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News and reviews

Neuropeptide Y (NPY) in tumor growth and progression: Lessons learned from pediatric oncology

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ABSTRACT

Neuropeptide Y (NPY) is a sympathetic neurotransmitter with pleiotropic actions, many of which are highly relevant to tumor biology. Consequently, the peptide has been implicated as a factor regulating the growth of a variety of tumors. Among them, two pediatric malignancies with high endogenous NPY synthesis and release – neuroblastoma and Ewing sarcoma – became excellent models to investigate the role of NPY in tumor growth and progression. The stimulatory effect on tumor cell proliferation, survival, and migration, as well as angiogenesis in these tumors, is mediated by two NPY receptors, Y2R and Y5R, which are expressed in either a constitutive or inducible manner. Of particular importance are interactions of the NPY system with the tumor microenvironment, as hypoxic conditions commonly occurring in solid tumors strongly activate the NPY/Y2R/Y5R axis. This activation is triggered by hypoxia-induced up-regulation of Y2R/Y5R expression and stimulation of dipeptidyl peptidase IV (DPPIV), which converts NPY to a selective Y2R/Y5R agonist, NPY_{3-36}. While previous studies focused mainly on the effects of NPY on tumor growth and vascularization, they also provided insight into the potential role of the peptide in tumor progression into a metastatic and chemoresistant phenotype. This review summarizes our current knowledge of the role of NPY in neuroblastoma and Ewing sarcoma and its interactions with the tumor microenvironment in the context of findings in other malignancies, as well as discusses future directions and potential clinical implications of these discoveries.

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1. Neuropeptide Y (NPY) as a pleiotropic factor with functions relevant to tumor biology

NPY is a 36 amino-acid sympathetic neurotransmitter abundant in the brain and released from peripheral sympathetic neurons during their activation, e.g. by chronic stress or hypoxia (Zukowska-Grojec, 1995). Acting via its Y1–Y5 receptors (Y1R–Y5R), the peptide exerts pleiotropic effects that control various functions of the organism. Importantly, many of these actions of NPY, including stimulation of cell proliferation, migration, and survival, as well as regulation of cell differentiation, are highly relevant to tumor growth and progression (Han et al., 2012; Hansel et al., 2001; Kitlinska et al., 2005; Lee et al., 2010; Pons et al., 2003; Son et al., 2011). Consequently, recent years brought significant progress in our understanding of the peptide's role in regulation of tumor growth, as well as some evidence for its contribution to cancer progression toward a metastatic and chemoresistant phenotype.

NPY has been implicated as a growth-promoting factor in various malignancies, including breast and prostate cancer (Lenkinski et al., 2008; Magni and Motta, 2001; Medeiros et al., 2011; Medeiros and Jackson, 2013; Ruscica et al., 2007; Sheriff et al., 2010; Ueda et al., 2013). Among them, two pediatric tumors with high endogenous NPY expression – neuroblastoma and Ewing sarcoma – have proven to be excellent tools to investigate the role of the peptide in tumor biology (Hong et al., 2015; Kitlinska et al., 2005; Lu et al., 2010; Lu et al., 2011; Tilan et al., 2014b; Tilan et al., 2013b). Our studies revealed that despite their different origins and means of NPY system regulation, these two tumor types share common functional responses to the peptide. These similarities implicate the universal nature of NPY actions and suggest that our findings can be relevant to other malignancies that do not express NPY, yet are exposed to the peptide released systemically from sympathetic neurons (Tilan and Kitlinska, 2010). Such an understanding of NPY's role in tumor biology is particularly important in relation to pathologies associated with elevated systemic levels of the peptide, e.g. severe chronic stress. In this review, we will describe the pleiotropic actions of NPY that we have identified in neuroblastoma and Ewing sarcoma and its interactions with the tumor microenvironment. We will present our results in the context of previously reported data gathered in other tumor types, as well as discuss the potential implications of these findings. As work on the role of NPY in tumor biology is ongoing, we will also identify gaps in the current knowledge and potential future directions in research.

2. Neuroblastoma and Ewing sarcoma as models of NPY-rich tumors

Neuroblastoma is a pediatric malignancy developing very early in life, often in infancy (Maris, 2010). The disease is extremely heterogeneous, with phenotypes ranging from spontaneously regressing to highly aggressive and metastatic tumors. While the low-grade tumors are curable, treatment of metastatic neuroblastoma remains a clinical challenge, with event-free survival for patients with high-risk disease remaining below 50% (Cohn et al., 2009). Neuroblastomas develop from precursors of sympathetic neurons, most often in adrenal glands or peripheral sympathetic ganglia, and metastasize mainly to the bone marrow and bones (Maris et al., 2010). A very specific type of neuroblastoma, stage 4S, develops in infancy and presents at diagnosis with metastases to skin, bone marrow, and liver, yet commonly regresses or matures with time without treatment (Cohn et al., 2009).

