Southall et al., 2014).

Appearing unlike teratocarcinomas/teratomas, common cancer tumors usually do not contain well-differentiated, histologically identifiable tissues/organs. Nevertheless, these tumors are composed of cell types with distinct functional features and/or expression of tissue- or cell type-specific markers, an indication of intratumor phenotypic heterogeneity. Two mainstream models are proposed to explain how phenotypic heterogeneity is generated. The clonal evolution model emphasizes that phenotypic heterogeneity is a result of genetic heterogeneity arising from Darwinian-like evolution. Nevertheless, how genetic heterogeneity causes phenotypic heterogeneity seems to be not understood at all and not testified experimentally. The cancer stem cell (CSC) model proposes that the differentiation ability of CSCs generates phenotypic heterogeneity (Beck and Blanpain, 2013; Burrell et al., 2013; Clevers, 2011; Marusyk et al., 2012; Meacham and Morrison, 2013; McGranahan and Swanton, 2015; Quintanal-Villalonga et al., 2020), which has been validated in many studies. In vitro generated cells with CSC property can differentiate into cell types expressing neuronal, endothelial and muscle cell markers (Scaffidi and Misteli, 2011). CSCs of glioblastoma give rise to tumor endothelium and vascular pericytes, supporting tumor growth (Cheng et al., 2013; Ricci-Vitiani et al., 2010; Wang R et al., 2010). Colon CSCs revealed the capacity of multilineage differentiation (Vermeulen et al., 2008).

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Nevertheless, a consensus idea could not be induced from these studies about the nature of CSCs except that they can differentiate. It was not known whether CSCs differentiate along the differentiation lineage of a tissue stem/progenitor cell or the lineages of other types of stem/progenitor cells. In other words, it was not clear whether CSCs of different cancer types have the property of stem/progenitor cells of their respective tissues of cancer origin, or all CSCs might have a common property of stemness, or CSCs might be of "cancer-specific" nature that is not comparable to any known stem cell types. In fact, similar to ECs, common cancer cells are also pluripotent because xenograft tumors formed by cancer cells show expression of markers of tissue/cell types derived from all three germ layers, for example, SOX1-expressing cells representing cells with neural stemness and derived from ectoderm, ACTA2-expressing cells derived from mesoderm, and AFP-expressing cells derived from endoderm (Xu et al., 2021; Cao, 2022; Zhang et al., 2022). These cells can be widely detected in different cancer types. Public databases show that a majority of transcripts and their protein products have low cancer specificity and are present in many cancer types. For example, BMI1, CDH2, DCLK1, FGFR4, MSI2 and SMARCA4 representing neural stemness; MAP2, NEUROG2 and TUBB3 representing neuronal differentiation; AFP, FOXA3, GATA6 and KRT8 representing endodermal tissue differentiation; and ACTA1, ACTA2, COL1A1, FXR1 and MEF2D representing mesodermal tissue differentiation (Figure 1). Noticeable is that ACTA2 and COL1A1 are also the markers of cancer associated fibroblasts (CAFs). Therefore, different cancer tumors contain basic elements representing cell/tissue differentiation during embryonic development. Cancer cells at different stage of tumorigenesis exhibit different degree of tumorigenicity. They are more similar to the cells of cancer origin and exhibit weak tumorigenicity at the beginning stage of tumorigenesis. Cancer cells at later stage of cancer progression are more dissimilar to the cells of cancer origin and show stronger tumorigenicity. Neural stemness and differentiation potential in cancer cells grow progressively with the progression of cancer, a rule that is confirmed by a serial xenotransplantation assay of cancer cells (Zhang et al., 2022). Although cancer cells share the regulatory networks and cell property with neural stem or embryonic neural cells, some essential disparities still exist, including extensive defects in genes (differentiation genes in particular) and genome in cancer cells and the difference in the microenvironments with which cancer cells or embryonic neural cells communicate, leading to chaotic differentiation of cancer cells. In some cases, however, tissue/organ formation in a tumor can be still observed, such as osteoid and bone formation in various cancers (Dekkers et al., 2019; Goto et al., 2010; Hoorweg et al., 1997; Kattepur et al., 2021; Tian et al., 2021). Common cancer tumors are degenerated forms of teratomas/teratocarcinomas, and tumorigenesis reflects a process resembling an ectopic neural induction and consequently embryonic tissue differentiation in postnatal animals. Therefore, a tumor can be considered as a degenerated embryoid body, and it is plausible that nearly every gene is associated with cancer (de Magalhães, 2022).

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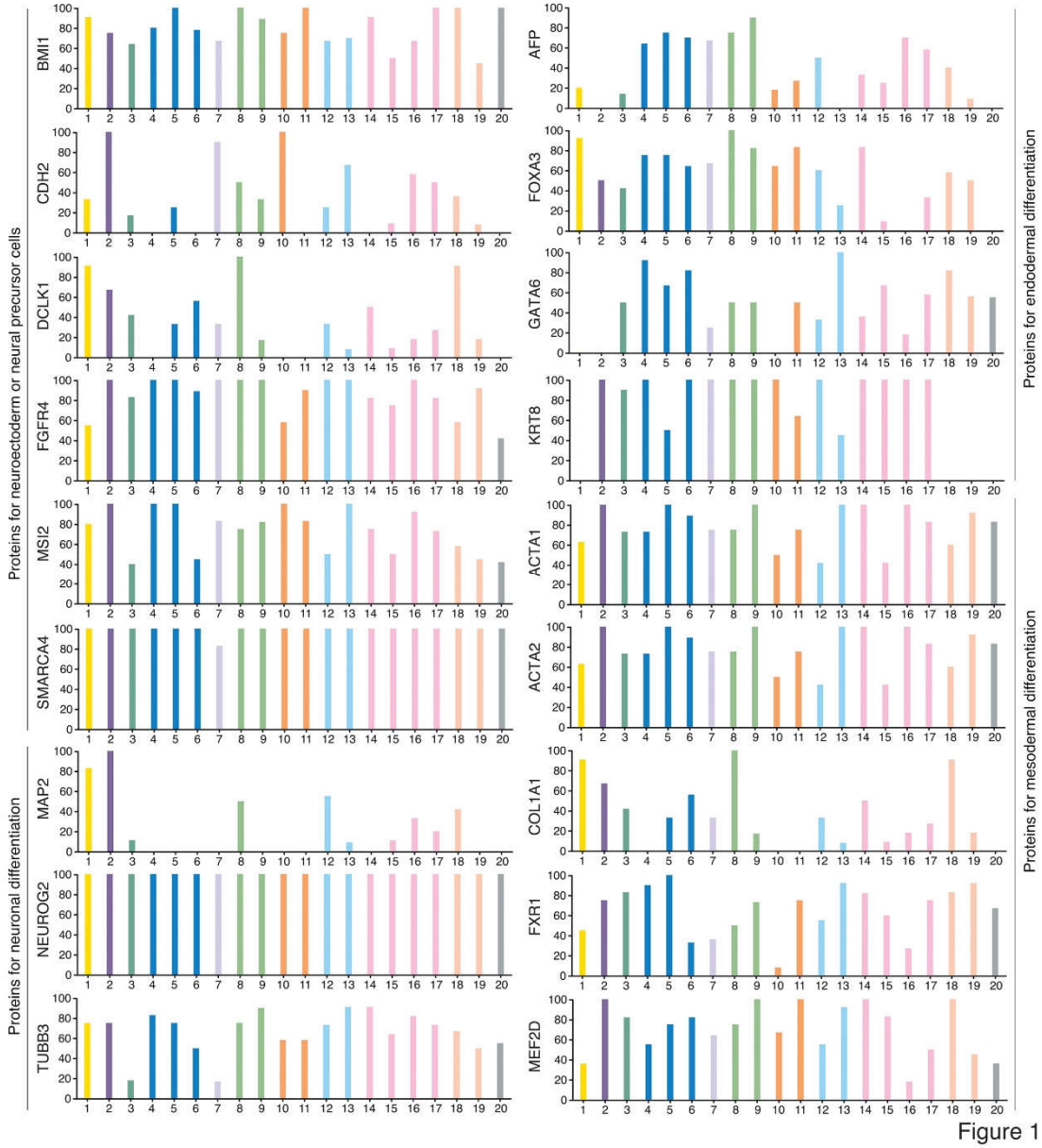

