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Spontaneous regression of neuroblastoma

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Abstract

Neuroblastomas are characterized by heterogeneous clinical behavior, from spontaneous regression or differentiation into a benign ganglioneuroma, to relentless progression despite aggressive, multimodality therapy. Indeed, neuroblastoma is unique among human cancers in terms of its propensity to undergo spontaneous regression. The strongest evidence for this comes from the mass screening studies conducted in Japan, North America and Europe and it is most evident in infants with stage 4S disease. This propensity is associated with a pattern of genomic change characterized by whole chromosome gains rather than segmental chromosome changes but the mechanism(s) underlying spontaneous regression are currently a matter of speculation. There is evidence to support several possible mechanisms of spontaneous regression in neuroblastomas: (1) neurotrophin deprivation, (2) loss of telomerase activity, (3) humoral or cellular immunity and (4) alterations in epigenetic regulation and possibly other mechanisms. It is likely that a better understanding of the mechanisms of spontaneous regression will help to identify targeted therapeutic approaches for these tumors. The most easily targeted mechanism is the delayed activation of developmentally programmed cell death regulated by the tropomyosin receptor kinase A (TrkA) pathway. Pan-Trk inhibitors are currently in clinical trials and so Trk inhibition might be used as the first line of therapy in infants with biologically favorable tumors that require treatment. Alternative approaches consist of breaking immune tolerance to tumor antigens but approaches to telomere shortening or epigenetic regulation are not easily druggable. The different mechanisms of spontaneous neuroblastoma regression are reviewed here, along with possible therapeutic approaches.

Keywords

Neuroblastoma; Regression; Spontaneous; TrkA; Telomerase

Introduction

Most infants with neuroblastoma, even with metastatic disease, can be cured with moderate intensity chemotherapy and some patients with a special pattern of metastasis have a high likelihood of undergoing spontaneous regression without chemotherapy (Diede 2014;

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Matthay 1998; Nakagawara 1998; Nickerson et al. 2000; Pritchard and Hickman 1994). Indeed, the prevalence of spontaneous regression has been well documented by mass screening programs undertaken in Japan, North America and Europe. Furthermore, children (and adults) can present with localized, benign ganglioneuromas, which presumably represent neuroblastic tumors that differentiated (Brodeur 2003; Garvin et al. 1984; Haas et al. 1988; Hoehner et al. 1995; Shimada et al. 1999a). The exact mechanisms responsible for spontaneous regression (or differentiation) are uncertain but several plausible mechanisms have been proposed to explain these phenomena (Brodeur and Bagatell 2014; Diede 2014; Matthay 1998; Nakagawara 1998; Nickerson et al. 2000; Pritchard and Hickman 1994). Here, the current understanding of the genomic, biological and immunological mechanisms that underlie spontaneous regression is reviewed and possible approaches to therapy are explored.

Historical perspective on neuroblastoma regression

Spontaneous regression of cancer has been documented in different cancer types for decades. Spontaneous regression is defined as the shrinking or disappearance of primary or metastatic disease without therapeutic intervention. Regression has been observed in renal cell carcinoma, malignant melanoma, choriocarcinoma and lymphoid malignancies (Challis and Stam 1990; Everson 1964; Everson and Cole 1966; Papac 1998). However, neuroblastoma is generally considered the disease in which this phenomenon is most prevalent. The actual prevalence of neuroblastoma regression is not unknown but recent studies have provided evidence that regression may be at least as common as clinically detected neuroblastoma.

Beckwith and Perrin (1963) studied the adrenal glands from autopsies of infants under 3 months old who had died for reasons other than neuroblastoma. Interestingly, they discovered foci of neuroblasts in the adrenal glands of 1 out of every 40 infants studied and they proposed that these neuroblastic nodules might eventually evolve into clinically detectable neuroblastoma, so they called them insipient or “in situ” neuroblastoma (Beckwith and Perrin 1963). If the prevalence of clinically detected neuroblastoma is about 1 in 8000 live births, then the prevalence of spontaneous regression of neuroblastoma would be 200 times more common than clinically detected disease (i.e., 2%), which seems very high.