Due to their sympathetic origin, neuroblastomas express neuronal markers, including NPY and its receptors (Kitlinska et al., 2005; Maris, 2010). We have shown that NPY and its Y2R are universally expressed in neuroblastoma cells and tissues, while Y5R is an inducible receptor, e.g. under hypoxic conditions (Table 1) (Czarnecka et al., 2015; Kitlinska et al., 2005; Lu et al., 2010). Further studies revealed a crucial role for both pathways in different aspects of neuroblastoma biology.

Ewing sarcoma is an aggressive malignancy developing in bones or soft tissues of children and adolescents (Lessnick and Ladanyi, 2012). These tumors frequently relapse after initial treatment and metastasize to the lungs and distant bones. While the outcome of patients with localized disease has recently improved, the prognosis remains dismal for those with metastases at diagnosis, particularly when dissemination to bone is present (8–14% event-free survival) (Ladenstein et al., 2010; Parasuraman et al., 1999; Womer et al., 2012). The Ewing sarcoma cell of origin is controversial, as the data point to neural crest, mesenchymal, or even endothelial cells at early stages of their differentiation (Coles et al., 2008; Monument et al., 2013; Staege et al., 2004; Todorova, 2014; von Levetzow et al., 2011). Nevertheless, these tumors exhibit some neuronal properties, including expression of specific markers. Importantly, despite differences in tumor localization and degree of neuronal differentiation, the common feature of Ewing sarcoma tumors is the presence of a characteristic chromosomal translocation leading to the fusion of the Ewing sarcoma breakpoint region1 (*EWSR1*) gene with an E26 transformation-specific (*ETS*) transcription factor (*EWS-ETS*), most often Friend leukemia integration 1 transcription factor (*FLI1*) (Toomey et al., 2010). This aberrant transcriptional activity of EWS-FLI1 fusion protein is believed to trigger a malignant transformation of Ewing sarcoma, but also induce a neuronal phenotype of Ewing sarcoma. Indeed, *NPY* and its *Y1R* and *Y5R* are transcriptional targets of EWS-FLI1 (Hancock and Lessnick, 2008; Smith et al., 2006). Consequently, an NPY/Y1R/Y5R autocrine loop is highly and constitutively expressed in Ewing sarcoma (Kitlinska et al., 2005; Korner et al., 2008; Lu et al., 2011; van Valen et al., 1992). However, we have also discovered that this pattern of NPY system expression and thereby its functions change dramatically in the hypoxic tumor environment, switching its activity to the NPY/Y2R/Y5R pathway (Table 1) (Lu et al., 2011; Tilan et al., 2013b).

In summary, even though basal expression of the NPY system measured in neuroblastoma and Ewing sarcoma cells cultured in vitro is utterly different, the same NPY/Y2R/Y5R axis is active in vivo in the hypoxic tumor microenvironment of both types of tumors. During the course of our studies, we have gathered compelling evidence that this pathway serves as a growth-promoting and potentially pro-metastatic mechanism that is common for both malignancies, and perhaps also other tumors.

3. Systemic NPY as a marker of adverse tumor phenotype

Due to high NPY synthesis within tumor tissues, both neuroblastoma and Ewing sarcoma tend to release the peptide into the systemic circulation, which results in its elevated levels in the blood (Cohen et al., 1990; Dotsch et al., 1998; Kitlinska et al., 2005; Kogner et al., 1994; Lu et al., 2010; Tilan et al., 2014b). Interestingly, however, despite constitutive and universal expression of NPY in both tumor types, its release varies between patients. Thus, in some cases, serum NPY concentrations are highly elevated, while in others, NPY levels are comparable to the healthy control (Tilan et al., 2014b). Importantly, elevated systemic NPY levels correlate with adverse tumor phenotype in both malignancies. In neuroblastoma, high plasma NPY is observed in children with advanced disease and associates with poor clinical outcome (Cohen et al., 1990; Dotsch et al., 1998; Kogner et al., 1994). A similar trend of increased serum NPY was observed in patients with metastatic Ewing sarcoma, as compared to those with localized disease and to healthy control (Tilan et al., 2014b). Such variability in peptide release independent of its levels of synthesis suggests secretion of the peptide as a potential mechanism regulating its functions that are mediated by surface receptors. In this way, the ability of tumor cells to release NPY may affect tumor phenotype.

In line with our findings in pediatric malignancies, other groups have reported associations of elevated plasma NPY with metastasis in pheochromocytoma, an adulthood tumor that develops from sympathoadrenal system (Table 1) (deS Senanayake et al., 1995;

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