Figure 1. Proteins representing the differentiation of three germ layers during normal vertebrate embryogenesis are widely detected in various types of cancers. 1, Glioma; 2, Thyroid cancer; 3, Lung cancer; 4, Colorectal cancer; 5, Head and neck cancer; 6, Stomach cancer; 7, Liver cancer; 8, Carcinoid; 9, Pancreatic cancer; 10, Renal cancer; 11, Urothelial cancer; 12, Prostate cancer; 13, Testis cancer; 14, Breast cancer; 15, Cervical cancer; 16, Endometrial cancer; 17, Ovarian cancer; 18, Melanoma; 19, Skin cancer; 20, Lymphoma. Data are from the Human Protein Atlas (www.proteinatlas.org) (Uhlen et al., 2017).

4. Epithelial-mesenchymal transition (EMT): transition from a relatively known state to an unknown state

EMT is described as a phenotypic change, in which a polarized epithelial cell loses its polarity and adhesion with neighboring cells, and assumes a mesenchymal phenotype with a motile property. At molecular level, the loss of epithelial phenotype is reflected by downregulation of the epithelial marker E-Cadherin (CDH1), and gain of mesenchymal phenotype is driven by a core set of EMT transcription factors, SNAI1, SNAI2, TWIST1, ZEB1, and ZEB2. EMT is believed to be the key driver of carcinogenesis and has been extensively investigated (Yang et al., 2020). Nevertheless, the concept has been controversial in cancer because of its essential flaws. I discussed the controversy in details previously (Cao, 2017). The main point is that both epithelial and mesenchymal states are

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highly heterogeneous among different tissues/organs and cannot be defined by a few "epithelial and mesenchymal" markers, and the alteration of EMT marker expression cannot be representative of the complex change during malignant transformation of epithelial cells (Cao, 2017). Moreover, some cancers are not originated from epithelial cells, but from mesenchymal cells, such as sarcomas. After two years of discussion, the EMT International Association (TEMTIA) in 2020 made a consensus statement about the guidelines and definitions of EMT (Yang et al., 2020). The statement pointed out that the definition of classical EMT cannot reflect the complicated intermediate states between the binary switch from fully epithelial to fully mesenchymal state. Therefore, TEMTIA recommends that the definition of EMT should be more flexible and use "EMT plasticity" (EMP) to describe these intermediate states (Yang et al., 2020). The revised term can now smoothly fit all possible situations encountered during EMT research. However, the mechanisms underlying the boundless plasticity or how the plasticity is derived have not been understood at all. Furthermore, "while the characteristics of fully epithelial cells are relatively clearly defined, our current knowledge does not allow us to define the mesenchymal state with specific cellular characteristic or molecular markers that are universal end-products of all EMT programmes" (Yang et al., 2020). This means that EMT represents the transition from a relatively known to an unknown state. Numerous elegant molecular mechanisms have been described for the regulation of EMT and EMT regulation of cancer progression in numerous publications (Yang et al., 2020), many of which appear in top journals that require higher stringency for publishing. However, what the "mesenchymal state" is has remained a mystery. In EMT or EMP, either the limitless plasticity (or "dynamics" in other literatures (Brabletz et al., 2021)) or the undefined mesenchymal state is used to define the characteristics of cancer cells. How this situation could fit for the regularly advocated logics of scientific research, e.g., rigor, precision, and physiological relevance, is rather intriguing and worthy of pondering.

4.1. The alteration of EMT marker expression cannot be representative of the complex change during malignant transformation of epithelial cells

Although epithelial cells of different tissues/organs express a same epithelial marker E-Cadherin, they are derived from different lineages during development and execute distinct physiological functions in tissues/organs, and therefore, have different intrinsic regulatory networks. For example, epithelial cells of liver, which is differentiated from endoderm, must be different in function and regulatory network from those of kidney or skin, which are derived from mesoderm and ectoderm, respectively, during embryonic development. That is to say, besides the common epithelial property, epithelial cells of different tissues/organs are defined by tissue-specific genes/factors. Downregulation of the epithelial marker is not the only event occurring during neoplastic transformation of epithelial cells. But rather, it is an associated or concurrent event among much more sophisticated changes: the gradual downregulation/silencing of tissue-specific and differentiation genes. This causes a dedifferentiation effect and loss of the property (including their epithelial state) and normal function of the original cells. On the other hand, many genes, including those encoding the "core EMT transcription factors", are upregulated/activated in cancer cells and play promoting roles during cancer initiation and progression. Unfortunately, this broad range of changes have not been considered by "EMT". Cancer promoting genes can express and play diverse functions in normal embryonic and adult cells. However, their primary expression and function-a link between different cancer promoting genes-had been neglected. In fact, these genes belong to a same cellular context because most (if not all) of them are either neural stemness genes or genes with enriched expression in embryonic neural cells during vertebrate embryogenesis (Zhang et al., 2017). Therefore, cancer cells share regulatory networks with NSCs or embryonic neural cells, but not other types of cells, and neural stemness is the determinant for cell tumorigenicity and pluripotent differentiation potential, a situation dictated by the evolutionary advantage of neural state. Tumorigenesis is driven by a neural induction-like event, which

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causes the loss of original cell identity and gain of neural stemness in somatic cells (Cao, 2017; Cao, 2022; Xu et al., 2021; Zhang et al., 2017; Zhang et al., 2022), including various epithelial cells.

4.2. The "mesenchymal state" shares little similarity with cancer cells in both cell features and regulatory networks

The "mesenchymal state" in "EMT" or "EMP" shares little similarity with cancer cells. Cancer cells are characteristic of rapid cell cycle and proliferation, stemness, dysregulated epigenetics and metabolism, cell motility, evasion of programmed cell death and immunosurveillance, resistance to therapies, plasticity, etc. (Bakir et al., 2020; Hanahan and Weinberg, 2011). There has been no evidence so far to demonstrate that any types of non-neural mesenchymal cells share these features and regulatory networks with cancer cells. Instead, these cell features are manifested by and the corresponding regulatory networks are enriched in NSCs or embryonic neural cells (Cao, 2017; Cao, 2022; Chen et al., 2021; Xu et al., 2021; Zhang et al., 2017; Zhang et al., 2022). The machineries for basic cell physiological functions, including cell cycle, ribosome biogenesis and protein translation, proteasome, spliceosome, epigenetic modifications, transcription, DNA replication, DNA damage and repair, and genes/factors promoting stemness, etc., are all enriched in embryonic neural cells (Cao, 2022; Xu et al., 2021). They work concertedly together, but not work alone, to define the property of high proliferation with pluripotent differentiation potential that serves as a basic cell property, i.e., neural stemness (Cao, 2022; Chen et al., 2021; Zhang et al., 2022). It is rather logical that all these basic machineries play active roles during tumorigenesis. Cancer cells always gain resistance to therapies, including immunotherapy, ultimately leading to a therapeutic failure. One of the most frequent mechanisms is the activation or upregulation of genes conferring resistance (Nussinov et al., 2017; Ramos et al., 2021). Actually, resistance is an intrinsic property of neural stemness. For example, EZH2 is involved in both chemoresistance and immunotherapy resistance (Hu et al., 2010; Kim et al., 2020; Reid et al., 2021). EZH2 is enriched in neural cells during vertebrate embryogenesis, maintains neural stemness, and is capable of dedifferentiating astrocytes into NSCs and confers stemness in cancer cells (Akizu et al., 2016; Gorodetska et al., 2019; Kim et al., 2013; Lei et al., 2019; Sher et al., 2011; Zhang et al., 2017). Cancer cells are characteristic of plasticity, which is usually explained as the consequence of EMP (Bakir et al., 2020; da Silva-Diz et al., 2018; Yuan et al., 2019). However, it should be kept in mind that genes in the regulatory networks of both cancer and embryonic neural cells are enriched in longer genes containing more exon/introns compared with those of non-neural cells (Cao, 2022; Sahakyan and Balasubramanian, 2016; Xu et al., 2021). Obviously, longer genes can serve as more flexible scaffold for regulatory signals for cell differentiation and functions, generate more splicing variants that contribute to phenotypic novelty and tissue identity (Baralle and Giudice, 2017; Bush et al., 2017). In agreement, the components of spliceosomes, the machinery responsible for alternative splicing, are expressed predominantly in embryonic neural cells and enriched in cancer cells, and promote cancers (Cao, 2022; Lee and Abdel-Wahab, 2016; Wang and Aifantis, 2020; Yamauchi et al., 2022). It was demonstrated recently that cell tumorigenicity and pluripotency are coupled properties unified by neural stemness. Synchronic enhancement of neural stemness, tumorigenicity and pluripotency is accompanied by increased level of proteins involved in translation, ribosome biogenesis and spliceosome assembly, etc., and accordingly, increased events of alternative splicing in cancer cells (Zhang et al., 2022). It can be concluded that cancer cells are characteristic of neural stemness, but not mesenchymal state, in both cell features and regulatory networks.