Later, other investigators studied the adrenal glands of fetuses that died prenatally at various gestational ages. They found similar neuroblastic foci in all the fetal adrenal glands they studied, with a peak between 16 and 20 weeks of gestation, after that these foci gradually disappeared (Ikeda et al. 1981; Turkel and Itabashi 1974). Based on this information, the neuroblastic rests seen by Beckwith and Perrin were likely the residual elements of normal sympathoadrenal development rather than insipient neuroblastoma. Nevertheless, these normal neuroblastic nodules may contain the cells from which adrenal neuroblastomas arise.

The phenomenon of neuroblastoma regression was already known but Evans and D’Angio identified a specific pattern of metastatic spread in infants less than a year of age that they called stage IVS (D'Angio et al. 1971; Evans et al. 1971). Infants with stage IVS generally

had small abdominal primary tumors with dissemination limited to the liver and skin, with or without minimal marrow involvement. These patients generally had a very good prognosis and some even underwent spontaneous regression in the absence of tumor-specific therapy (D'Angio et al. 1971; Evans et al. 1971). In contrast, patients over 12–18 months of age with metastatic disease generally had a different pattern of dissemination that included bone lesions and extensive marrow involvement and patients with this pattern generally had a very poor prognosis and never regressed (George et al. 2006; Matthay et al. 1999).

The definition of stage IVS was refined by the International Neuroblastoma Staging System (INSS) as stage 4S (Brodeur et al. 1988, 1993) and by the International Neuroblastoma Risk Group Staging System as stage MS (M for metastatic, S for special) (Monclair et al. 2009); this stage will be referred to as 4S in this review. The main difference now is that children up to 18 months of age can be considered to have stage 4S (George et al. 2005; London et al. 2005; Monclair et al. 2009). However, it is clear that spontaneous regression is not restricted to stage 4S, because regression can be seen in infants with virtually any stage of disease if they have biologically favorable tumors (Cozzi et al. 2013; Fisher and Tweddle 2012; Kushner et al. 1996; Taggart et al. 2011).

Genomic and biological features of regressing neuroblastomas

It is difficult to know for certain which neuroblastomas will regress based on age and stage alone. Therefore, investigators have focused on stage 4S tumors as a surrogate for neuroblastomas that are likely to regress. Lavarino et al. (2009) conducted a study on 35 infants with metastatic neuroblastoma—25 with stage 4 and 10 with stage 4S. The tumors from patients with stage 4 disease were characterized by segmental chromosomal aberrations, whereas 90% of stage 4S tumors were near-triploid with whole chromosome gains (Lavarino et al. 2009). These investigators found differential expression of certain genes (such as *CHD5, GNB1* and *RERE*) in stage 4 and stage 4S neuroblastoma, with higher expression of genes mapping to the short arm of chromosome 1 in stage 4S tumors and to chromosome 11 for stage 4 tumors. Benard et al. (2008) studied 29 cases of metastatic neuroblastoma lacking *MYCN* amplification. They developed a genetic signature of 45 genes that was significantly associated with stage 4S (12 cases) versus stage 4 tumors (17 cases) and this was validated in an independent set of 22 tumors. A smaller proteomic study was performed on eight tumors from infants with stage 4 and 4S that identified another set of differentially expressed proteins between the two stages (Yu et al. 2011). There was essentially no overlap of genes (or proteins) that were differentially expressed by regressing 4S versus non-regressing infant tumors among these studies, so more studies are needed.

Insights from mass screening for neuroblastoma

Mass screening studies for neuroblastoma were undertaken in Japan, North America and Europe to identify neuroblastomas early, because the outcome of infants with neuroblastoma is substantially better than that of older patients. Almost all neuroblastomas produce catecholamines and their metabolites, so mass screening was conducted by measuring urinary catecholamine metabolites of infants at specific times between 3 weeks and 6 months of age. Mass screening of infants for neuroblastoma was initiated in Japan and initial

results were promising (Bessho 1999; Sawada et al. 1984; Yamamoto et al. 2002), so similar efforts were initiated in North America and in Europe (Erttmann et al. 1998; Woods et al. 1996). However, mass screening for neuroblastoma resulted in a substantial increase in the prevalence of neuroblastoma in screened compared with unscreened populations (~1:2000 vs. 1:8000 respectively) and the overall mortality from neuroblastoma was unchanged (Bessho 1999; Schilling et al. 2002; Woods et al. 2002; Yamamoto et al. 2002). Thus, mass screening did not reduce neuroblastoma mortality and screening efforts have essentially stopped worldwide.