4.3. The association between "EMT" or "EMP" and cancer cell features is within the context of neural induction-like program

Many studies have shown the association between "EMT" or "EMP" programs and cancer cell features, such as stemness, resistance to therapies, plasticity, etc. (Singh and

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Settleman, 2010; Brabletz et al., 2021). E-cadherin is usually used as a typical marker of epithelial cells in adult tissues/organs. It is primarily expressed in non-neural ectoderm during embryogenesis. The typical "mesenchymal markers and transcription factors", SNAI1, SNAI2, TWIST1, ZEB1, ZEB2, Ncadherin (CDH2), Vimentin, are localized or at least enriched in embryonic neural cells, neuroepithelium, neural plate and neural crest (Wang C et al., 2015; Zhang et al., 2017) (Figure 2). "EMT" marker expression change during cancer progression reflects downregulation of non-neural or tissue-specific genes and upregulation of embryonic neural genes or neural stemness genes, a neural induction-like effect. Like most cancer promoting factors, the "core EMT transcription factors" are components of embryonic neural regulatory networks. Therefore, they are components of regulatory networks of cancers and cancer cell features, such as stemness, resistance to therapies, plasticity, etc. The mechanisms underlying the contribution of "EMT" to cancer cell stemness remain elusive (Lambert and Weinberg, 2021). Occasional studies demonstrated that stemness factors SOX2, BMI1 and OCT4 can be triggered by "EMT" factors ZEB1, SNAI1 and SNAI2 (Kurrey et al., 2009; Mitra et al., 2018; Wellner et al., 2010). Genes encoding Sox2, Bmi1 and Oct4 are specifically expressed in or at least enriched in embryonic neural cells during neural induction and early neural development during vertebrate embryogenesis (Cao, 2022). Therefore, "EMT factors" and stemness factors are components of the regulatory networks of a same cellular context, and regulatory relationship between these factors/genes is not a surprise. One major mechanism for "EMT" associated therapy resistance is that "EMT factors" are able to induce transcription of genes encoding ABC transporters, such as ABCC4 and ABCC5 (Saxena et al., 2011). Resistance can also be enhanced by "EMT" via disruption of TP53 function, repression of tumor suppressor PTEN, or upregulation of pro-survival protein BCL-XL/BCL2L1 (Brabletz et al., 2021). The primary location of transcription of genes encoding ABC transporters, TP53, PTEN and BCL2L1 is embryonic neural tissues (Xu et al., 2021; Zhang et al., 2007). The mechanisms underlying the contribution of "EMT" to cancer cell plasticity is also elusive. In the context of "EMT", cancer cell plasticity is defined by the expression levels of "EMT markers". A high level of epithelial marker expression in cancer cells indicates epithelial phenotype, whereas a high level of mesenchymal marker expression indicates mesenchymal phenotype. The intermediate states like "partial EMT", "intermediate EMT", etc., are represented with hybrid expression of different levels of epithelial and mesenchymal markers, and hence, cancer cells can be grouped into distinct subtypes (Bakir et al., 2020; Brabletz et al., 2021; Esquer et al., 2021). Cancer cells with stronger "mesenchymal" phenotype are more strongly tumorigenic (Esquer et al., 2021). This is a logical dilemma because the undefined mesenchymal state is used to define the phenotypic diversity of cancer cells. So far, it has not been figured out mechanistically how the expression levels of "EMT markers" control cell plasticity. The situation will be changed when considering that the "mesenchymal markers" are actually integral components of the regulatory networks of NSCs or embryonic neural cells (Figure 2), i.e., neural stemness, a defined and plastic cell state. A key mechanism underlying cell plasticity is the enrichment of long genes and spliceosomes and hence alternative splicing in both cancer and embryonic neural cells (Cao, 2022; Sahakyan and Balasubramanian, 2016; Xu et al., 2021; Zhang et al., 2022). "EMT" is a concurrent event during the neural induction-like process underlying tumorigenesis, but it has been misinterpreted as a causal or central factor. As having been proofed, it is difficult to find mechanisms and physiological relevance for a misinterpreted effect. In summary, neural stemness, but not the unfathomable mesenchymal state, shows physiological relevance with and integrates different characteristics of cancer cells and tumorigenesis, because of the evolutionary priority of neural state (Xu et al., 2021; Cao, 2022).

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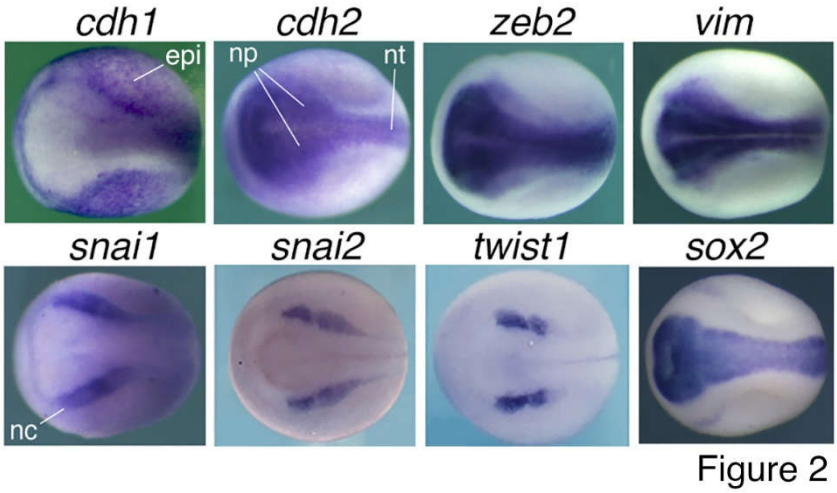

Figure 2. Expression patterns of "EMT" marker genes in neurula embryos of *Xenopus laevis*. Neural induction during gastrulation leads to formation of embryonic neural tissues in the subsequent developmental stage, during which the nervous system and various tissues/organs begin to form. Whole mount in situ hybridization revealed specific expression of *cdh1* in epidermis excluding the embryonic neural tissues, whereas *cdh2*, *zeb2* and *vim* are localized to neural plate, the precursor tissue of the central nervous system, and *snai1*, *snai2* and *twist1* are localized to neural crest, which give rise to the peripheral nervous system and many non-neural tissues. *sox2*, a marker gene for pluripotent stem cells and NSCs, is localized to neural plate and used as a control. The specific expression in neural plate and neural crest cells readily establishes the correlation between the "core mesenchymal factors" and neural stemness, the ground state of pluripotency and tumorigenicity, and implies a far-fetched relationship between the "core mesenchymal factors" and "mesenchymal state". Dorsal view is shown for each embryo with the anterior to the left. epi, epidermis; np, neural plate; nt, neural tube; nc, neural crest. Expression pattern data are from Zhang et al. (2017) and Wang C et al. (2015).

5. Understanding causality in cancer

Cancer research was dominated by a cancer cell-intrinsic view before 1980s since mutations in oncogenes and tumor suppressor genes were seemingly sufficient to determine cancer initiation and progression. However, this view could not explain smoothly the mechanisms governing cancer metastasis. Studies on tumor microenvironment (TME) and interactions between different cell types in the TME and between tumor and normal tissues might provide reasonable explanations, leading to a shift from the cancer cell-centric view to a tumor environment-centric view (Garner and and de Visser, 2020; Maman and Witz, 2018; Vogelstein and Kinzler, 1993). Tumor-host interaction and crosstalks in TME is important for tumor growth and cancer progression. However, understanding the causal and supporting factors involved in the interactions and crosstalks is crucial not only for cancer biology, but also for the development of more efficient strategies of cancer therapy.

A tumor consists of heterogeneous populations of cells. A widely held view is that normal tissue cells infiltrate tumors or cancer cells acquire magic power to hijack normal cells, for example, nerves, immune cells, fibroblasts, blood vessels, etc., and recruit them into TME to promote cancer progression (Brandao et al., 2019; Cervantes-Villagrana et al., 2020; Lugano et al., 2020; Maman and Witz, 2018; Saxena and Bhardwaj, 2018). The crosstalks between cancer cells and recruited normal tissue cells have been a major topic of study in cancer biology. However, how the cells in the TME are originated and the functions of the cells are related with tumorigenesis have remained elusive.

5.1. The nerve-cancer crosstalk

The presence of nerves was observed in about one century ago and numerous subsequent studies have demonstrated that neural infiltration contributes to tumor progression and dissemination. Accordingly, high intratumor nerve intensity is correlated with poor

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prognosis and high recurrence across many cancer types (Boilly et al., 2017; Jobling et al., 2015; Reavis et al., 2020; Cervantes-Villagrana et al., 2020; Silverman et al., 2021). It is believed that neural infiltration is achieved by primarily three ways: axonogenesis induced by neurotrophic factors (NGF, BDNF, GDNF) and axon-guidance molecules (Netrin-1, Ephrin B1) that are released from cancer cells, neural reprogramming or conversion of nerve types via extracellular vesicles derived from cancer cells, and neurogenesis as a result of differentiation of neural progenitor cells recruited by cancer cells (Silverman et al., 2021). Extracellular vesicle-induced neural reprogramming is dependent on Rab27A and Rab27B in cancer cells (Amit et al., 2020), which are required for extracellular vesicle release from cells (Colombo et al., 2014; Ostrowski et al., 2010). At least, Rab27A is predominantly expressed in neural tissues during vertebrate embryogenesis (Wuttke et al., 2016), suggesting that it is involved primarily in neural development. Neurogenesis in tumors via recruitment of circulating progenitor cells from brain subventricular zone is rather provocative (Mauffrey et al., 2019). However, it needs to find out how neural progenitor cells break the brain-blood barrier and enter circulation and the physiological significance of circulating neural progenitor cells. Under normal developmental processes and physiological conditions, neural cells are the primary source of neurotrophic factors and axon-guidance molecules. Either neural factors or extracellular vesicles released by cancer cells indicate that cancer cells have intrinsic features of neural cells, which can communicate with and shape normal nerves. Single-cell RNA-sequencing analyses indicate that genes in prometastatic cancer cells predominantly relate to a neural signature (Pascual et al., 2021), suggestive of the feature of neural cells in cancer cells. Studies have shown that cancer cells have the intrinsic potential of differentiation of neuronal cells (Lu et al., 2017; Zhang et al., 2017; Lei et al., 2019; Chen et al., 2021; Zhang et al., 2022), which compose of at least a part of nerves in a tumor (Reavis et al., 2020).

5.2. Cancer associated fibroblasts (CAFs)

There are many other types of crosstalks in TME. CAFs are one of the major cell types of tumor stroma and communicate with tumor cells and immune cells, thereby promoting or suppressing cancer progression (Alguacil-Núñez et al, 2018; Biffi and Tuveson, 2021; Kalluri and Zeisberg, 2006; Kobayashi et al., 2019; Miki et al., 2020; Miyai et al., 2020; Xouri and Christian, 2010). Very much similar to the "mesenchymal state", CAFs are also an undefinable cell state because they are heterogeneous in marker expression, function and inter- and intra-tumoral phenotype (Biffi and Tuveson, 2021; Kobayashi et al., 2019). CAFs are different from normal fibroblasts in both morphological and growth properties (Delinassios et al., 1983; Rønnov-Jessen et al., 1996). Little is known about the origin of CAFs in tumors, but a few possibilities are proposed (Xouri and Christian, 2010; Kobayashi et al., 2019). At the early stage of tumorigenesis, CAFs might be the remnant native fibroblasts from the tissue or organ of cancer origin. With the progression of tumorigenesis, new CAFs might be derived from transdifferentiation from a non-fibroblastic lineage, activation of existing resident fibroblasts, recruitment of circulating cells of a remote source (particularly the bone marrow mesenchymal stem cells), differentiation from cells with a stem or progenitor property, and even "EMT" (Kalluri and Zeisberg, 2006; Kobayashi et al., 2019; Xouri and Christian, 2010). Nevertheless, how different CAF types are related with their cellular origins has not been validated. For example, local fibroblasts, bone marrow mesenchymal stem cells and pericytes were considered as the origins of CAFs (Hosaka et al., 2016; Kalluri and Zeisberg, 2006; Koliaraki et al., 2017). Intriguingly, other studies have shown that $COL1A1^{+}$ and alpha-SMA^{+} CAFs are predominantly derived from local precursor cells rather than mesenchymal stem cells (Arina et al., 2016). Although studies with mouse models and human patients showed that transplanted bone marrow cells are able to migrate to tumor sites and differentiate into some portion of CAFs in a tumor (Quante et al., 2011; Worthley et al., 2009), this does not mean that the circulating bone marrow progenitors are the only or main origin of CAFs. Cancer cells are pluripotent, they can differentiate into different cell types, including alpha-SMA+ cells. Cancer

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cells with stronger tumorigenicity and pluripotency can differentiate more efficiently, and alpha-SMA+ cells are more abundant in xenograft tumors formed by cancer cells with stronger tumorigenicity (Xu et al., 2021; Zhang et al., 2022). Stromal content is correlated with cancer progression and responses to therapy, and a high stromal content and a high level of CAFs in stroma is an indicator of poor patient prognosis (Almangush et al., 2021; Hagenaars et al., 2021; Huijbers et al., 2013; Sandberg et al., 2019; Vangangelt et al., 2020). These correlations might be due to that tumorigenicity and pluripotency are coupled cell properties (Cao, 2022; Zhang et al., 2022).