Nevertheless, these mass-screening studies provided valuable insights into the pathogenesis and clinical behavior of biologically favorable tumors. The increased prevalence of neuroblastoma observed in the screened populations indicates that spontaneous regression of neuroblastoma (without clinical detection) occurs at least as frequently as clinically detected neuroblastoma. In addition, genomic analyses performed on screened tumors showed that most of them, regardless of their stage, were biologically favorable with respect to *MYCN* status and tumor cell ploidy (Brodeur et al. 1998; Hayashi et al. 1992; Kaneko et al. 1990). This is in contrast to the unfavorable biological features generally found in clinically detected tumors from older children. Importantly, these studies also suggested that biologically favorable tumors rarely evolve into biologically unfavorable tumors. There have also been reports of incidental prenatal detection of neuroblastoma by maternal ultrasound (Acharya et al. 1997; Ho et al. 1993; Saylors et al. 1994). These cases are similar both clinically and biologically to those identified by screening and the vast majority does well with little or no therapy.

Mechanisms of spontaneous regression

Neurotrophin receptors and regression

Neuroblastomas are derived from sympathetic neuronal precursors and many more precursor cells are produced during normal development than are necessary to form the sympathetic nervous system. Those that make a proper connection to a target organ or tissue will survive and those that do not are destined to undergo developmentally programmed cell death (Estus et al. 1994; Ham et al. 1995). This process is regulated primarily by the TrkA neurotrophin receptor and the limiting availability of its cognate ligand, nerve growth factor (NGF) at their target site. Nevertheless, these neuronal precursors survive, migrate and proliferate in the absence of NGF during early embryogenesis, so there must be a developmental switch from an NGF-independent to an NGF-dependent state.

TrkA (encoded by NTRK1), a neurotrophin receptor, is a member of a family of receptor tyrosine kinases that includes TrkB (encoded by NTRK2) and TrkC (encoded by NTRK3). Each of these receptors plays a critical role in the development and maintenance of the central and peripheral nervous systems. These receptors also have important roles in neuroblastoma pathogenesis (Brodeur et al. 1997, 2009; Thiele et al. 2009). High TrkA expression is associated with favorable clinical and biological features, such as younger age, lower stage and absence of *MYCN* amplification and these patients have an excellent outcome (Kogner et al. 1993; Nakagawara et al. 1992, 1993; Suzuki et al. 1993). In contrast, TrkB is coexpressed at high levels along with its ligand, BDNF, in clinically and biologically

unfavorable tumors, especially those with *MYCN* amplification (Nakagawara et al. 1994). Autocine activation of TrkB by BDNF leads to invasion, metastasis, angiogenesis and drug resistance (Acheson et al. 1995; Jaboin et al. 2002; Matsumoto et al. 1995; Nakagawara et al. 1994; Nakamura et al. 2006). TrkA and TrkC are dependence receptors, because the absence of ligand activation leads to apoptotic signaling and cell death, whereas TrkB is not (Goldschneider and Mehlen 2010; Nikoletopoulou et al. 2010; Rabizadeh et al. 1999). Co-expression of the P75/NGFR receptor can increase the sensitivity and specificity of all three Trk receptors for their cognate ligands (Hantzopoulos et al. 1994; Ho et al. 2011) but activation of P75/NGFR in the absence of TrkA signaling leads to apoptosis (Bamji et al. 1998; Rabizadeh et al. 1999).

Tumors from infants, especially with low-stage or 4S disease, generally have high levels of TrkA expression (Kogner et al. 1993; Nakagawara et al. 1992 1993; Suzuki et al. 1993). When cells derived from these tumors are put in primary culture with exogenous NGF, they undergo neuronal differentiation and survive for months. In contrast, the same cells undergo apoptosis within a week if cultured in the absence of exogenous NGF (Nakagawara et al. 1993; Nakagawara and Brodeur 1997) (Fig. 1a). Taken together with the pivotal role of TrkA and NGF in development of the sympathetic nervous system, these results mimic the behavior of TrkA-expressing neuroblastomas in patients: tumors undergo neuronal differentiation to a ganglioneuroma, or they undergo spontaneous regression (apoptosis), depending on the presence or absence (respectively) of NGF in their microenvironment.