5.3. Cancer-immune crosstalk

Immune cells, either innate (macrophages, neutrophils, dendritic cells, innate lymphoid cells, myeloid-derived suppressor cells, and natural killer (NK) cells) or adaptive (T and B cells), are important constituents of tumor stroma (Hinshaw and Shevde, 2019; Maman and Witz, 2018). Cancer-immune crosstalk has been a mainstream study in cancer research, which sets up the basis for cancer immunotherapy. However, many inconsistencies exist in the functions of immune cells in the TME. Some reports demonstrated that tumor infiltrating T cells exhibit antitumor cytotoxicity (Brunner et al., 1981; Vose et al., 1977), but others revealed that they have immune suppressive and thus, cancer-promoting activities (Vose and Moore, 1985; Marcucci and Rumio, 2020; Wang JJ et al., 2020). The tumor-infiltrating lymphocytes exhibit a weaker cytotoxicity than lymphocytes from distant locations (Chiou et al., 2005). The M1 subset of macrophages exhibits antitumor activity, whereas the M2 subset plays a tumor-promoting role. The functions of dendritic cells, neutrophils, NK cells, etc., all play both anti- and pro-tumor roles, depending on the subtypes of immune cells or on the types of cancers (Hinshaw and Shevde, 2019). Based on these understandings, researchers have made the best of anti-tumor function of immune cells and developed strategies of immunotherapy, particularly the engineered cytotoxic T cells (CAR-T) and inhibitors of immune checkpoints. Immunotherapy has greatly revolutionized cancer therapy. However, the number of patients who can benefit from these therapies is still very limited. CAR-T therapy has shown high efficiencies in eliminating cancer cells of B-cell malignancies, but achieved little success in solid cancers due to high antigen heterogeneity in solid tumors, physical barriers preventing T cell infiltration, and highly immunosuppressive TME leading T cell exhaustion and dysfunction (De Bousser et al., 2021; Hou et al., 2021; Sterner and Sterner, 2021). Likewise, immune checkpoint inhibition achieves responses in only a minority of patients due to primary or intrinsic resistance of cancer cells (Gide et al., 2018; Kalbasi and Ribas, 2020; Sharma et al., 2017; Vitale et al., 2021), and sometimes cause even an adverse effect of hyperprogression (Champiat et al., 2018; de Miguel and Calvo, 2020; Kamada et al., 2019; Marcucci and Rumio, 2021). Meanwhile, therapy efficacy declines or disappears because cancer cells acquire resistance as therapy continues (Draghi et al., 2019; Gide et al., 2018; O'Donnell et al., 2019; Schoenfeld and Hellmann, 2020; Sharma et al., 2017). The mechanisms for resistance to immunotherapy are also a complicated issue and seem to be not more easily understood than understanding cancer itself. In general, resistance to immunotherapy is caused by insufficient tumor antigenicity due to the lack of tumor neoantigens, defects in transduction of anti-tumor immune response mediated by tumour-intrinsic IFNγ signaling, impaired antigen processing and presentation machinery, regulation by oncogenic signaling, and tumor dedifferentiation and stemness (Draghi et al., 2019; Kalbasi and Ribas, 2020; Schoenfeld and Hellmann, 2020; Sharma et al., 2017). These seemingly distinct mechanisms are actually interconnected together by the core feature of cancer cells, as exemplified in the following examples. MEX3B allows melanoma cells to evade tumour-specific T cells via repression of HLA-A post-transcriptionally (Huang et al., 2018). Inhibition of CDK4/6 boosts antitumor immunity by increasing IL-2 production and tumor infiltration of T cells (Kalbasi and Ribas, 2020). ADAR1 inhibition overcomes resistance to immune checkpoint blockade caused by inactivation of antigen presentation by tumour cells (Ishizuka et al., 2019). EZH2 plays an important role in immune checkpoint blockade

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resistance by regulating antigen presentation and antitumor immunity (Kim et al., 2020; Zhou et al., 2020). beta-Catenin activation impairs dendritic cell recruitment, promotes expression immune checkpoint genes, or represses T cell genes in cancers (Perry et al., 2020; Ruiz de Galarreta et al., 2019; Spranger et al., 2015). SETDB1 promotes immune exclusion and resistance to immune checkpoint blockade in cancer cells by suppressing immunostimulatory genes (Griffin et al., 2021). Many studies established an association between "EMT" and tumor immunity, by showing that "EMT" is linked with upregulation of inhibitory checkpoint ligands, down-regulation of tumor-associated antigens and inhibition of T cell infiltration, etc. (Marcucci and Rumio, 2021). The intrinsic connection between these different mechanisms is that all these factors promoting immune therapy resistance are enriched in embryonic neural cells, and plays critical roles in neural development and tumorigenesis. This suggests that the resistance effect should be concurrent with the gain or enhancement of tumorigenicity in cancer cells, i.e, neural stemness. In agreement, melanoma cells non-responsive to anti-PD-1 therapy showed upregulation of a series of embryonic neural genes (*AXL*, *ROR2*, *WNT5A*, *LOXL2*, *TWIST2* and *TAGLN*) compared with responsive cells (Hugo et al., 2016); and dedifferentiation and stemness of cancer cells is the key factor driving resistance to immunotherapy (Miao et al., 2019; Lei and Lee, 2021; Li and Stanger, 2020). Cancer-initiating cells exhibit immune privilege, protecting cells from immune attack by making use of the mechanisms above and the expression of immune checkpoints (Galassi et al., 2021; Joyce and Fearon, 2015). Accordingly, NSCs and embryonic stem cells, whose default state is NSCs, also exhibit immune privilege, because they form teratomas in immunocompetent mice as the result of low expression of immune-related proteins, including MHC class I and II antigens, HLA-DR and co-stimulatory molecules (Itakura et al., 2017; Magliocca et al., 2006; Ozaki et al., 2017). Immune privilege is manifested by the nervous system (Carson et al., 2006). Therefore, immune privilege is an integral feature of neural cells. In comparison, adult cells and non-neural cells are more susceptible to immune rejection as shown by the failure of teratoma formation in immunocompetent mice (Drukker et al., 2006; Xu et al., 2021), suggesting that immunogenicity is correlated with differentiation state. Immune cells are maturely differentiated, highly professional cells derived from the mesodermal lineage. Immune-related genes are primarily expressed in immune cells and non-neural tissues/organs. Differentiation is concurrent with the upregulation of tissue- or organ-specific genes, including immune-related genes. This is to say that differentiation is a process from a cell state with low immunogenicity to cell states with high immunogenicity. By contrast, tumorigenesis is a process of dedifferentiation, leading to loss of original cell identity and gain of neural stemness in cells, which means a process from a cell state of high immunogenicity to a state of low immunogenicity (Cao, 2017; Cao, 2022; Li and Stanger, 2020). In a serial xenotransplantation assay, the downregulated genes in cancer cells of xenograft tumors formed by later transplantation are mainly associated with immune response and immune system process, suggesting that cancer cells lose their immunogenicity gradually with cancer progression (Zhang et al., 2022).

It is believed that immune checkpoints promote tumorigenesis by regulating immune response of tumor cells to immune attack. However, inhibition of immune checkpoints may not achieve any significant responses in patients. IDO1 functions in suppression of anti-tumor immunity by degrading tryptophan and producing a series of toxic kynurenine metabolites to promote immune evasion of tumors (Munn and Mellor, 2013; Uyttenhove et al., 2003), but the inhibitor of IDO1 failed in a phase 3 clinical trial (Long et al., 2019). The failure is in contrast to the elegant mechanisms underlying IDO1 function in suppression of anti-tumor immunity. Emerging studies have elucidated some novel functions of the immune checkpoint PD-1 (PDCD1), which might be provocative for these failures. PD-1 is primarily expressed in bone marrow and lymphoid tissues, and accordingly, enriched in activated T cells. Therefore, PD-1 expression is an indication of differentiated cell state. The basic rationale for the function of PD-1 in suppression of anti-tumor immunity is that binding of PD-1 to its ligand PD-L1 transduces downstream signaling pathways and inhibits T cell activation, thereby dampening T cell cytotoxicity against

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tumor cells (Boussiotis, 2016). Blockade of PD-1/PD-L1 has been a mainstream strategy for cancer immune therapy. However, PD-1 expression was also detected in some subpopulations of cells of different cancers (Du et al., 2018; Ieranò et al., 2022; Wang X et al., 2020). Overexpressed PD-1/PD-L1 suppressed the viability, growth, proliferation and tumorigenicity of cancer cells, and inhibited tumor growth, whereas blocking PD-1/PD-L1 generated an opposite effect. Therefore, in contrast to its tumor-promoting function in the context of immunity, cancer cell-intrinsic PD-1/PD-L1 works actually as a tumor suppressor (Du et al., 2018; Ieranò et al., 2022; Wang X et al., 2020), a finding that complicates cancer therapy using PD-1/PD-L1 blockade and the outcomes of patients in response to therapy. Mechanistically, inhibition of cancer cell-intrinsic PD-1/PD-L1 enhances AKT and ERK1/2 activity (Wang X et al., 2020). Noticeable is that the genes for AKT (AKT1/2/3) and ERK1/2 (MAPK1/3) are all enriched in embryonic neural cells (Magdaleno et al., 2006; Xu et al., 2021), play critical roles in embryonic neural induction and neurodevelopment (Kuroda et al., 2005; Sittewelle and Monsoro-Burq, 2018), and inevitably, promote tumorigenesis. Previous studies generalized that cancer promoting genes are mostly embryonic neural genes, which confer cells with neural stemness, and tumor suppressor genes are mainly non-neural or pro-differentiation genes, which suppress tumorigenicity by inhibiting neural stemness and confer cells with non-neural cell property (Yang et al., 2021; Zhang et al., 2017; Cao, 2017; Cao, 2022). Loss of pro-differentiation or cell specific factors will cause the loss of cell identity and gain of neural stemness and tumorigenicity (Cao, 2022; Xu et al., 2021). Loss of PD-1 might cause a dedifferentiation effect in cancer cells and enhances their tumorigenicity. These studies indicate that it is not enough to understand the functions of immune checkpoints merely in the context of cancer-immune crosstalk.

Immune cells in tumors have been considered as a result of infiltration of circulating cells. However, data from public databases demonstrate that cancer cells also express surface marker genes of various immune cells. For example, transcription of the genes for the monocyte marker CD14, macrophage marker CD68, neutrophil marker CD44 and CD55, natural killer (NK) cell differentiation marker NKG2A, CD7 and CD133, T cell marker CD57 and CD8A, is detected at various levels in cell lines of cancers with different origins (Figure 3). Cancer cell lines are uniform cell populations excluding the infiltration of circulating cells. RNAseq data also revealed the expression of an NK cell signature in different types of cancers (Cózar et al., 2021). This raises the question whether the use of these surface markers could distinguish the origins of the immune cells. Cancer cells with expression of immune cell surface markers should behave very differently from genuine immune cells, a high possibility that seems to be neglected.

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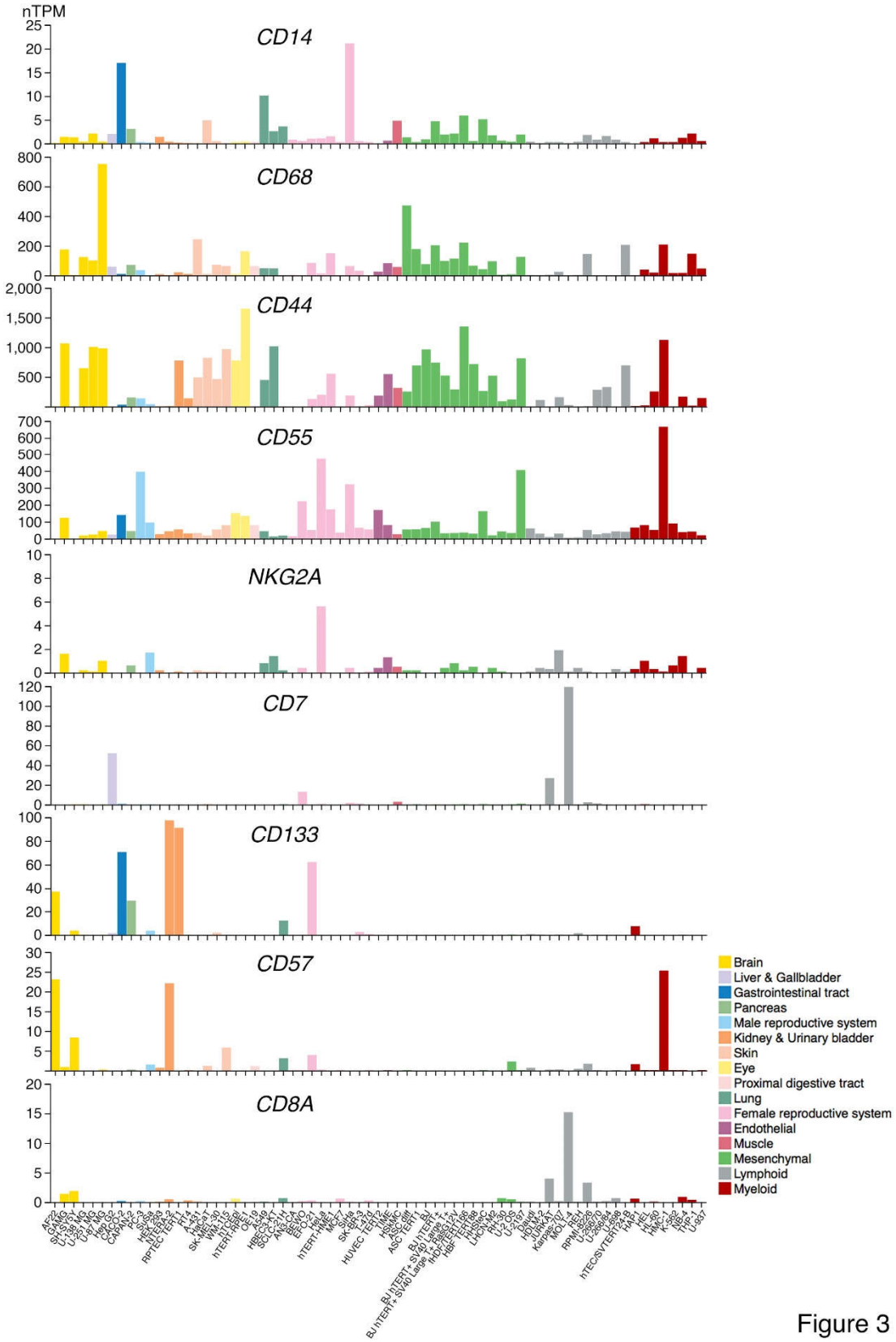

Figure 3

Figure 3. Expression of genes of immune cell surface markers in various cancer cells originating from different tissues/organs. Expression level of a gene is indicated with the normalized transcript per million (nTPM) values of tissue culture cell lines. Data are from the Human Protein Atlas (www.proteinatlas.org) (Uhlen et al., 2017).

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5.4. Cancer cell-centric or tumor environment-centric?

There are some other cell/tissue types in tumors and more complicated crosstalks between multiple cell types have been described, e.g., the tumor-neuro-immune crosstalk (Kuol et al., 2018). As the mainstream viewpoint, cells in the TME are derived from normal tissues because of infiltration of circulating cells, invasion of cancer into normal tissues or hijacking of normal cells. However, in addition to these possible sources, it should be kept in mind that cancer cells are capable of pluripotent differentiation. The intra- and inter-tumoral phenotypic heterogeneity should be primarily resulted from differentiation of cancer cells and the cell types in a tumor might reflect a differentiation hierarchy of cancer cells, under the control of intra- and extracellular signals (Cao, 2022; Xu et al., 2021; Zhang et al., 2022). Teratocarcinoma is a particular type of malignant tumors, which exhibit differentiation of histologically identifiable tissues/organs derived from all three germ layers, such as cartilage, bone tissues, neural epithelia, gut structures, etc. Formation of these tissues/organs in teratocarcinomas can be explained by the pluripotency of carcinoma cells and experimentally testified, but cannot be explained by hijacking of normal cells or cell infiltration. Osteoid and bone formation in primary tumors of various extraskeletal tissues, such as skin, breast, liver and rectum (Dekkers et al., 2019; Goto et al., 2010; Hoorweg et al., 1997; Kattepur et al., 2021; Tian et al., 2021) should be a consequence of cancer cell differentiation rather than recruitment of normal cells. It is possible that cancer cells can also be induced to differentiate into cells resembling immune cells, a topic remaining to be investigated.