It is unclear why migrating neural crest precursors and favorable TrkA-expressing neuroblastomas survive (at least initially), despite a lack of available NGF. Initially, TrkA expression on these precursor cells is low, as is P75/NGFR and these cells are not dependent on NGF (Nikoletopoulou et al. 2010). NGF-independent neuronal precursors could depend on an alternative receptor or pathway for survival (such as TrkC or RET) (Kahane and Kalcheim 1994; Pachnis et al. 1993; Tsuzuki et al. 1995) and then switch dependence to TrkA, only to undergo apoptosis and regress in the absence of NGF. Another possibility is that these migrating cells express TrkAIII, a TrkA(I) isoform that is expressed in normal sympathoadrenal progenitors as well as in some neuroblastomas (Tacconelli et al. 2004, 2005). This isoform results from alternative splicing and maintains the reading frame but removes the ligand-binding site, leading to constitutive kinase activation. Thus, the conversion from a TrkA-expressing, NGF-independent neuroblastoma to a NGF-dependent tumor could result simply from a developmentally programmed isoform switch from TrkAIII to TrkAI. Thus, a switch in TrkA dependence could explain spontaneous regression of neuroblastomas but there are additional mechanisms to explain this phenomenon as well.

Telomerase, telomeres and regression

High telomerase activity is generally associated with more-aggressive behavior and poor prognosis in patients with neuroblastoma (Krams et al. 2003; Ohali et al. 2006 Peifer et al. 2015; Streutker et al. 2001). However, telomere shortening has been proposed as another possible explanation for spontaneous regression of neuroblastoma. Telomeres are specialized structures at the ends of chromosomes that are important for the replication and stability of chromosomes and regulation of the telomere length is controlled in part by the enzyme

telomerase. Telomerase expression is frequently high in cancer and immortalized cells but generally low in most normal and senescent cells Kim et al. 1994). Hiyama et al. (1995) examined the telomere length and telomerase activity of 100 neuroblastoma samples. Most tumors with high telomerase activity had a poor prognosis and all tumors with *MYCN* amplification had high telomerase activity. However, most of the 4S neuroblastoma samples had low telomerase activity or short telomeres, a pattern usually associated with senescent cells (Fig. 1b) (Hiyama et al. 1995). Interestingly, Samy et al. (2012) transfected a neuroblastoma cell line with a dominant negative form of telomerase and tumors formed by these cells showed increased apoptosis and reduced tumorigenicity compared to untransfected cells in a mouse xenograft model. Together, these data suggest that loss of telomerase activity and telomere shortening is a plausible mechanism to explain spontaneous regression of neuroblastoma and possibly of other tumors.

Immunological mechanisms and regression

Spontaneous regression of primary and metastatic cancers (including neuroblastoma) has occurred in association with acute infection (Everson 1964; Everson and Cole 1966). Furthermore, tumor-infiltrating lymphocytes have been observed in neuroblastomas and there is evidence for both tumor-targeted T-cells and antineural antibodies in patients with neuroblastoma (Antunes et al. 2000; Kataoka et al. 1993; Valteau et al. 1996). Thus, another potential explanation of spontaneous regression is tumor destruction mediated by an anti-tumor immune response (Fig. 1c). Interestingly, the paraneoplastic opsomyoclonus syndrome (OMS) is associated with the presence of antineural antibodies and a favorable outcome in patients with neuroblastoma (Antunes et al. 2000; Cooper et al. 2001; Pranzatelli et al. 2004; Rudnick et al. 2001; Russo et al. 1997). About 50% of patients with OMS have neuroblastoma, which suggests that the other 50% either had a neuroblastoma that regressed or they have a de novo autoimmune disease. However, it is still unclear if spontaneous regression can be mediated by a humoral or cellular immune response.