Targeted therapy of cancer is primarily achieved by disruption of the neural regulatory network because cancer-promoting genes are mostly (if not all) neural stemness genes and genes with enriched expression in embryonic neural cells (Cao, 2017; Cao, 2022; Xu et al., 2021; Zhang et al., 2017; Zhang et al., 2022). Additionally, strategies of targeting TME components, e.g., vasculature, neuronal cells, CAFs, immune cells, etc., have been emerging (Chung et al., 2010; Hao et al., 2021; Kaduri et al., 2021; Maia et al., 2021; Saw et al., 2022). TME is highly heterogeneous in context, functions and regulatory networks. For example, CD146– CAFs inhibit ER expression in ER+ breast cancer cells, increasing resistance of tumor cells to Tamoxifen. By contrast, CD146+ CAFs maintain the expression of ER in ER+ breast cancer cells and sustain sensitivity to Tamoxifen (Brechbuhl et al., 2017), suggesting that similar subsets of CAFs can have distinct functions within different cancer subtypes. Different immune cells and subpopulations of a same type of immune cells also generate contrasting effects on tumors, as mentioned above. These complexities and inconsistencies make it a complicated issue to evaluate the efficacy of targeting TME (Maia et al., 2021).

Cancer cell intrinsic PD-1/PD-L1 being a tumor suppressor raises the question whether other immune checkpoints or TME molecular targets might also be expressed in cancer cells and serve as tumor suppressors. Targeting CAFs in TME via interference of TGF-beta1/2, Furin, etc., has been extensively investigated (Saw et al., 2022). These proteins are also expressed in cancer cells and play complex roles in tumorigenesis. TGF-beta cytokines play dichotomous roles during tumor progression, they suppress cancer initiation but later promote cancer cell metastasis and immunoevasion (Yeh et al., 2019). Furin has been suggested as a potential target of therapy of some cancer types, but inhibition of Furin in some other cancers led to aggressive phenotypes (He et al., 2022). This means that inhibition of CAF-related proteins suppresses CAFs, and at the same time might also cause a promoting effect on cancer cells. Therefore, it needs to be clarified how TME is derived from and how a gene/protein functions in cancer cells. A central role of neural stemness in tumorigenicity and pluripotent differentiation potential should be considered in both basic research and development of therapeutic strategies of cancer. A preliminary study showed that non-neural pro-differentiation factors inhibit cancer cell tumorigenicity effectively via conferring non-neural property in cancer cells and meanwhile inhibition of neural stemness and neural regulatory network (Yang et al., 2021).

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6. Neural is fundamental

Neural stemness represents the general stemness or the ground state of pluripotency (Cao, 2022). This is manifested by 1) the neural default state of embryonic pluripotent cells and ESCs, 2) pluripotent differentiation potential of primitive NSCs derived from ESCs and NSCs from different developmental stages, and 3) the evolutionary advantage of neural state (Cao, 2022; Clarke et al., 2000; Tropepe et al., 2001; Xu et al., 2021). Different states of pluripotency, e.g. naïve and primed pluripotency, have been described for pluripotent stem cells (Davidson et al., 2015; Nichols and Smith, 2009; Weinberger et al., 2016). Besides the difference in gene expression, naïve pluripotency is characteristic of formation of compact dome shaped colonies in culture, unbiased differentiation, and high chimeric contribution in rodents; whereas primed pluripotency is featured by formation of flattened colonies, variable differentiation bias, and low chimeric contribution (Davidson et al., 2015; Nichols and Smith, 2009). Correspondingly, different NSCs also exhibit such differences. The primitive NSCs derived from mouse ESCs, which represent naïve pluripotency, show unbiased tissue differentiation patterns in teratoma formation and contribute to all embryonic tissues in chimeric mice (Tropepe et al., 2001; Xu et al., 2021), as seen in naïve pluripotent stem cells. However, NSCs derived from E9, E13.5 and adult mice show weaker tissue differentiation in teratoma formation assay and relatively lower chimeric contribution (Clarke et al., 2000; Xu et al., 2021). These results demonstrate that the state of pluripotency corresponds to the state of neural stemness. In fact, NSCs and pluripotent stem cells are exchangeable in different cultures. Mouse ESCs are maintained in medium containing LIF and high concentration of fetal bovine serum, which contains various growth factors. They turn into primitive NSCs when cultured in defined serum-free medium and change back again in ESC medium (Tsang et al., 2013; Ying et al., 2013a). Therefore, turning into neural stem/precursor cells from ESCs in the absence of extracellular factors should not be considered as a differentiation effect, but rather a restoration of their ground state. Traditionally, pluripotent states are considered to be transient only in peri-implantation stages during rodent and human embryogenesis. Nevertheless, neural stemness being the ground state of pluripotency means that pluripotency is present continuously not only in early embryos, but also in an adult animal. In addition to the chimeric contribution of adult NSCs (Clarke et al., 2000), various types of cancer cells, including teratocarcinoma, leukemia, neuroblastoma and melanoma cells, can contribute to chimeric formation or be induced to differentiate into different types of cells when transplanted into an embryo. The differentiated offspring cells are similar to host cells and not tumorigenic anymore (Brinster, 1974; Cooper and Pinkus, 1977; Gerschenson et al., 1986; Gootwine et al., 1985; Illmensee and Mintz, 1976; Kulesa et al., 2006; Papaioannou et al., 1975; Podesta et al., 1984; Webb et al., 1984; Wells and Miotto, 1986). Moreover, transplantation of the nuclei of different cancer cells into enucleated oocytes led to development of normal embryos (DiBerardino et al., 1983; Hochedlinger et al., 2004; King and DiBerardino, 1965; Li et al., 2003; McKinnell et al., 1969), suggesting the pluripotent nature of cancer cells. Therefore, characterization of cancer cells and NSCs suggests that variants of pluripotent state can be numerous and are present throughout the life of an animal from a pre-implantation blastocyst to an adult, depending on neural stemness. All pluripotent cells, including cancer cells, NSCs and embryonic pluripotent cells, can be integrated into the development of an embryo and induced to differentiate into normal cells in an embryonic milieu, but form embryoid structures, i.e., tumors, in the absence of correct inducing cues, such as in the process of tumorigenesis or under the skin of an immunodeficient mouse. These studies, together with a recent study (Yang et al., 2021), also suggest that differentiation of cancer cells induced by embryonic inducing factors could be an efficient therapeutic strategy of cancers. The common features of these cells were summarized previously (Cao, 2022).