Neuroblastoma cells from patients with high-risk disease may evade immune destruction by downregulating human leukocyte antigen (HLA) class I molecules (Raffaghello et al. 2005). However, most tumors from patients with stage 4S neuroblastoma express normal levels of HLA class I antigens (Squire et al. 1990). In vitro exposure to interferon-γ can induce upregulation of the expression of class I antigens in neuroblastoma cells (Raffaghello et al. 2005). Thus, upregulation of HLA class I might be a strategy to augment immune surveillance and promote tumor regression. Although in vitro exposure to interferon-γ can enhance the recognition of neuroblastoma cells by cytotoxic T cells, it can also reduce their susceptibility to killing by natural killer (NK) cells (Raffaghello et al. 2005). Only a few low stage and 4S neuroblastomas have been studied, so further study of the role of cytokines in mediating regression is needed.

Asgharzadeh et al. (2012) studied tumor-associated macrophage (TAM) infiltration in tumors from patients with various stages of *MYCN* non-amplified disease. However, this study reported that the number of TAM in INSS 4S tumors is similar to locoregional neuroblastomas. Metastatic tumors (stages 4 and 4S) from young patients (<18 months old) had significantly higher expression of genes representing TAMs than did metastatic tumors

from older patients. This suggests that the inflammatory response and the tumor microenvironment might contribute to the behavior of neuroblastoma in patients based on age at diagnosis or stage of disease (Asgharzadeh et al. 2012). This study did not specifically evaluate regressing tumors, so further investigation is needed to understand the contribution of the immune system and tumor microenvironment to neuroblastoma regression.

Epigenetic regulation and other mechanisms

Gene expression is affected by promoter methylation, histone modification or chromatin remodeling, which in turn may effect neuroblastoma cell survival or differentiation (Fig. 1d). Epigenetic changes affecting expression of genes relevant to neuroblastoma development were initially reported over a decade ago (Astuti et al. 2001; Takita et al. 2000) and several studies have suggested that alterations in gene methylation or histone modification are related to patient outcome (Barbieri et al. 2014; Decock et al. 2011; Grau et al. 2010; Yang et al. 2007). Diskin et al. (2014) identified global differences in the methylomes of 22 stage 4S neuroblastomas compared to low-risk tumors, high-risk tumors and normal brain tissues. Reduced promoter methylation in the 4S samples was observed in 97% of the genes for which differential methylation was detected. Others have also reported different patterns of methylation in tumors from patients with stage 4S compared to other stages (Decock et al. 2011). However, additional studies are needed to validate these findings and develop more specific information regarding DNA methylation, histone modification, or chromatin modification during differentiation and regression (Baylin 2005; Gros et al. 2012; McCabe and Creasy 2014).

Therapy to induce neuroblastoma regression

TrkA inhibitors

Inhibition of the TrkA receptor pathway is a promising approach to induce tumor regression in biologically favorable neuroblastomas. TrkA-expressing neuroblastoma cells placed in culture survive and differentiate in the presence of NGF but they undergo apoptosis in its absence (Nakagawara and Brodeur 1997). Thus, depriving cells of NGF or inhibiting TrkA signaling may be an effective approach to induce regression. Lestaurtinib (CEP-701) is a small molecule inhibitor of TRK receptors (TrkA, TrkB and TrkC) and it has shown preclinical activity against TrkB-expressing neuroblastoma xenografts (Evans et al. 1999, 2001; Ho et al. 2002; Iyer et al. 2010). Furthermore, lestaurtinib showed significant clinical activity in a phase I trial for recurrent and/or refractory neuroblastoma (Minturn et al. 2011). These studies provide evidence that Trk-selective inhibitors could be effective in the treatment of Trk-driven neuroblastomas. Indeed, several second-generation Trk inhibitors are currently in phase 1 clinical trials or in preclinical development (Croucher et al. 2015, Doebele et al. 2015, Drilon et al. 2017; Iyer et al. 2012, 2016; Nagasubramanian et al. 2016). These agents are potent inhibitors of all three Trk family neurotrophin receptors, so the same agent could be used to target TrkA in biologically favorable tumors and TrkB in unfavorable tumors. If second-generation Trk inhibitors prove to be safe and effective against TrkB-expressing, high-risk disease, these agents could be used to treat patients with TrkA-expressing 4S neuroblastoma who have massive liver involvement in lieu of chemotherapy

or radiation therapy. We hypothesize that a Trk inhibitor would initiate apoptosis and regression in these tumors, obviating the need to wait for spontaneous regression to occur.

Immunological therapy

Immunotherapy using a chimeric antibody (ch14.18) directed against the disialoganglioside GD_2 has been incorporated into frontline treatment of patients with high-risk neuroblastoma (Yu et al. 2010) and preliminary studies have been carried out using adoptive immunotherapy in patients with recurrent/refractory disease (Louis et al. 2011). Future studies of the immunology of neuroblastoma regression should influence the evolution of current immunotherapeutic approaches and lead to new strategies to accelerate regression in young infants with life-threatening but biologically favorable disease. Immune modulation to induce regression could be advantageous for patients with 4S or locoregional disease, because there is a trend to reduce conventional cytotoxic therapy and avoid aggressive surgery in patients with a favorable prognosis (Baker et al. 2010; Hero et al. 2008; Nuchtern et al. 2012). Treatment with interferon-γ may upregulate HLA class I expression and increase immune cell recognition. However, strategies to enhance one component of the immune system may diminish the anti-tumor effects of another key component. A better understanding is needed of the complex interactions between neuroblastoma cells, the tumor microenvironment and the immune system, as well as the implications of immune modulation in very young children.

Other approaches

At the present time, there are no therapeutic approaches to influence telomere length in neuroblastomas. However, there are other approaches that might be considered for these patients. For example, retinoids are a class of compounds that have been shown to induce cellular differentiation and decrease proliferation of neuroblastoma cells in vitro, presumably mediated by the upregulation of neural differentiation genes (Yuza et al. 2003). Indeed, 13-cis-retinoic acid has been incorporated into frontline therapy for children with high-risk neuroblastoma to induce differentiation in states of minimal residual disease following intensive, multimodality therapy (Shimada et al. 1999b). The mechanisms by which isotretinoin induces differentiation are unclear but retinoids are associated with increased expression of Trk receptors, which may explain the induction of differentiation (Rodriguez-Tebar and Rohrer 1991; Yuza et al. 2003). Vorinostat, a histone deacetylase inhibitor, has been given to children with relapsed or refractory disease. Further studies of epigenetic modifiers may alter gene expression in neuroblastomas and consequently induce tumor regression.

Conclusions

Neuroblastomas show a remarkable capacity to undergo spontaneous regression. The prevalence of this phenomenon is hard to determine precisely but the experience from mass screening programs suggests that there are at least as many children who have tumors undergoing spontaneous regression without clinical detection as there are patients with neuroblastoma detected clinically. Further exploration of this issue and a greater understanding of the normal mechanism(s) of spontaneous regression might allow the

identification of tumors that have the capacity to undergo spontaneous regression and to induce regression in susceptible tumors using pharmacological, biological or immunological approaches. To this end, we would need to study samples from regressing tumors, such as skin nodules from stage 4S patients. These go through three phases of growth (proliferation), a plateau of growth and then disappearance. The potential mechanisms of regression described above could each lead to these successive changes, once the mechanism was activated (TrkA dependence, telomere shortening, immune response, or epigenetic modification).

At the present time, the most promising therapeutic approach would be aimed at inhibiting the TrkA receptor pathway. However, most Trk inhibitors are potent inhibitors of TrkA, TrkB and TrkC. Before these agents are used to treat infants with stage 4S disease, clinical trials of second-generation Trk inhibitors would need to demonstrate safety and efficacy against TrkB-expressing recurrent and/or refractory neuroblastomas, especially in young children. Currently, there are no opportunities to selectively promote telomere shortening, initiate a targeted immune response, or preferentially induce epigenetic modifications in tumor tissue.

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Abbreviations

HLA	Human leukocyte antigen
INSS	International Neuroblastoma Staging System
NK	Natural killer
NGF	Nerve growth factor
OMS	Opsomyoclonus syndrome
TAM	Tumor-associated macrophages
TRK	Tropomyosin receptor kinase