The regulatory network of neural stemness or neural ground state is composed of high level of neural specific factors and factors required for the functions of basic cellular physiological machineries, including cell cycle, protein translation and turnover,

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alternative splicing, epigenetic modification, etc. (Cao, 2022; Chen et al., 2021; Xu et al, 2021; Zhang et al., 2022). It is no wonder that disruption of genes with enriched expression in NSCs or embryonic neural cells usually causes an early embryonic lethal effect, as a consequence of disruption of the neural ground state. There are cases that gene disruption leads to embryonic lethality, but ESCs can still be derived from embryos, for example, knockout of *Prmt1*, an oncogene with enriched expression in embryonic neural cells, in mouse embryos (Pawlak et al., 2000). *Prmt1*$^{-/-}$ ESCs are similar in growth and morphology to wild-type ESCs in normal ESC culture medium (Pawlak et al., 2000). However, functional disruption of Prmt1 causes neuronal differentiation in ESC-derived primitive NSCs when cultured in serum-free medium but not in normal medium (Chen et al., 2021), suggesting a reduced neural stemness and thus pluripotency. Disruption of embryonic neural regulatory network will cause the changes in basic cellular physiological machineries (Chen et al., 2021; Zhang et al., 2022) in embryonic cells and thus generate essential influences on basic properties of cells, such as proliferation, survival, etc. The disruption could also cause a failure of neural induction process, leading to defect of subsequent developmental programs. In conclusion, neural stemness and its regulatory network is the unique base on which an embryo or a tumor is built up. It gives rise to the nervous system in an adult animal, which controls essentially every aspect of animal life. Figure 4 summarizes that neural induction is the general principle governing embryogenesis and tumorigenesis.

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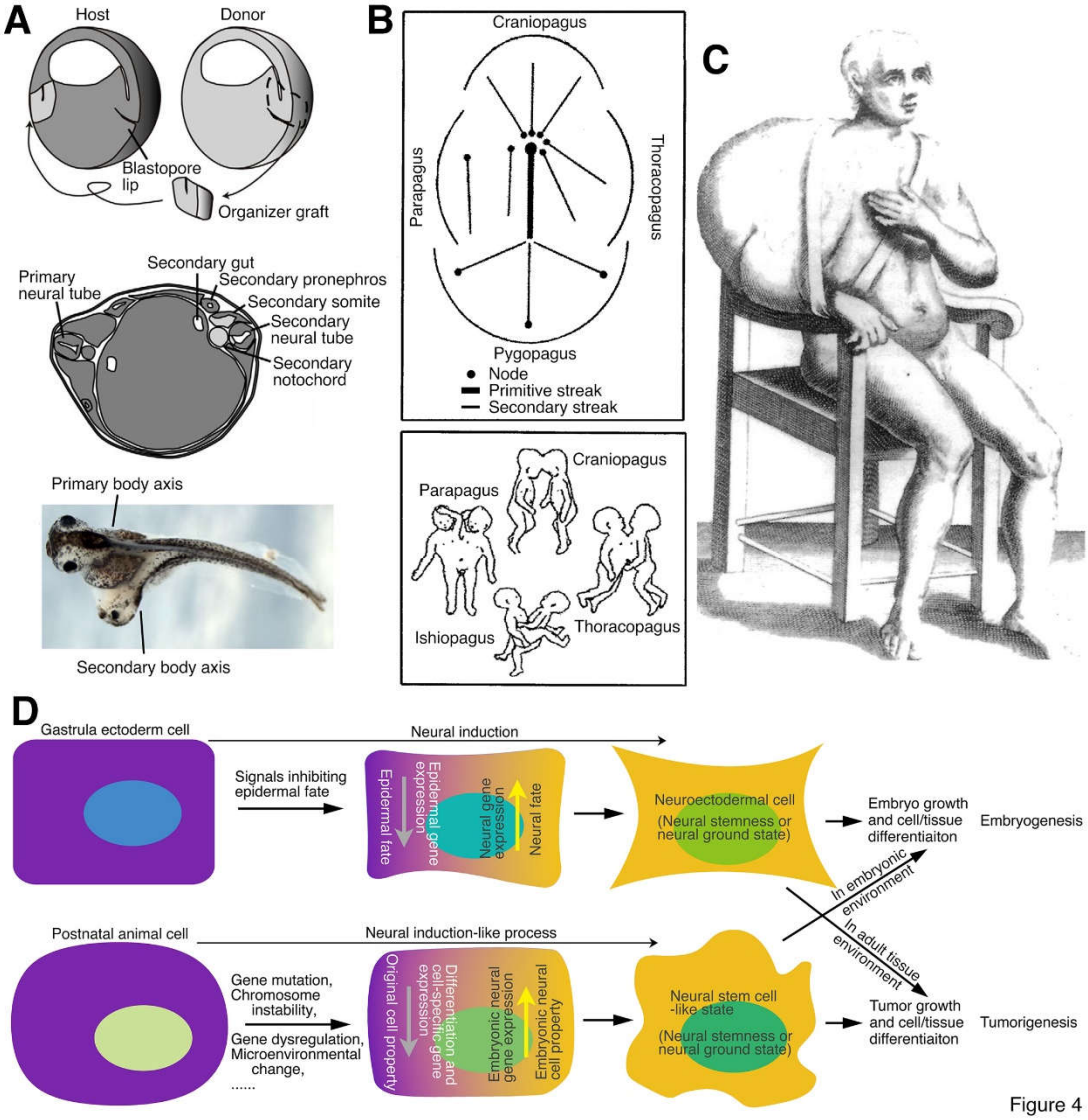

Figure 4

Figure 4. Neural induction, conjoined twin formation and tumorigenesis. (A) (Upper) A schematic illustration depicting the organizer graft transplantation experiment done by Spemann and Mangold, in which the organizer graft (the dorsal blastopore lip) of an early gastrula of a light-gray newt (*Triturus cristatus*) was grafted to the site opposite to the dorsal lip of an early gastrula of a dark-gray newt (*Triturus taeniatus*). (Middle) An illustration showing conjoined twin formation by organizer grafting. A section through the trunk of a conjoined twin embryo demonstrated that the light-gray graft contributed to the notochord, medial somite and floor plate of the secondary body axis, but the secondary neural tube, somites, pronephros, and archenteron cavity were induced from the dark-gray host embryo. (Lower) Conjoined twin formation of frog (*Xenopus laevis*) embryo by organizer grafting performed at early gastrula stage. (B) Conjoined twin formation in human as the result of ectopic formation of primitive streak and the node, the mammalian homologous structures of blastopore and the organizer in gastrulating embryos. The position of ectopic primitive streak and node in a gastrula (Upper) predicates the formation of different types of conjoined twins (Lower). (C) Tumor formation in human. The first clinical illustration of tumor, a large scapulohumeral tumor, most likely a sarcoma, in a book by a surgeon Marco Aurelio Severino published in 1632 (Hajdu, 2011). (D) Neural induction or a similar process underlying both conjoined twin and tumor formation. During embryonic development, the organizer or node secretes proteins inhibiting epidermal fate of gastrula ectoderm, leading to the gain of neural fate in ectoderm and formation of neuroectoderm, a process known as "neural induction". This is required not only for the differentiation of the nervous system but also for many non-neural tissues, such that the body axis of an embryo can form. Neural induction can occur ectopically during gastrulation, caused by either an ectopic organizer or node activity or ectopic expression of embryonic neural genes, causing the formation of secondary embryonic structures or a conjoined twin. This process might occur in any cell

and at any time of animal life. Cells of a postnatal animal may suffer various extracellular (e.g., microenvironmental change) and/or intracellular (e.g., gene mutations) insults. If occasionally the insults cause activation of neural stemness regulatory network and/or downregulation/silencing of tissue-specific or differentiation genes/factors, cells progressively lose their original cell identity and gain of neural stemness or restore the neural ground state, similar to the neural induction process in gastrula ectodermal cells. The resulting cells can self-renew and differentiate into tissue/cell types of all three germ layers, resembling a defected process of embryonic development, that is, tumorigenesis. Tumorigenic cells (cancer cells, NSCs and embryonic pluripotent cells) are induced to differentiation into normal cells and integrate into normal embryonic development when they are placed in an embryonic environment, but they form tumors instead and cannot integrate into animal tissues/organs when they are in an environment in a postnatal animal because of lack of embryonic inducing signals. Tumorigenicity is a property of pluripotent cells manifested in a microenvironment of a postnatal animal. (A) is adapted from Harland (2008), (B) is from Levin (1999), (C) from Hajdu (2011), and (D) is from Zhang et al. (2022).

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