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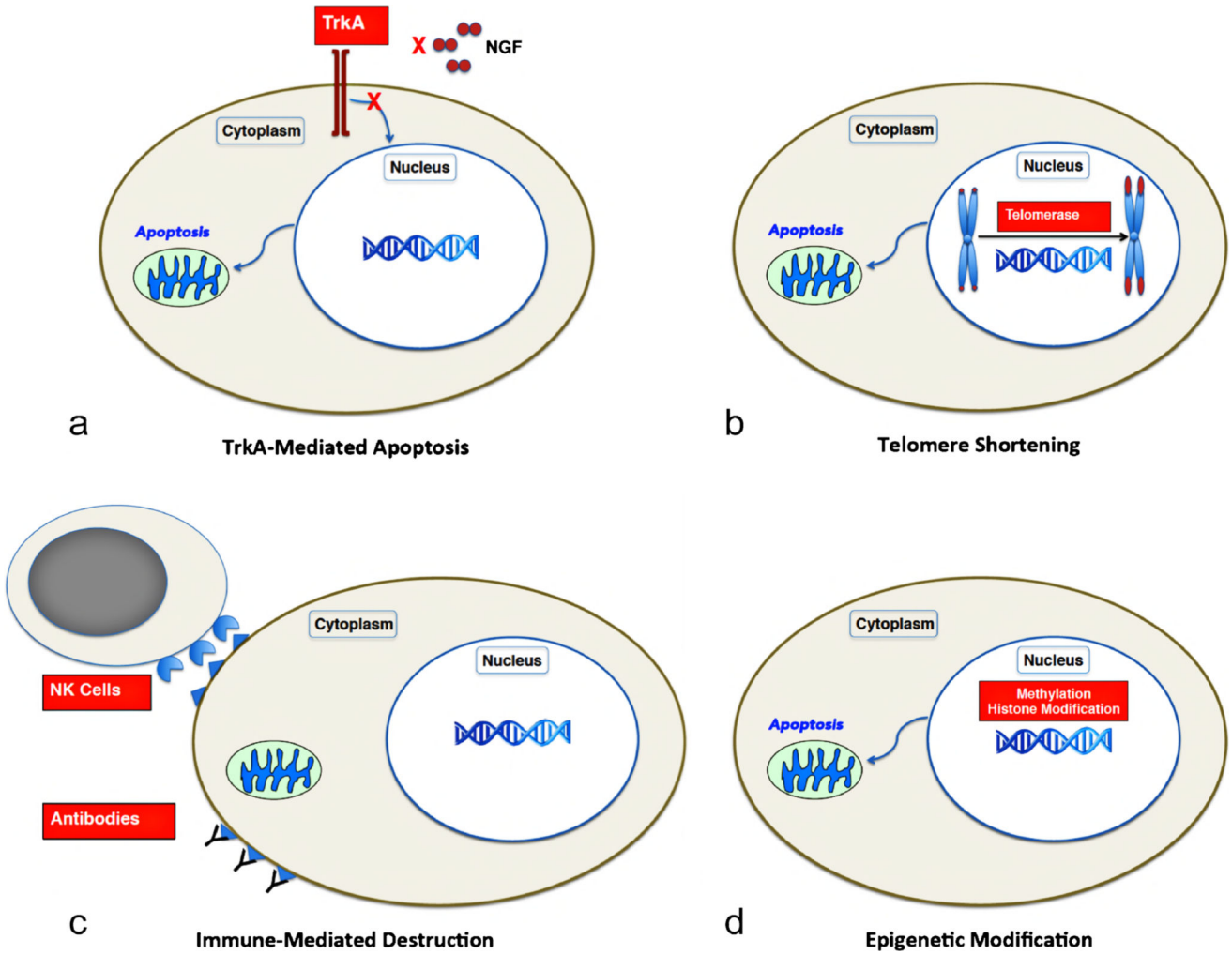

Fig. 1.

Mechanisms of spontaneous regression. **a** The TrkA-NGF pathway and apoptosis. Neurotrophin deprivation (TrkA without NGF) leads to activation of developmentally programmed apoptosis and regression of neuroblastomas. **b** Telomere shortening and apoptosis. Telomere shortening results from low/absent levels of telomerase and triggers apoptosis and regression of neuroblastomas. **c** Immune-mediated destruction. Immune-mediated cell killing by anti-neuroblastoma antibodies (and antibody-dependent cellular toxicity) or by NK cells leads to death of neuroblastoma cells and tumor regression. **d** Epigenetic modification. Alterations of gene expression can occur by promoter methylation, histone modification or chromatin remodeling, leading to neuroblastoma regression